Reinventing Medicine with Protein Degradation

August 2024

KYMERA

Forward Looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. These statements include, but are not limited to, implied and express statements about our strategy, business plans and objectives for our programs; Sanofi's intent to expand the Phase 2 clinical trials of KT-474/SAR-444656, plans and timelines for the preclinical and clinical development of our product candidates, including the therapeutic potential, clinical benefits and safety profiles of such product candidates; expectations regarding timing, success and data announcements of ongoing preclinical studies and clinical trials; our ability to initiate new clinical programs, including plans to submit investigational new drug (IND) applications; the initiation, timing, progress and results of our current and future preclinical studies and clinical trials of our current and prospective product candidates; our plans to develop and commercialize our current and any future product candidates and the implementation of our business model and strategic plans for our business, current and any future product candidates. All statements other than statements of historical facts contained in this presentation, including express or implied statements regarding our strategy, future financial condition, expected cash runway into the first half of 2027, future operations, projected costs, prospects, plans, objectives of management and expected market growth, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "anticipate," "assume," "believe," "could," "estimate," "expect," "goal," "intend," "may," "milestones," "objective," "plan," "predict," "potential," "seek," "should," "target," "will," "would" and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. You should not rely upon forward-looking statements as predictions of future events and actual results or events could differ materially from the plans, intentions and expectations disclosed herein.

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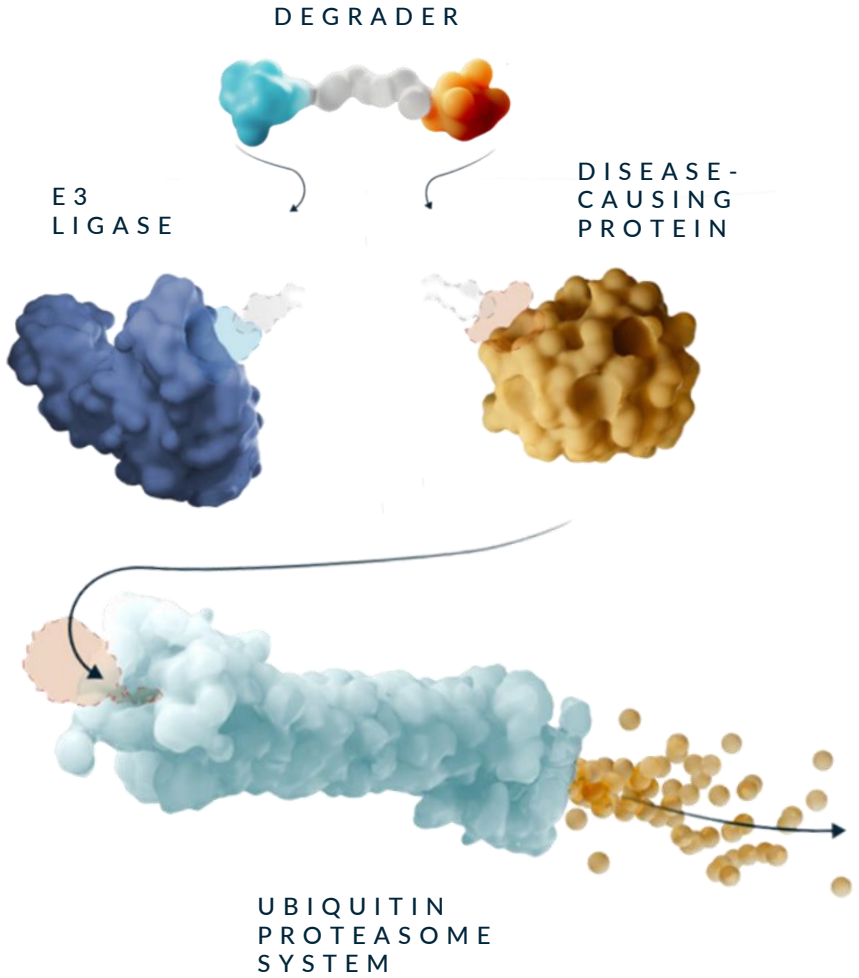
Harnessing a Game-Changing, Novel Modality

Kymera, a Leader in Targeted Protein Degradation

- Focused on unlocking high value, undrugged targets using TPD
- Highly productive and reproducible platform for discovery of innovative medicines
- Leading platform and pipeline IP, developed internally
- Well-capitalized with $930[1] million in cash and expected runway into mid 2027, enabling expansion into areas with large clinical and commercial opportunities

Industry Leading Execution

- Since founding Kymera in 2016:
  - Advanced four first-in-class programs to the clinic
  - Demonstrated clinical translation of degradation and safety
  - Achieved early clinical POC in I&I and oncology programs
- Extensive validation of target selection and molecular design
- Successful track record delivering multiple new drug mechanisms in clinic, expecting up to 10 novel INDs within first 10 years

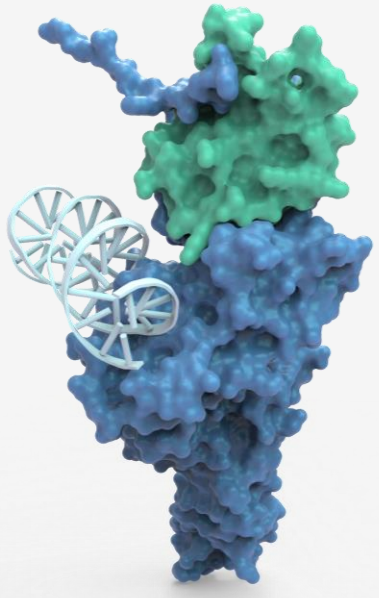


[1]Unaudited, estimated cash as of August 21, 2024, inclusive of approximately $246 million of net proceeds from the company's recently-closed equity offering.

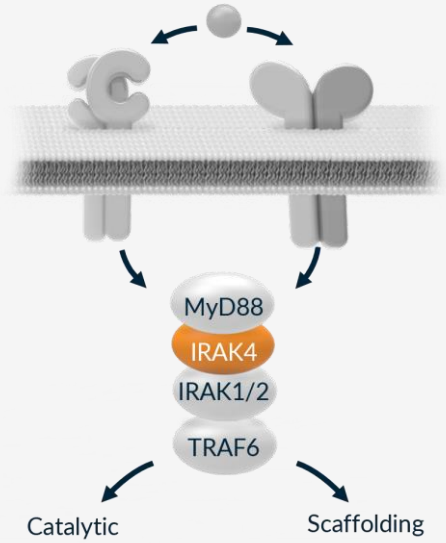
Target Selection Strategy

Focus on First- or Best-in-Class Opportunities

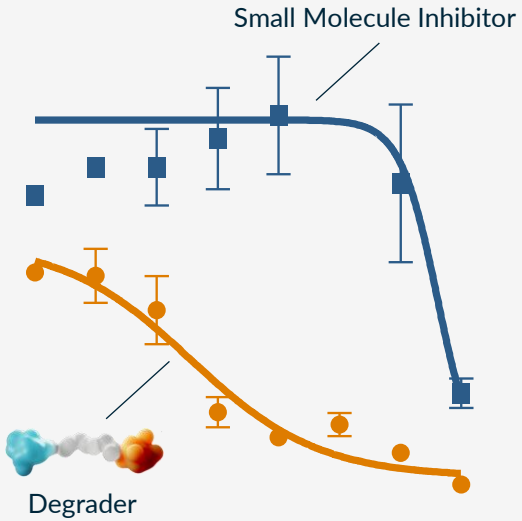
Undrugged or Inadequately Drugged targets	Strong Genetic/Pathway Validation	Clear Path to Early Clinical Differentiation	Large Clinical/Commercial Opportunities



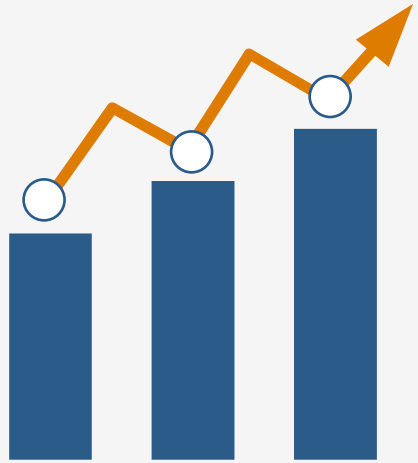
TRANSCRIPTION FACTORS & SCAFFOLDING PROTEINS



APPROVED DRUGS IN SAME PATHWAY



SUPERIORITY VS PATHWAY DRUGS



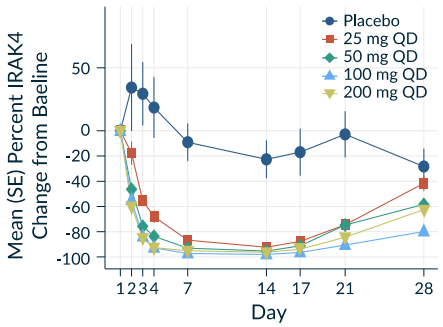
AREAS OF SIGNIFICANT VALUE CREATION

Demonstrating Reproducible and Scalable Clinical Innovation

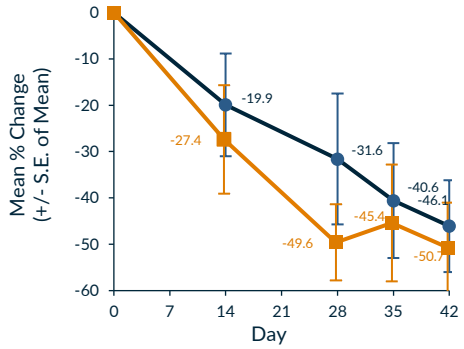
IRAK4 KT-474

IRAK4 Degradation leads to Early POC in HS and AD

IRAK4 Levels

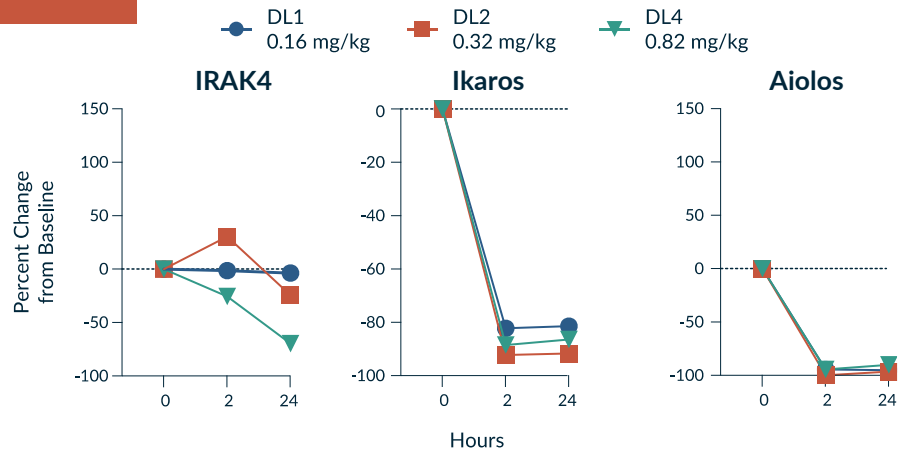


Reduction of AN Counts in HS Patients



IRAKIMID KT-413

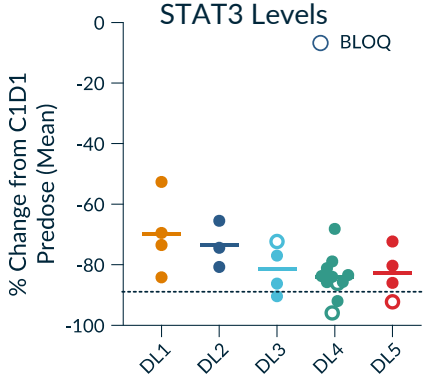
Degradation of IRAK4 and Ikaros/Aiolos



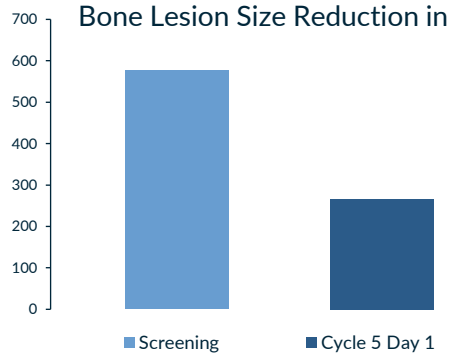
STAT3 Degradation Leads to Major Response in cHL Patient

STAT3 KT-333

STAT3 Levels



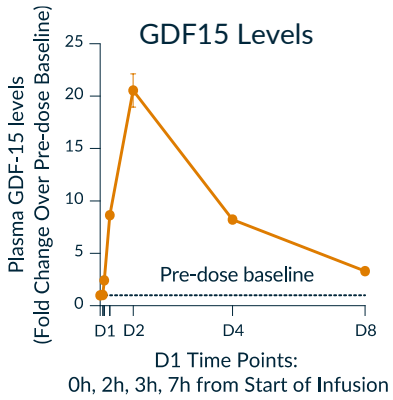
Bone Lesion Size Reduction in cHL Patient



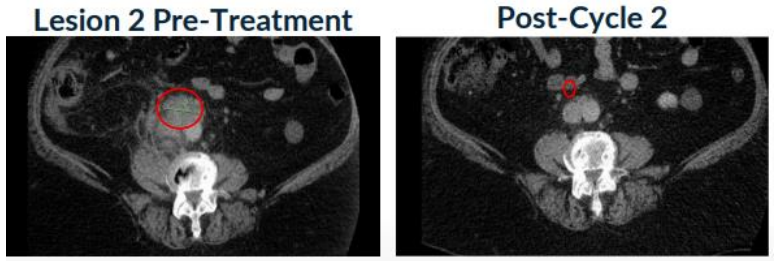
MDM2 Degradation Leads to Major Response in MCC Patient with no Heme-tox

MDM2 KT-253

GDF15 Levels

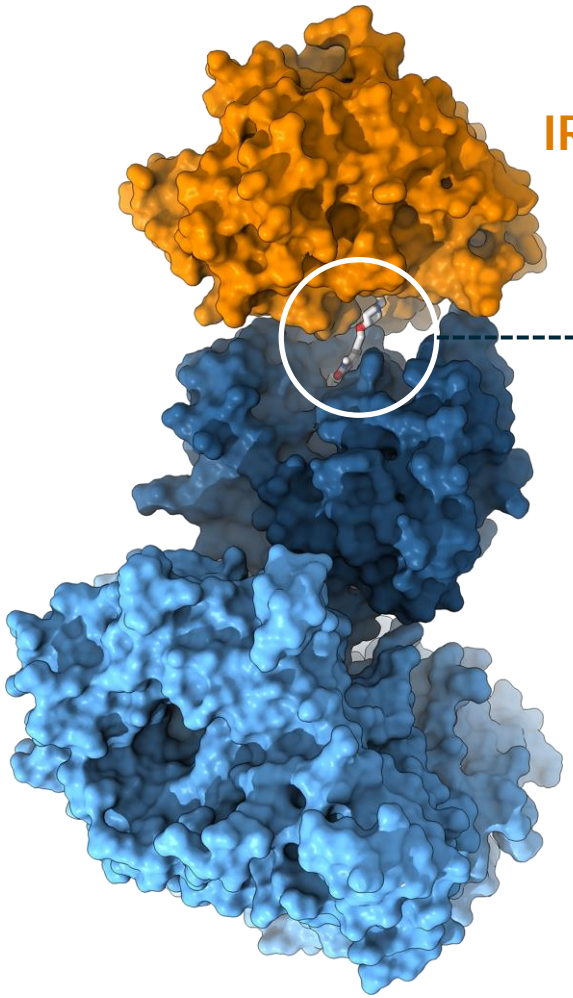


Lesion Size Reduction in MCC Patient



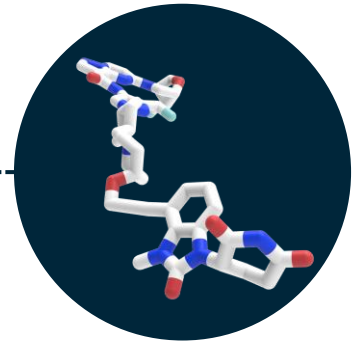
Chemistry and Structural Biology Leadership

Ternary Complex Cryo-EM Structures Enable Design of Highly Specific and Potent Degraders

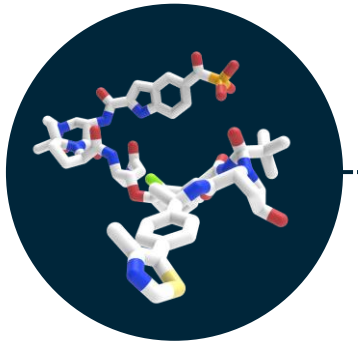


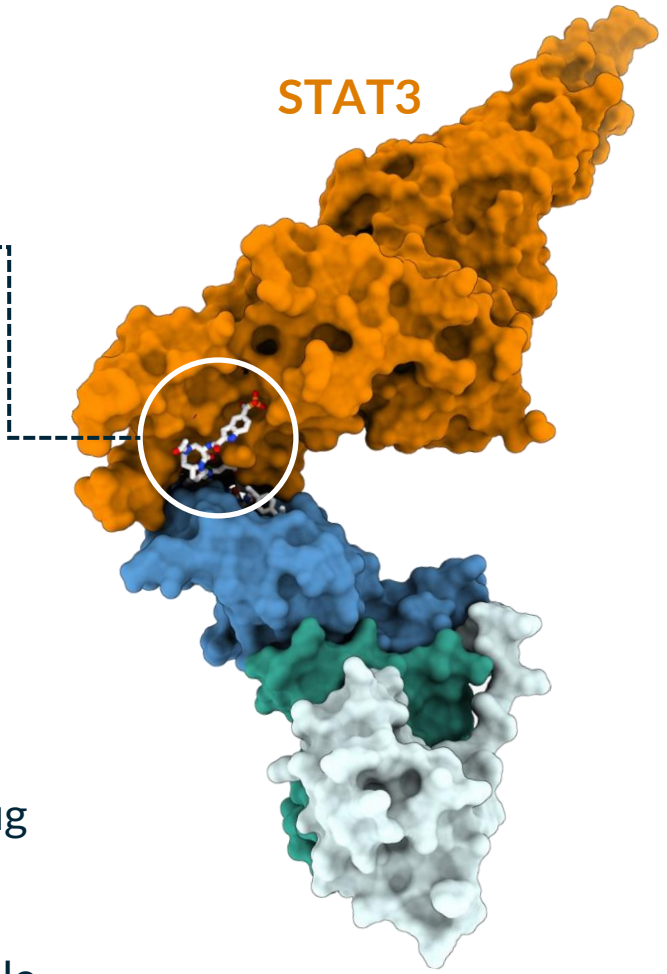
Cereblon-(KT-474)-IRAK4

KT-474



KT-333





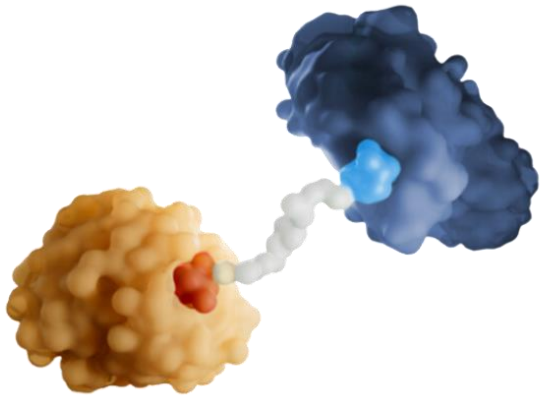
VHL-(KT-333)-STAT3

Command of E3 ligase pairing | **Ternary complex Cryo-EM** | **Advanced accuracy of PK/PD**

Validated molecular design and translational strategies: Ability to fine-tune the potency of drug candidates based on their drug-like properties, relationship with target protein properties, and downstream PK/PD effects, resulting in impeccable translation of our pipeline in the clinic

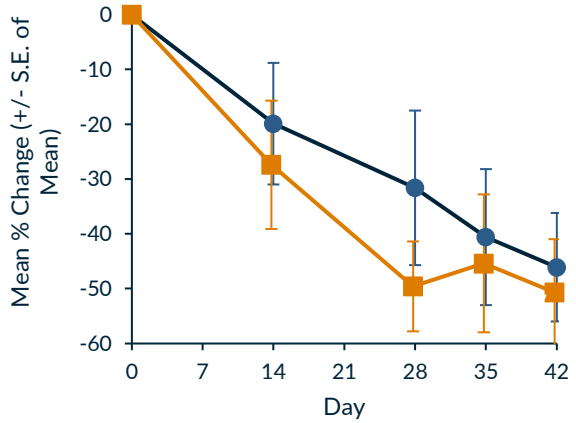
Building a Global Medicines Company

Pioneering a new modality
2016-2020



- Focused on undrugged targets within clinically validated pathways
- Forged multiple strategic partnerships to forward integrate (>$3B total value)
- Developed industry leading capabilities in TPD and novel E3s

Demonstrating early POC
2021-2023



- Advanced four drug candidates into clinic demonstrating clinical activity in oncology and immunology
- Initiated two Phase 2 studies in significant immunology indications with Sanofi
- Demonstrated potential for biological and clinical superiority of degrader vs. SMIs

Delivering a new generation of medicines
2024-2028

- Focus on large clinical/commercial opportunities with oral degraders
- Increase investments in I&I
- Complete multiple POC studies in large indications and launch several registrational studies
- Build towards a fully integrated global biotech

Clear Line of Sight to Substantial Patient Impact and Value Creation

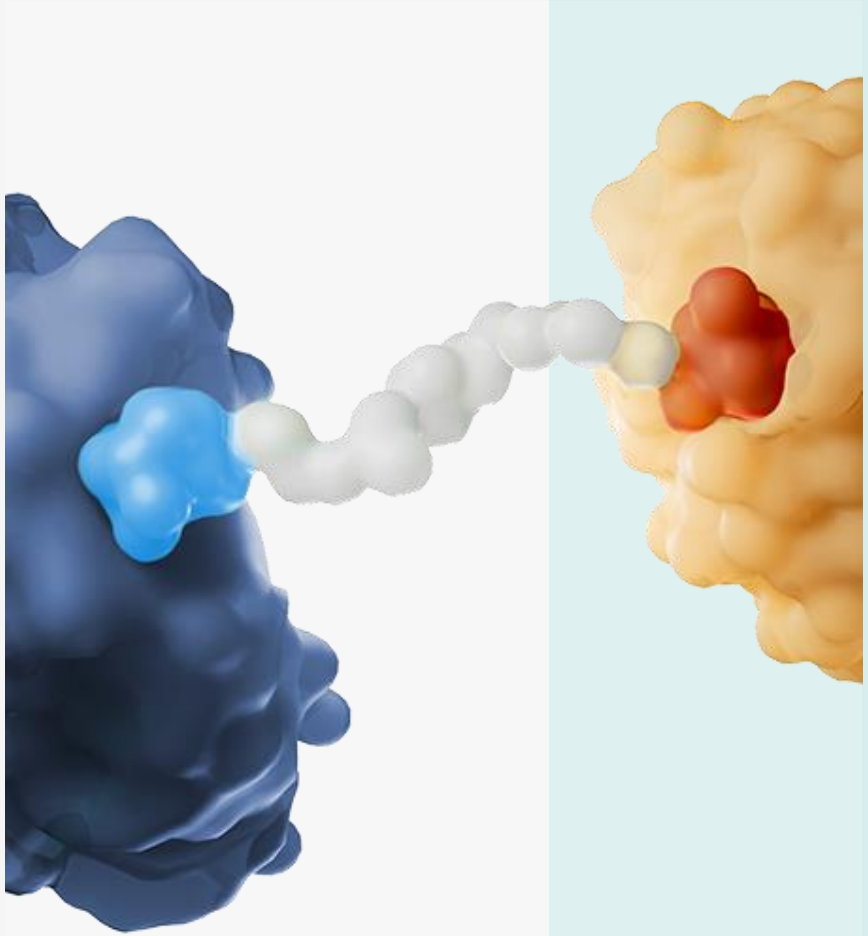
	Potential Indications	IND-enabling	Phase 1	Phase 2	Upcoming Milestones	Rights
Immunology – Oral QD Small Molecule Degraders						
IRAK4[1]	HS, AD, RA, Asthma, IBD, others[2]	KT-474 - HS KT-474 - AD			Phase 2 HS & AD: Expanding to accelerate development[3]	50/50 US sanofi KYMERA
STAT6	AD, Asthma, COPD, PN, CRSwNP, EoE, others	KT-621			Phase 1 Start: 2H24	KYMERA
TYK2	Psoriasis, IBD, PsA, Lupus, others	KT-294			Phase 1 Start: 1H25	KYMERA
Oncology						
STAT3[4]	cHL, PTCL, LGL-L, CTCL, Solid Tumors	KT-333 Arm A: Lymphomas, Solid Tumors Arm B: T-Cell Leukemias			Complete Recruitment & Phase 1 Data: 2H24	KYMERA
MDM2	Liquid & Solid Tumors	KT-253 Arm A: Solid Tumors/Lymphomas Arm B: AML, ALL, MF			Complete Recruitment: 2H24 Followed by Phase 1 Data	KYMERA

[1]KT-474 (SAR444656) partnered with Sanofi, with Kymera option to participate in the development and commercialization, and 50/50 profit split, in the United States. Double digit tiered royalties in ROW.

[2]Current indications: HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities.

[3]Trial designs and timing for the expanded Phase 2 completion dates and data readouts to be updated once Sanofi completes ongoing expansion-enabling activities.

[4]Assessment of STAT3 I/I opportunity is ongoing.



Kymera's Immunology Pipeline

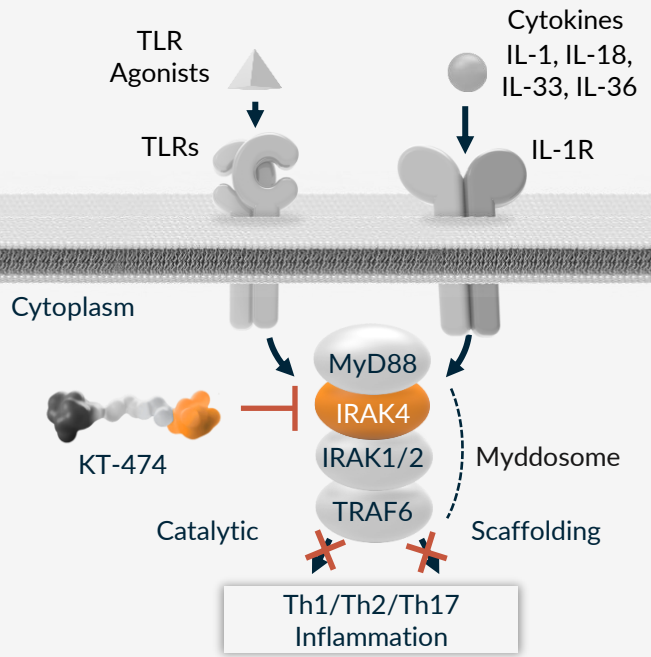
IRAK4, STAT6, TYK2

Kymera Immunology Oral Degrader Portfolio

Complementary, First-in-class Mechanisms

IRAK4
SCAFFOLDING KINASE

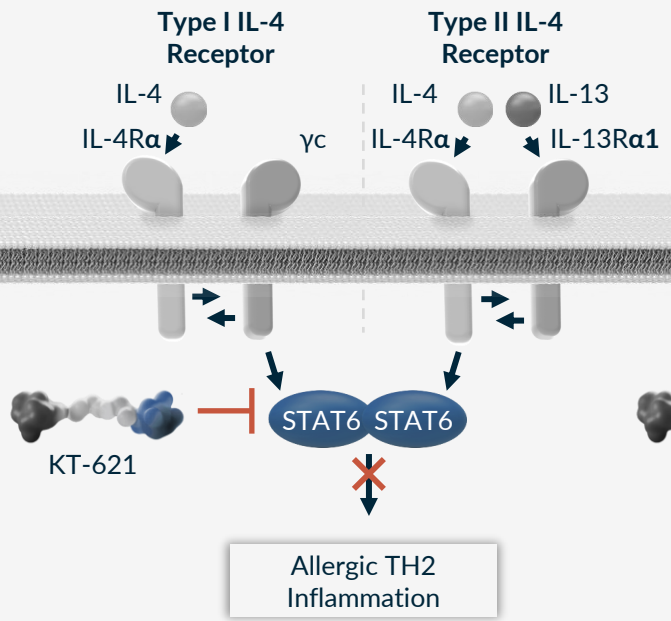
IL-1R/TLR Pathway



IRAK4 is master regulator of **innate immunity** with scaffolding and kinase functions

STAT6
TRANSCRIPTION FACTOR

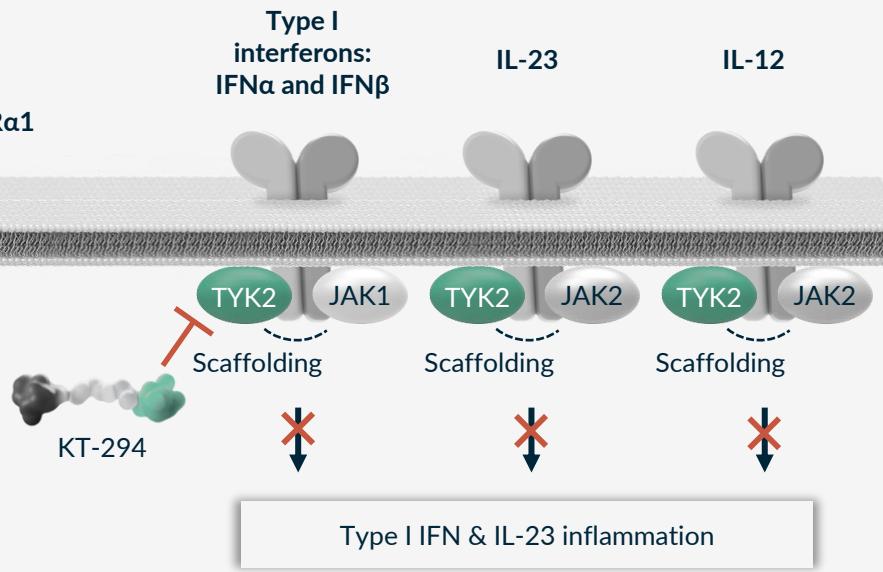
IL-4/13 Pathway



STAT6 is the only specific transcription factor responsible for **IL-4/13 signaling**

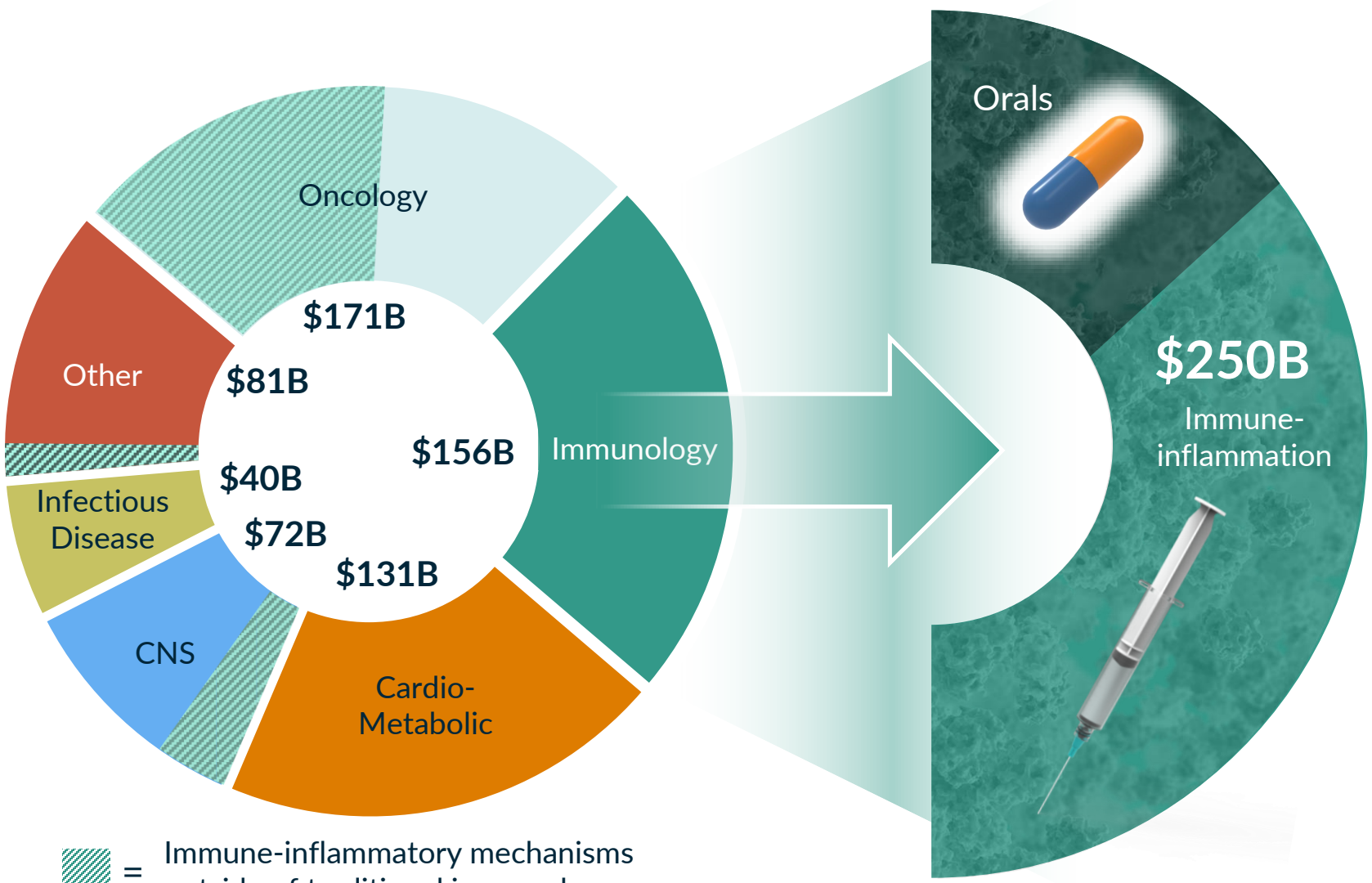
TYK2
SCAFFOLDING KINASE

IL-12/23/IFN Pathways



TYK2 is a JAK family scaffolding kinase required for **Type I IFN, IL-12 and IL-23** cytokine signaling

The Opportunity in Immunology



= Immune-inflammatory mechanisms outside of traditional immunology

Immune-inflammation is a **$250B WW market**[1] spanning multiple therapeutic areas.

Injectables dominate, comprising >75% of the established market.

[1]Revenues from Top 1,000 worldwide brands by revenue; Source: GlobalData; 2022 Non-Covid, Non-Vaccine Rx Market

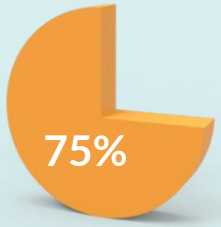
Why Small Molecule Oral Degraders in Immunology

Cosentyx® (secukinumab)

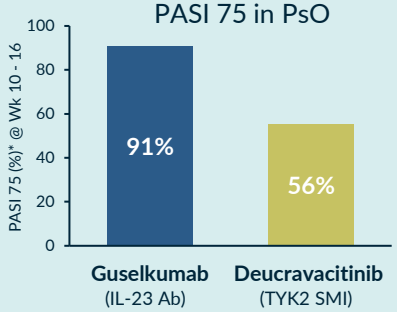
Stelara® (ustekinumab)

DUPIXENT® (dupilumab) Injection

Patients on Biologics that Would Switch to Orals[1]



IL-23 Biologics vs TYK2 SMI[2]
PASI 75 in PsO



Key pathways/cytokines validated as drivers of many diseases in I&I

Biologics blocking these pathways/cytokines have revolutionized treatment

Biologics are injected, can be inconvenient for patients and costly to manufacture

Traditional small molecule inhibitors insufficiently block these pathways, limiting efficacy

Oral Degraders Can Offer Biologic-like Activity in a Pill

Degraders can provide **comparable pathway inhibition to biologics**, convenience of **oral dosing**, **ease of manufacturing** and potentially access **broader populations**

[1]J&J Business Review Dec '23 (survey of N=395 patients with moderate-to-severe psoriasis); [2]Tremfya (IL-23 biologic) package insert, Sotyktu (TYK2 SMI) package insert

Revolutionizing Immunology with Small Molecule Oral Degraders

	IRAK4 (KT-474) SCAFFOLDING KINASE	STAT6 (KT-621) TRANSCRIPTION FACTOR	TYK2 (KT-294) SCAFFOLDING KINASE
Status	• Phase 2 Trials in HS and AD with Sanofi	• IND-Enabling	• IND-Enabling
Potential Indications	• HS, AD, RA, Asthma, COPD, IBD, others[1]	• AD, Asthma, COPD, PN, CRSwNP, EoE, others	• PsO, IBD, PsA, Lupus, others
Next Milestone	• Expanding Phase 2 studies to accelerate development[2]	• FIH: 2H 2024	• FIH: 1H 2025
Opportunity	• First-in-class broad anti-inflammatory oral degrader	• Dupilumab-like activity in a pill	• Biologic-like activity in a pill
Commercial Rights	• Up to 50% US with Sanofi, tiered royalties in ROW[3]	• Wholly owned	• Wholly owned

[1]Current indications; HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities;
[2]Trial designs and timing for the expanded Phase 2 completion dates and data readouts to be updated once Sanofi completes ongoing expansion-enabling activities;
[3]KT-474 (SAR444656) partnered with Sanofi, with Kymera option to participate in the development and commercialization, and 50/50 profit split, in the United States. Double digit tiered royalties in ROW.

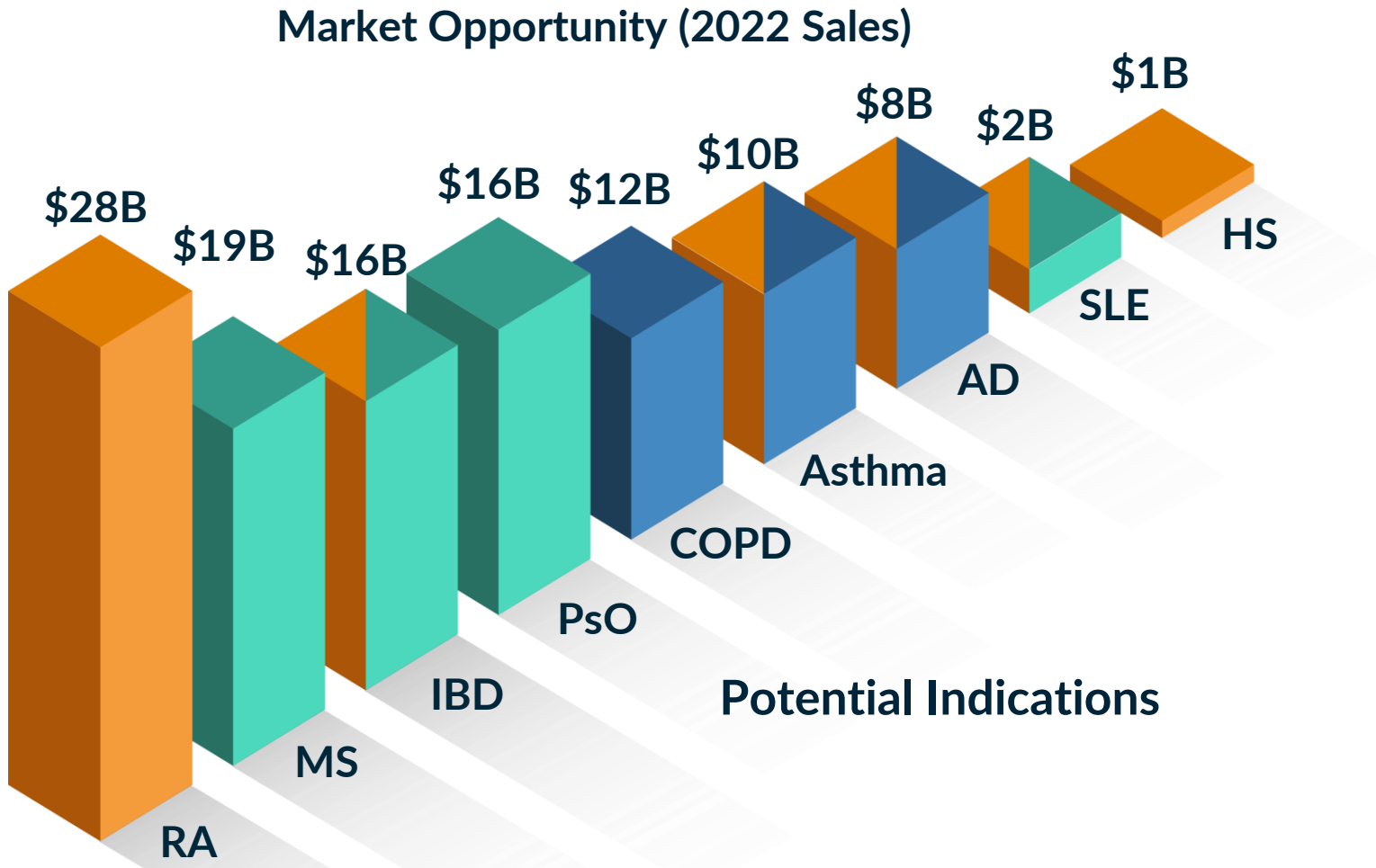
Kymera Immunology Oral Degrader Portfolio

Complementary Mechanisms Each with Mega-blockbuster Potential

IRAK4[1]: **IL-1R/TLR pathway**
Th1/17/Th2 biology

STAT6: **IL-4/13 pathway**
Th2 biology

TYK2: **IL-23/IFN pathway**



GlobalData, focused only on large markets based on 2022 sales of approved drugs

[1]Current indications; HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities

First-in-Class Oral IRAK4 Degrader Program

IRAK4 Biology and Target Rationale

Target Rationale

- IRAK4 is an obligate node in IL-1R/TLR signaling, and its degradation is the only approach to fully block the pathway

Human Genetics

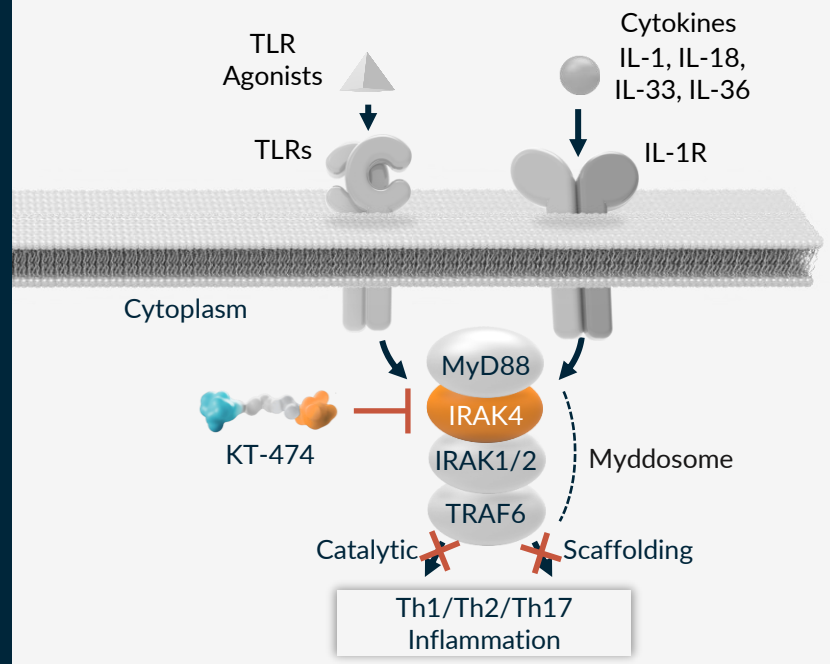
- Adult humans with IRAK4 null mutation are healthy

Clinical Pathway Validation

- IRAK4 degradation has the potential to achieve a broad, well-tolerated anti-inflammatory effect
- Multiple development opportunities in immune-inflammatory diseases which signal through MyD88/IRAK4 have been validated[1]:
  - IL-1α/IL-1β : RA, CAPS, HS, AD, Gout
  - IL-18: AD, Macrophage Activation Syndrome
  - IL-36: Generalized Pustular Psoriasis, AD
  - IL-33: Asthma
  - IRAK4 SMI: RA

IRAK4
SCAFFOLDING KINASE

IL-1R/TLR Pathway

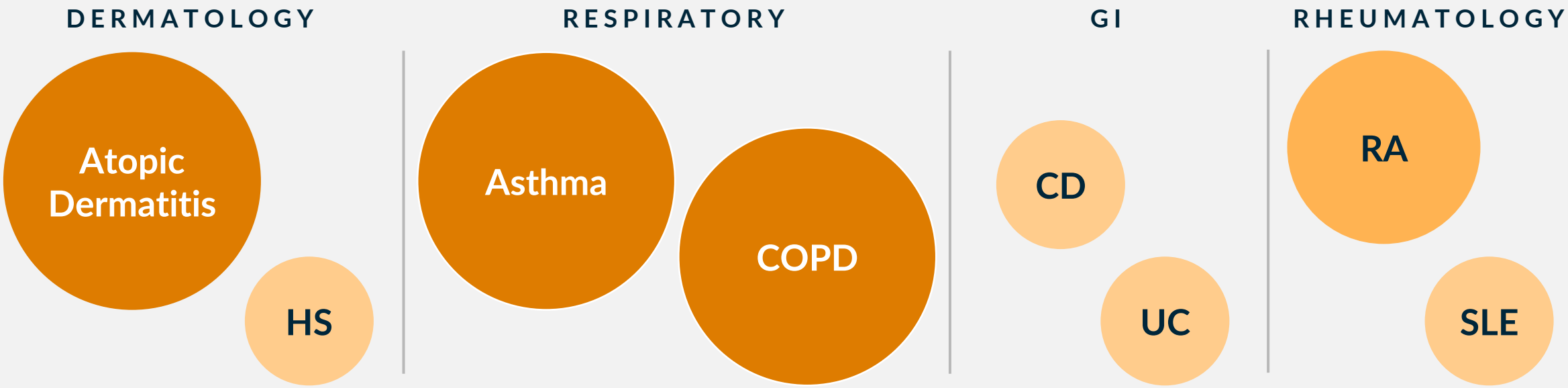


IRAK4 is master regulator of **innate immunity** with scaffolding and kinase functions

Adapted from West NT. Front Immunol 2019

[1]Current indications; HS and AD. Other diseases shown, where IL-1R/TLR pathway has been implicated in pathogenesis, are additional potential opportunities

IL-1R/TLR Pathway Potential Impact Across Multiple Immune-Inflammatory Diseases

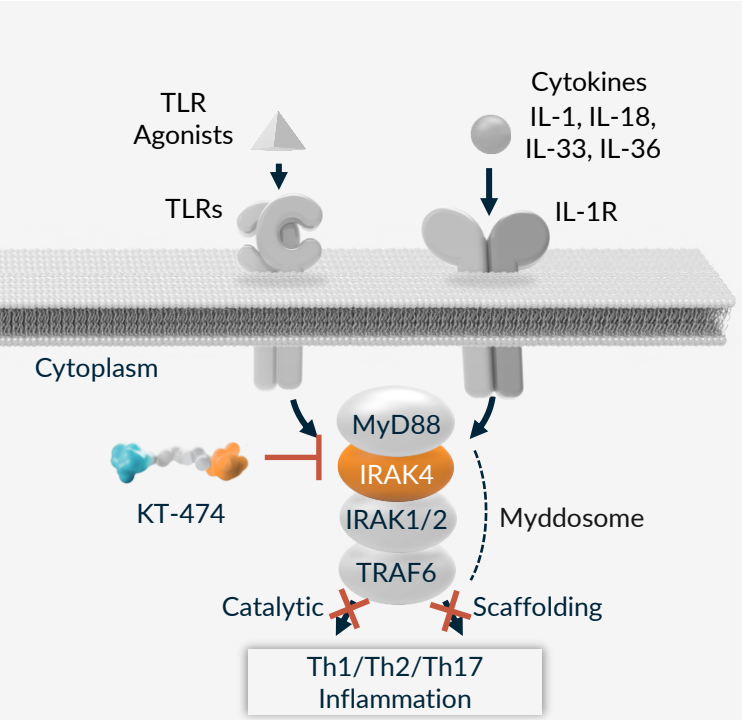


Total Potential Patient Impact[1]: **>150M patients**

- Numerous indication opportunities across multiple therapeutic areas validated by sub-optimal pathway inhibitors
- IRAK4 degradation leading to full pathway inhibition has the potential to deliver superior profile to upstream biologics
- Oral degrader medicines offer opportunity to reach broader patient populations

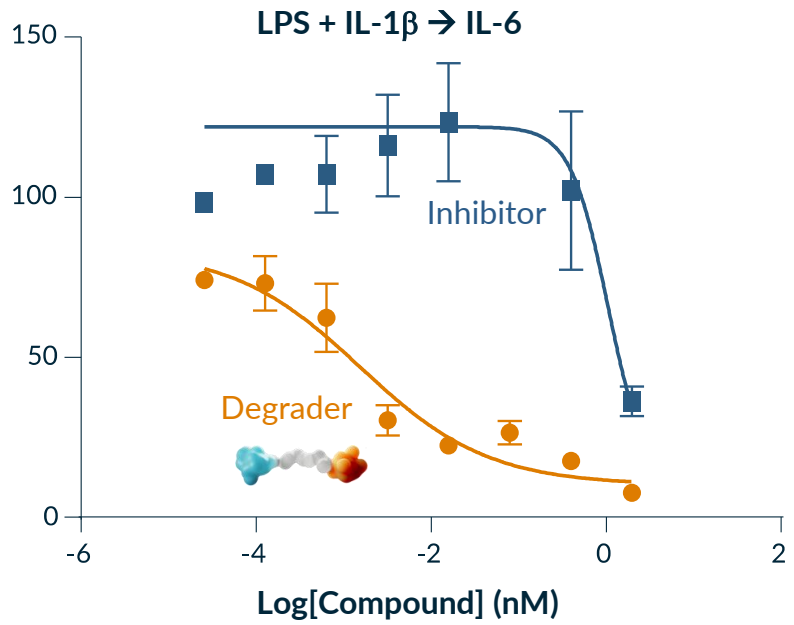
[1]GlobalData (2022 diagnosed prevalent patient population for US/EU5/JP)

IRAK4 Degrader Advantage



IRAK4 caps the oligomer size of MYD88 to trigger myddosome formation

Only Degrader Can Fully Block Inflammation



Preclinical Data *(Kymera IRAK4 Backgrounder)*

- IRAK4 KO is able to block TLR activation unlike the kinase dead rescue
- IRAK4 **scaffolding function** is critical in Myddosome formation and pathway signaling
- IRAK4 degradation, but not kinase inhibition, can **block TLR induced NF-κB translocation** and **IL1R+TLR activation**
- IRAK4 degradation is superior to kinase inhibition at **blocking downstream phosphoproteome**
- IRAK4 degradation is superior to inhibition in a **variety of preclinical efficacy models**

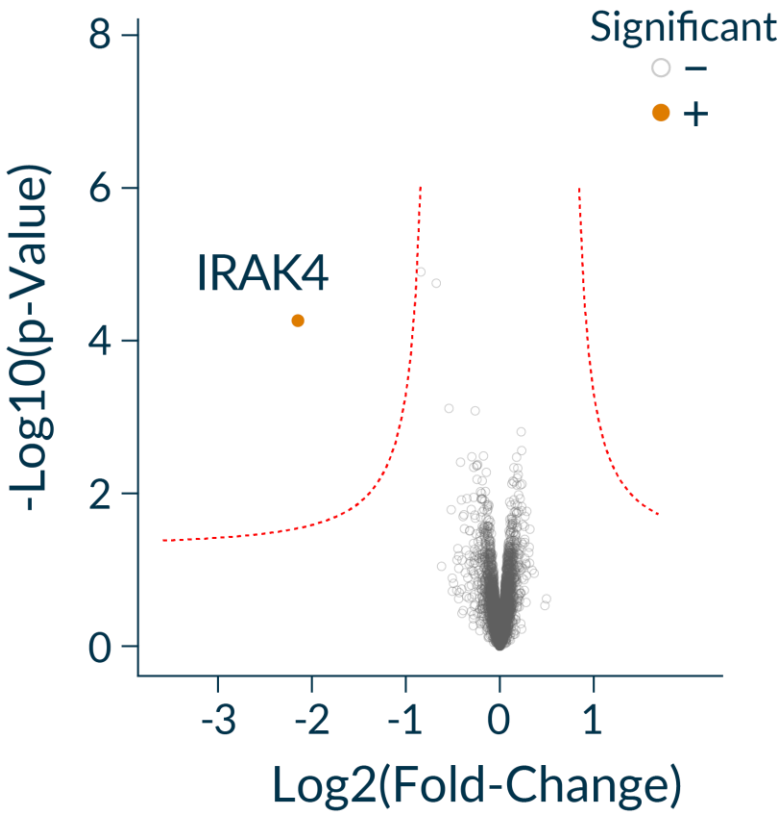
Clinical Data *(Nature Medicine*)*

- IRAK4 degradation **reduces signs and symptoms of HS and AD**, while IRAK4 SMI inactive in Phase 2 HS trial
- IRAK4 blocks inflammation in blood and skin of HS and AD patients

*Ackerman, et al., *Nature Medicine* (2023).

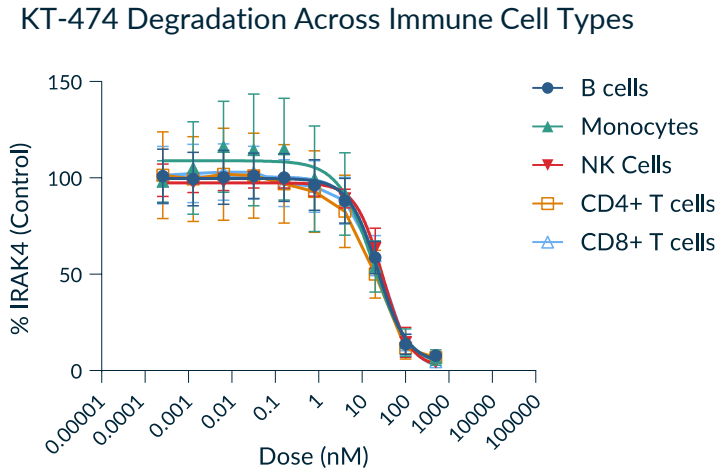
KT-474: Selective and Potent IRAK4 Degrader Active in Multiple Cell Types

Selectivity in PBMC



- KT-474 selectively degrades IRAK4 in human immune cells at concentration 10-fold above the DC_{90}
- Potent degradation in PBMC subsets and skin cells including fibroblasts, with single-digit nM DC_{50}
- Associated with functional inhibition of TLR- and IL-1β-stimulated cytokine production
- Comprehensive understanding of degradation kinetics across cell types to enable human translation

Potency in Blood and Skin Cells



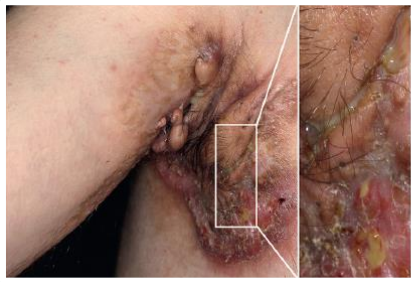
Cell type (Human)	Source	KT-474 DC_{50} (nM)
Monocytes	Blood	2.6
B cells	Blood	2.7
CD4 T cells	Blood	1.5
CD8 T cells	Blood	1.5
NK cells	Blood	1.8
Fibroblasts	Skin	1.5
Keratinocytes	Skin	7.8

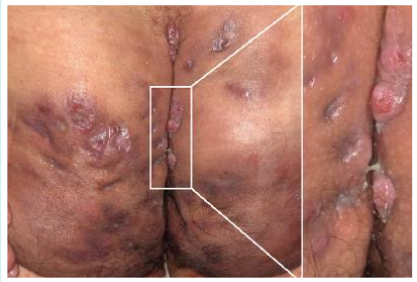
Initial Clinical Focus for KT-474: Moderate to Severe HS and AD

Hidradenitis Suppurativa (HS)

Chronic and debilitating skin disease with painful nodules, abscesses and draining fistulae/tunnels

Major QoL impact: Pain, itching, depression, social isolation





Many diagnosed in their 20s/30s; more common in females (~3:1); prevalence estimated to be up to 1-3% of population in US and EU

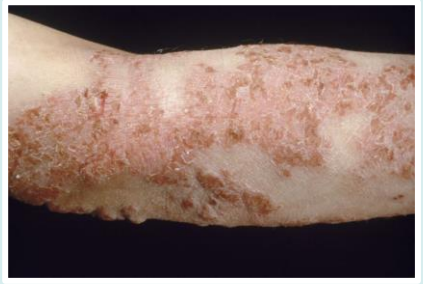
Lesions characterized by pleotropic inflammation with Th1/Th17 skewing; bacterial infection and tissue destruction leading to TLR activation; IL-1 and IL-36 production

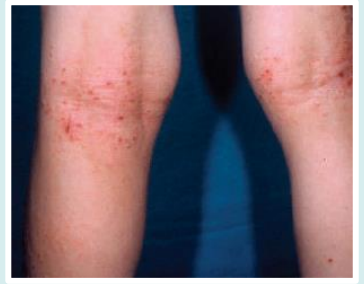
Active agents approved or in development target TNF-α, IL-17 and JAK/STAT pathways

Atopic Dermatitis (AD)

Chronic inflammatory skin disease with scaly, dry, erythematous lesions; intense itching/scratching, predisposition to infections

Major QoL impact: Itching, pain, sleep disturbance





Onset usually in early childhood; affects an estimated 98 million adults in US/EU5/JP[1]

Lesions characterized by pleotropic inflammation with Th2 skewing; bacterial infection and skin barrier breakdown leading to TLR activation; IL-33 and IL-1 production

Active agents approved or in development target IL-4/IL-13, JAK/STAT and OX40/OX40-L pathways

KT-474 Opportunity: Potential for broad anti-inflammatory effect, competitive efficacy vs. pathway biologics and convenience of once-daily oral dosing

[1]GlobalData – undiagnosed, all-age prevalence

KT-474 Phase 1: Compelling Data and Early POC in HS and AD

Healthy Volunteers (HV): SAD and MAD

- Evaluated safety, tolerability and pharmacokinetics in 105 healthy volunteers
  - SAD: Oral doses of 25-1600 mg
  - MAD: Escalating doses up to 200 mg were administered for 14 consecutive days
- Robust (>95%) and sustained IRAK4 degradation with single and multiple daily doses
- Broad inhibition of *ex vivo* TLR-mediated cytokine induction
- Generally well-tolerated across all dose groups

HS and AD Patient Cohort

- Open label study in 21 patients with HS and AD
- Dose: 75 mg QD with food (equivalent exposure to 100 mg fasted), administered for 28 consecutive days
- Safety, PK and PD comparable to healthy volunteers
- Robust IRAK4 degradation in blood and skin with associated systemic anti-inflammatory effect in HS and AD patients
- Promising clinical activity observed in HS and AD


nature medicine

Article https://doi.org/10.1038/s41591-023-02635-7

IRAK4 degrader in hidradenitis suppurativa and atopic dermatitis: a phase 1 trial

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Check for updates

Lindsay Ackerman[1], Gerard Acloque[2], Sandro Bacchelli[3], Howard Schwartz[4], Brian J. Feinstein[5], Phillip La Stella[6], Afsaneh Alavi[7], Ashwin Gollerkeri[8], Jeffrey Davis[8], Veronica Campbell[8], Alice McDonald[8], Sagar Agarwal[8], Rahul Karnik[8], Kelvin Shi[8], Aimee Mishkin[8], Jennifer Culbertson[8], Christine Klaus[8], Bradley Enerson[8], Virginia Massa[8], Eric Kuhn[8], Kirti Sharma[8], Erin Keaney[8], Randy Barnes[8], Dapeng Chen[8], Xiaozhang Zheng[8], Haojing Rong[8], Vijay Sabesan[8], Chris Ho[8], Nello Mainolfi[8], Anthony Slavin[8] & Jared A. Gollob[8]


News & views

Targeted therapy https://doi.org/10.1038/s41591-023-02622-y

PROTACs reach clinical development in inflammatory skin disease

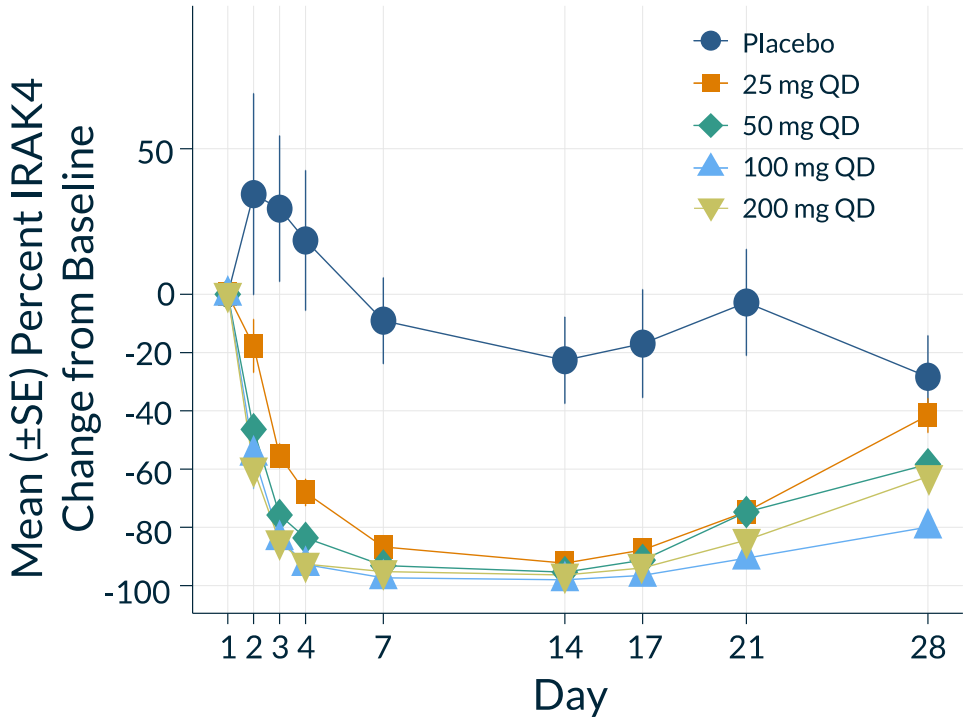
Fleur M. Ferguson

Check for updates

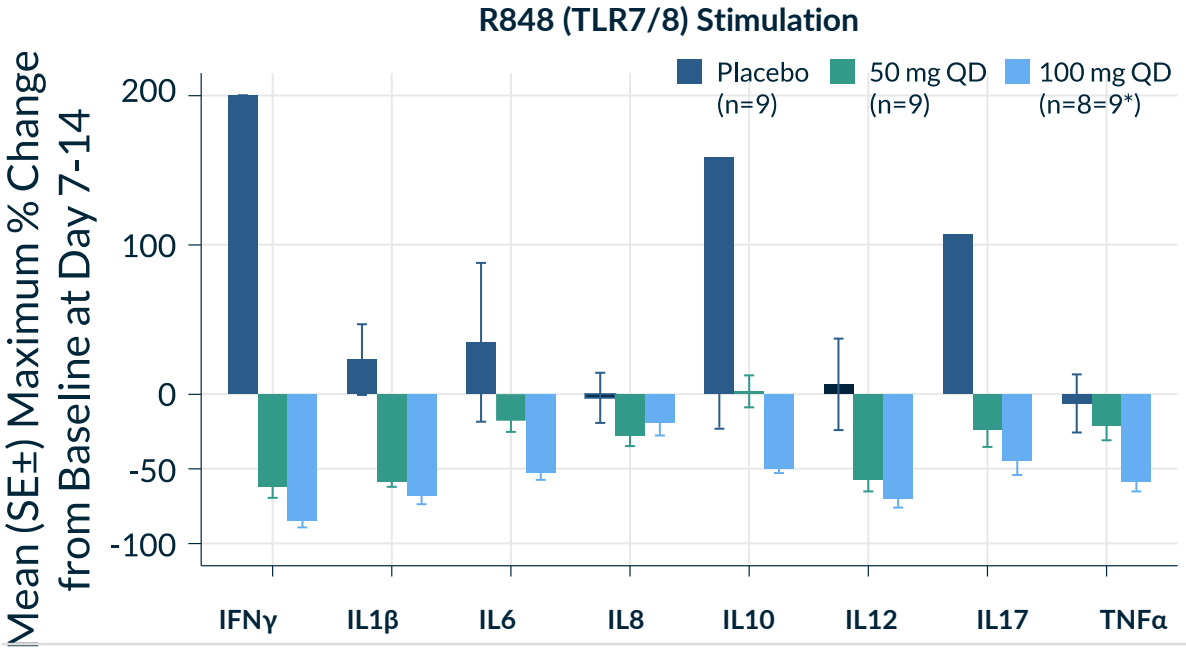
A phase 1 trial of an IRAK4-targeted protein degrader in patients with chronic inflammatory skin diseases hits an important milestone for the safe application of this drug class beyond oncology.

Near-Complete Degradation and Broad Cytokine Impact in Healthy Volunteers

Mean % Reduction of IRAK4
(Daily oral doses for 14 days)



Ex Vivo Inhibition of 9 Disease-Relevant Cytokines, Day 7-14

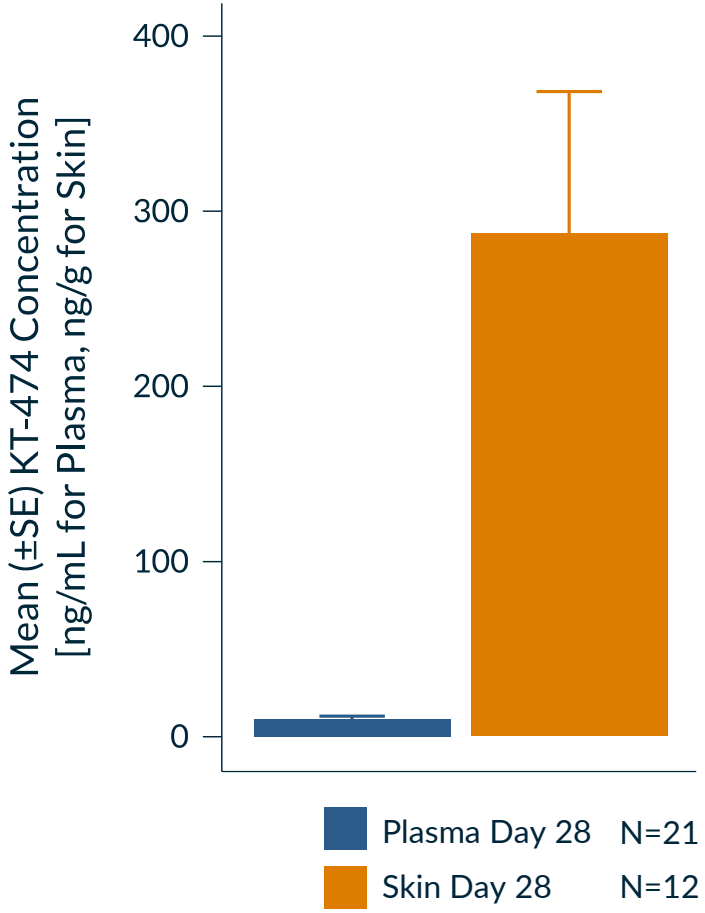


	IFNγ	IL1β	IL6	IL8	IL10	IL12	IL17	TNFα
Pbo	>500%	15%	35%	-5%	-23%	3%	107%	-7%
50 mg QD	-62%	-59%	-18%	-28%	2%	-58%	-24%	-21%
100 mg QD	-85%	-68%	-53%	-32%	-50%	-72%	-46%	-59%

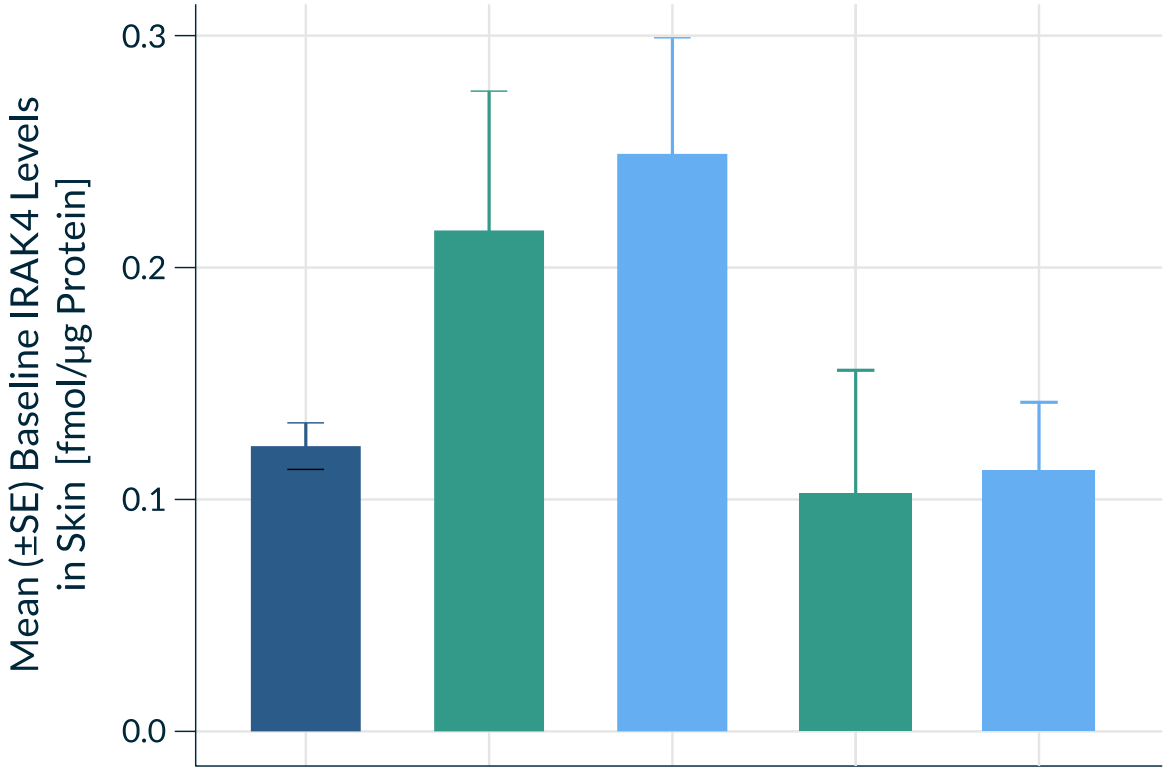
- High fidelity of PKPD translation from preclinical species to humans.
- Human efficacious concentrations (C_{trough} 3 ng/mL) and doses (50-200 mg) were correctly predicted

High Skin Exposure and Degradation in Skin of HS and AD Patients

High KT-474 Exposure in HS and AD Patients Skin



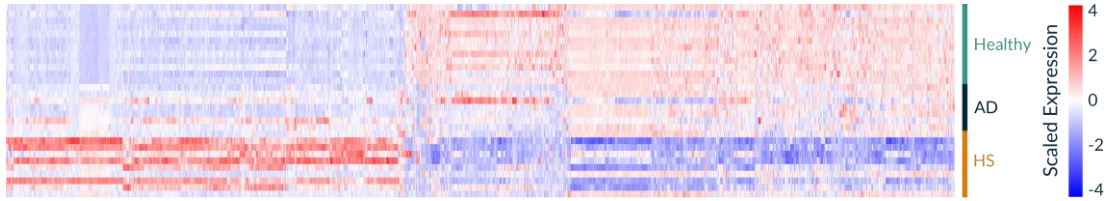
Reduced IRAK4 in Skin Lesions of AD and HS Patients

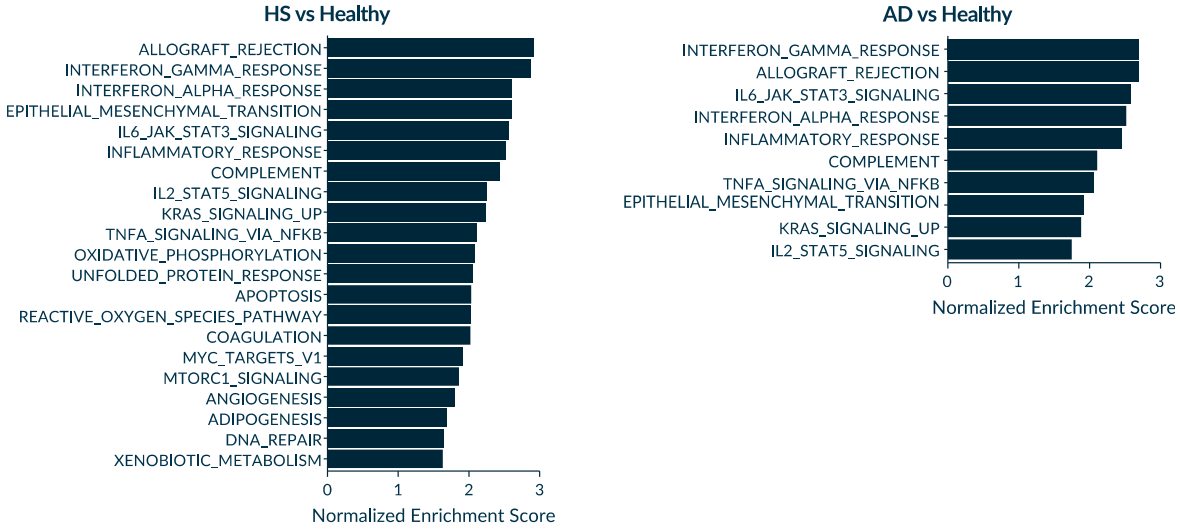


	MAD Healthy Subjects **(Baseline)**	AD Patients **(Baseline)**	HS Patients **(Baseline)**	AD Patients **(Day 28)**	HS Patients **(Day 28)**
N	46	7	11	6	9
Mean	0.12	0.22	0.24	0.1	0.11

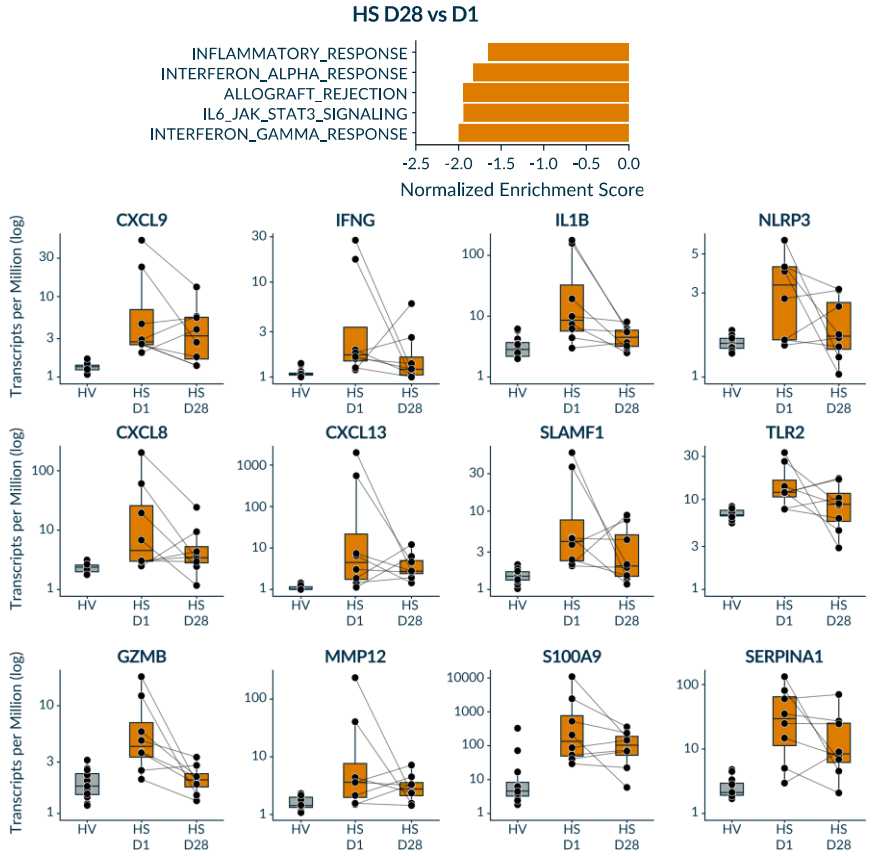
Upregulation of Multiple Inflammatory Pathways in HS and AD Skin Lesions and Impact of KT-474 Treatment

Upregulation of Inflammatory Genes/Pathways in HS and AD





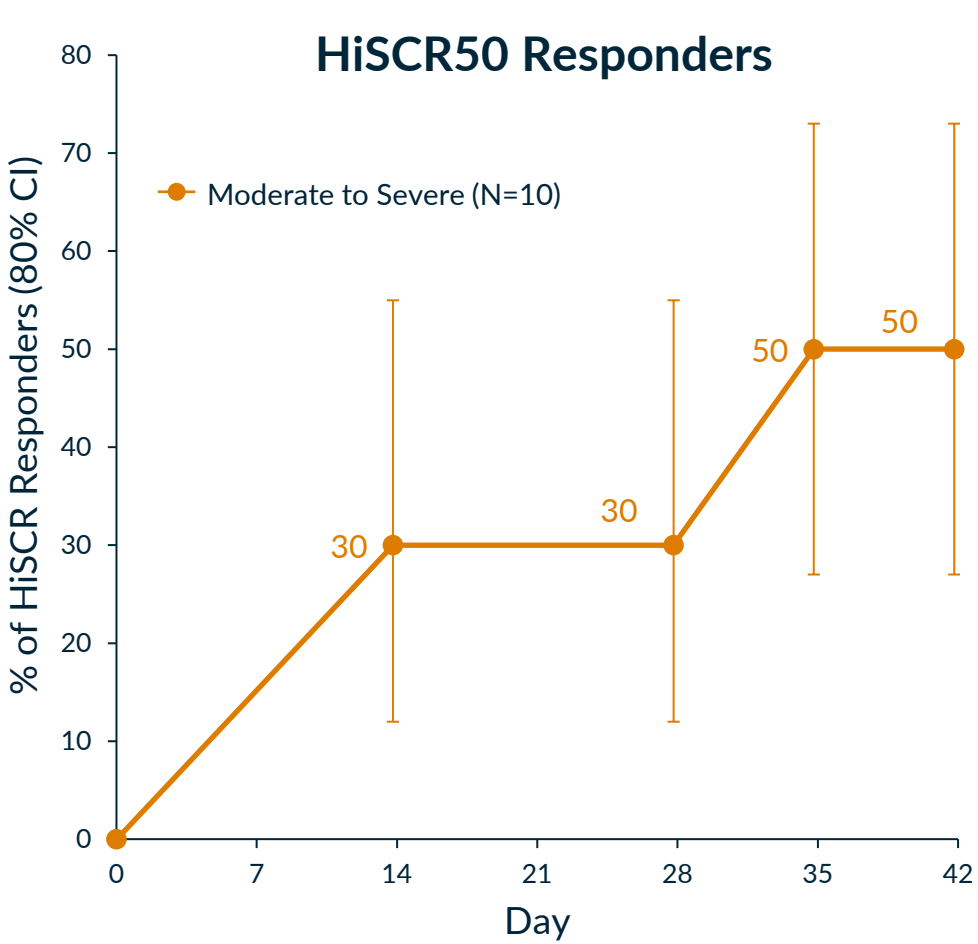
Anti-inflammatory Effect of KT-474 Treatment in HS

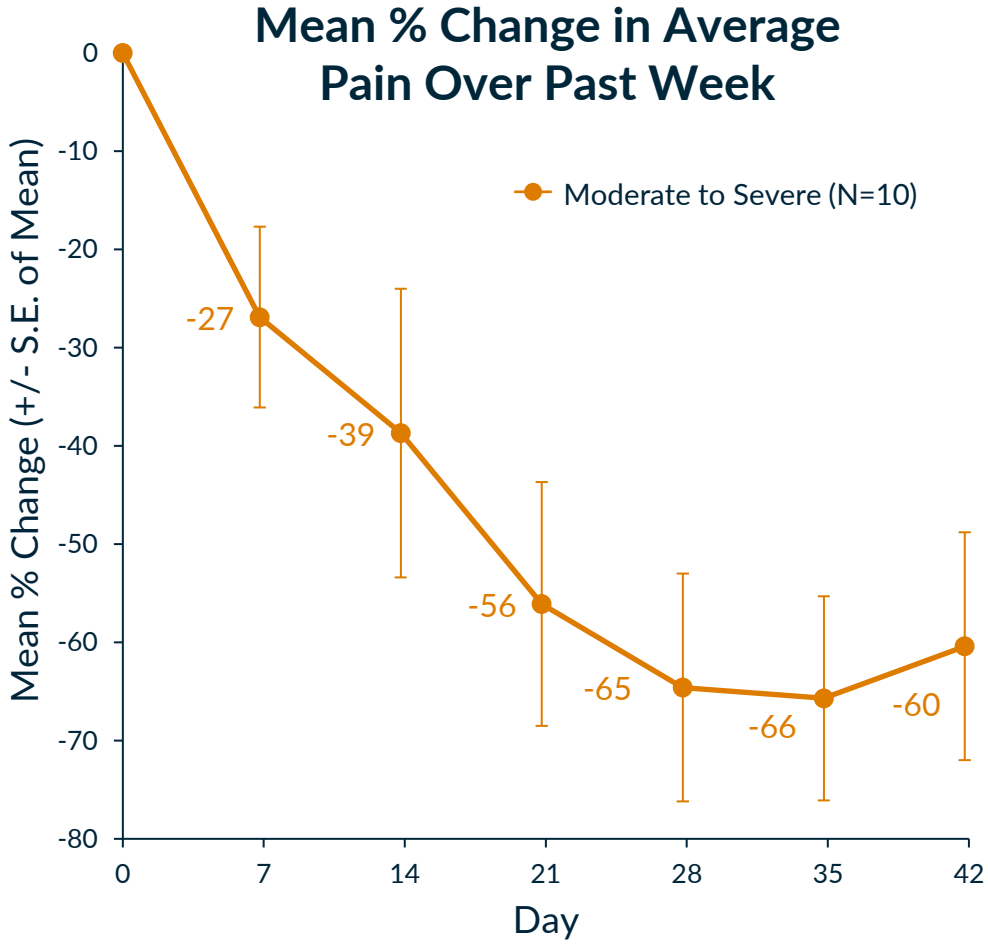


- Upregulation of pro-inflammatory genes and pathways in HS and AD skin lesions relative to healthy subjects
- Inflammatory burden greater in HS compared to AD, facilitating detection of downregulation following KT-474 treatment
- Multiple Th1 and innate immunity genes linked to IRAK4-controlled IL-1R and TLR pathways downregulated in HS

Ackerman, et al., *Nature Medicine* (2023)

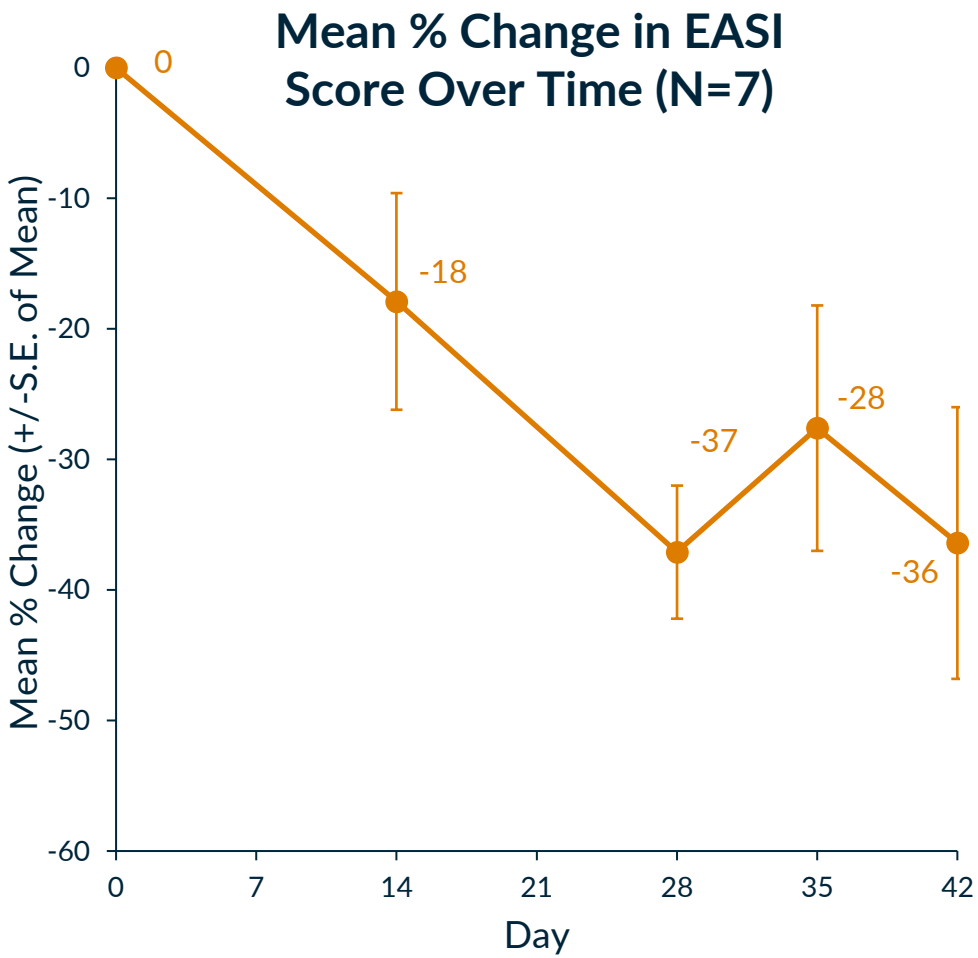
Robust Clinical Impact in HS After Only 28 Days of Dosing

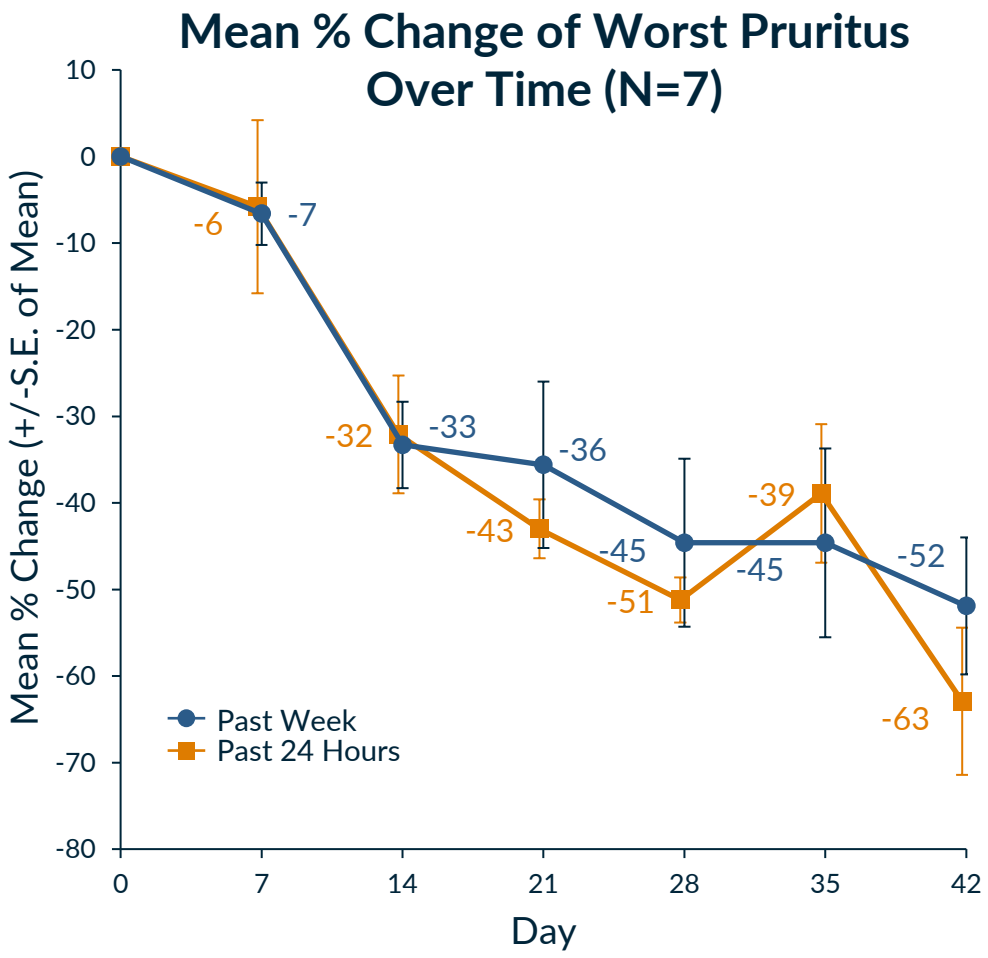




HiSCR50 response rate of up to 50% and pain reduction of up to 66% in moderate to severe HS patients

Robust Clinical Impact in AD After Only 28 Days of Dosing





EASI score reduction of up to 36% and pruritus reduction of up to 63% in moderate to severe AD patients

KT-474/SAR444656: Positioned for Clinical Success

Phase 2 HS Trial[1] (ZEN)

- Double-blind, placebo-controlled
- Up to 99 patients, dosed for 16 weeks
- 1 KT-474 dose arm, 1 placebo arm
- Primary endpoint: % Change in AN Count
- Additional endpoints (select):
  - HiSCR50, IHS4, HS-Skin Pain-NRS30

Phase 2 AD Trial[1] (ADVANTA)

- Double-blind, placebo-controlled
- Up to 115 patients, dosed for 16 weeks
- 2 KT-474 dose arms, 1 placebo arm
- Primary endpoint: % Change in EASI
- Additional endpoints (select):
  - EASI 50/75/90, vIGA-AD, PP-NRS

Sanofi, following a safety/efficacy IA, expanding ongoing Phase 2 program to more rapidly progress toward pivotal trials

Additional information on the Phase 2 studies can be found at www.clinicaltrials.gov; identifier NCT06028230 (HS) and NCT06058156 (AD); Study Sponsor: Sanofi
[1]Trial designs and timing for the expanded Phase 2 completion dates and data readouts to be updated once Sanofi completes ongoing expansion-enabling activities.

Oral IRAK4 Degrader: KT-474

A best-in-pathway broad oral anti-inflammatory agent for multiple inflammatory diseases

Validated Biology

Mediates signaling through IL-1 and toll-like receptors

Upstream cytokine blockers with proven clinical activity across many diseases

Scaffolding kinase at the interface of innate and adaptive immune responses with a variety of functions

Competitive Profile

Potential for Broad Activity Across Th1-Th17 and Th2 Diseases

>$50B in combined global drug sales[1] opportunity

Large potential for oral degraders with best in pathway efficacy

KT-474 Progress

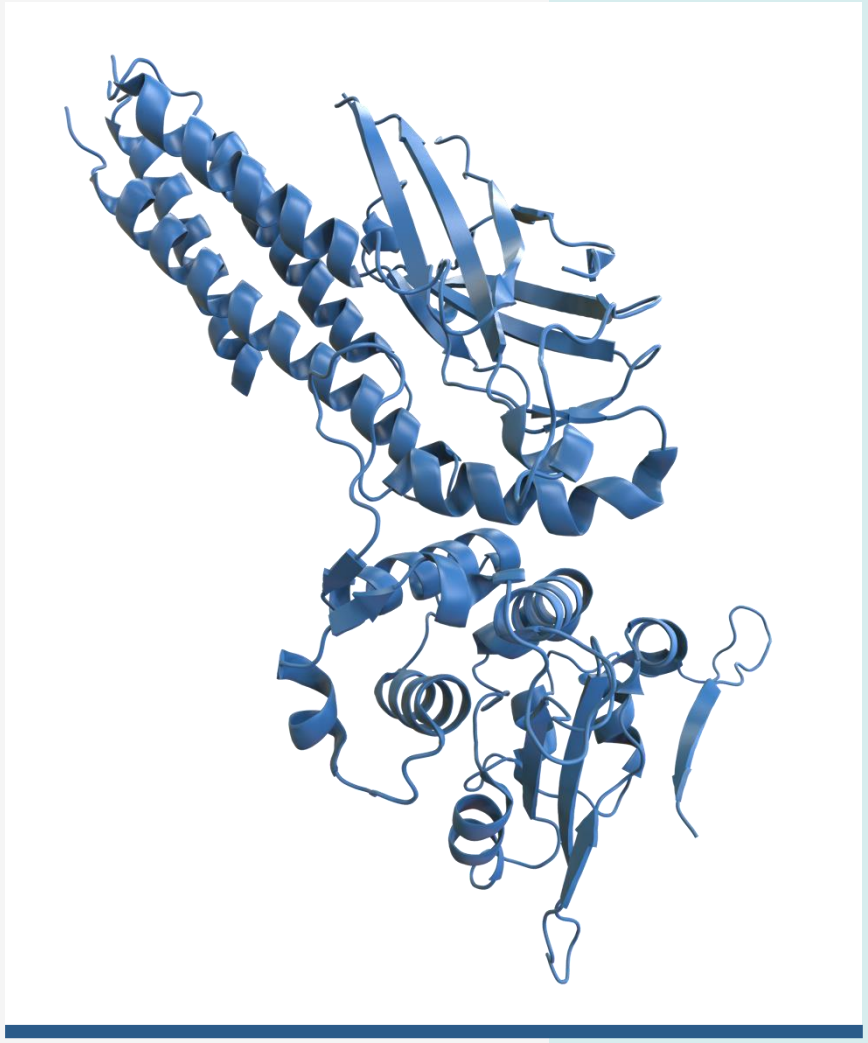
Phase 1 complete:

- Robust IRAK4 degradation
- Favorable safety profile
- Systemic suppression of proinflammatory cytokines and chemokines
- Early signs of strong clinical activity

Partner Sanofi, after safety/efficacy IA, intends to expand the ongoing Phase 2 trials in HS and AD to accelerate timelines and inform future pivotal trials[2]

Activity and fidelity of translation of TPD platform in KT-474 Phase 1 trial informs probability of success with STAT6 and TYK2 immunology programs

[1]GlobalData (2022 sales for AD, HS, Asthma, COPD, UC, CD, RA, SLE);
[2]Trial designs and timing for the expanded Phase 2 completion dates and data readouts to be updated once Sanofi completes ongoing expansion-enabling activities.



First-in-Class Oral STAT6 Degrader Program

STAT6 Biology and Target Rationale

Target Biology and rationale

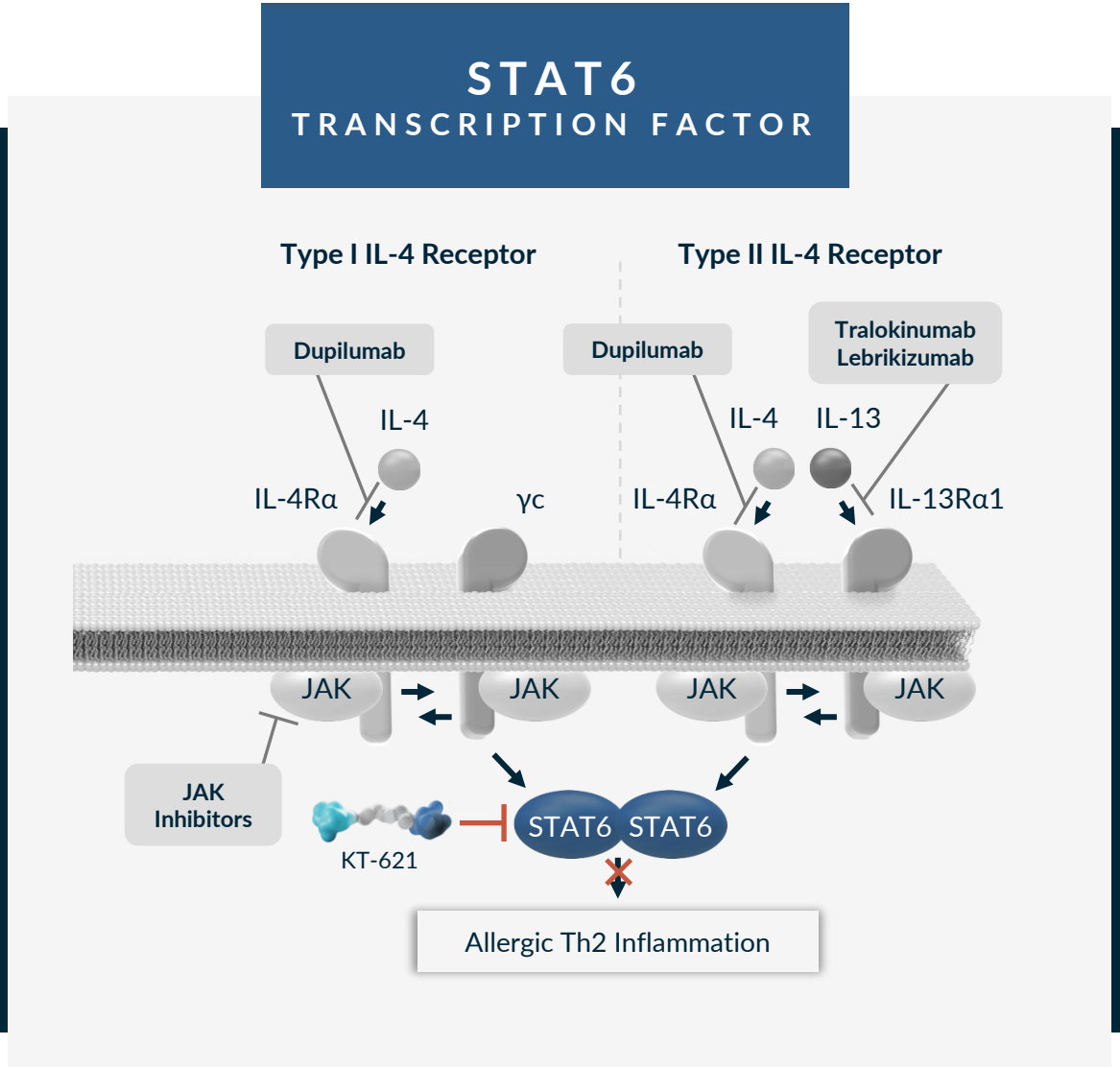
- STAT6 is the specific transcription factor required for IL-4 and IL-13 cytokine signaling
- STAT6 regulated cytokines are clinically validated targets for allergic diseases

Human and Mouse Genetics

- Gain of function (GOF) mutations of STAT6 cause severe allergic diseases in human
- STAT6 KO mice develop normally, are viable and fertile

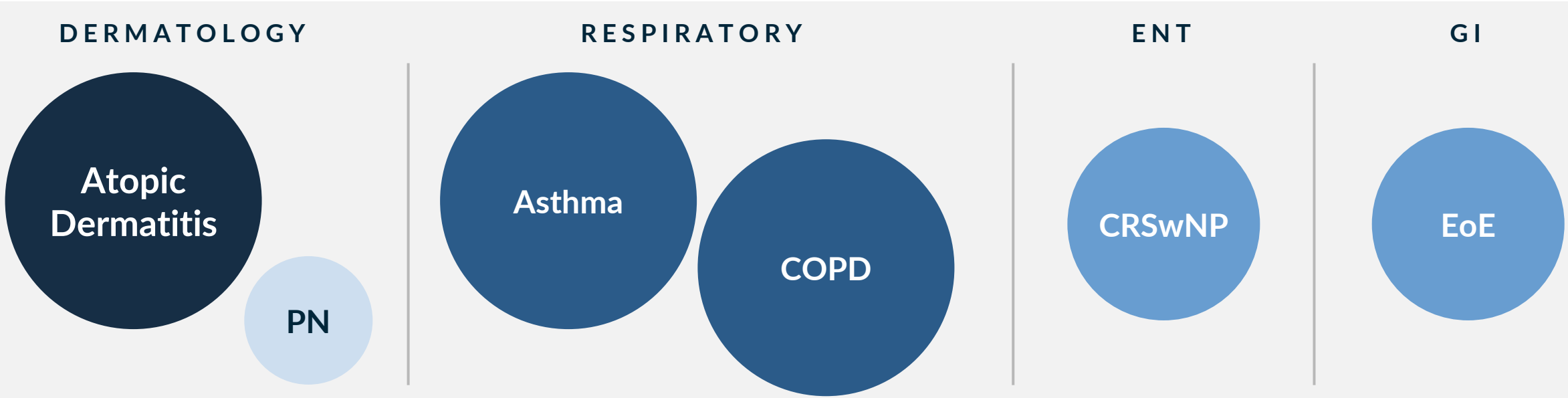
Clinical Pathway Validation

- Dupilumab, an IL-4Rα monoclonal Ab that blocks IL-4/IL-13 signaling, has been approved in: Atopic dermatitis, Asthma, CRSwNP, Eosinophilic Esophagitis, Prurigo Nodularis, has positive Phase 3 data in COPD and is in development for multiple additional indications
- STAT6 degradation can fully block IL-4/IL-13 signaling*



Adapted from Junttila. Front Immunol. 2018; Sharma et al. J Exp Med. 2023; Suratannon et al. J Allergy Clin. Immunol. 2022; Takeuchi et al. J Allergy Clin Immunol. 2022
*Statements regarding STAT6 degrader biology throughout this presentation are based upon preclinical experiments in human cells and preclinical species conducted by Kymera

Oral STAT6 Degraders Can Transform Treatment Paradigm in Multiple Indications De-risked by Dupilumab

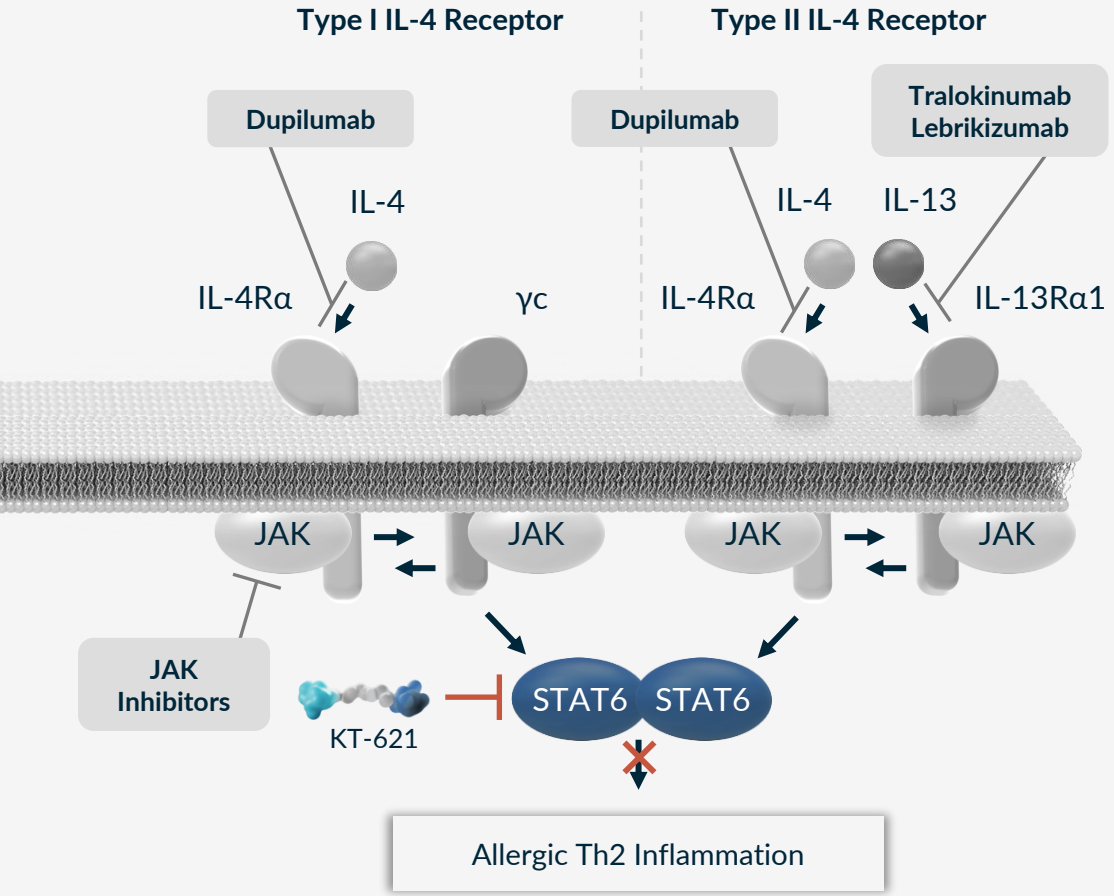


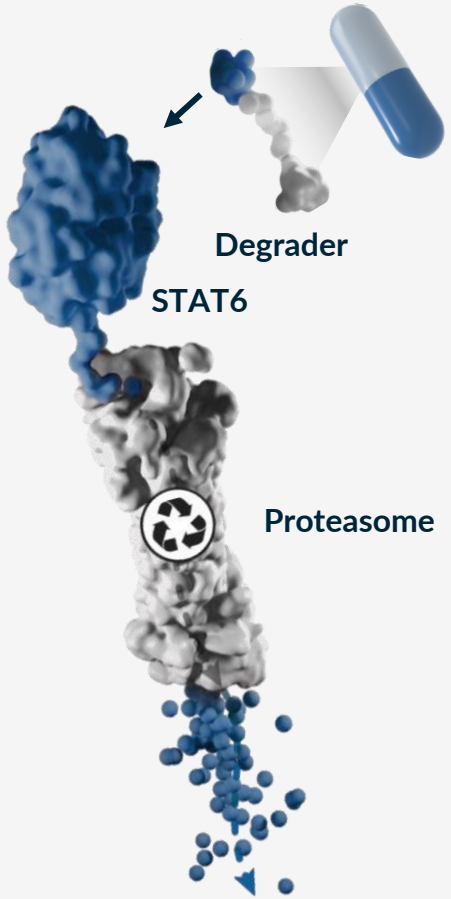
Total Potential Patient Impact[1]: >150M patients

- Numerous indication opportunities across multiple therapeutic areas de-risked by dupilumab
- STAT6 degradation leading to full pathway inhibition has the potential to deliver dupilumab-like activity
- Oral degrader medicines offer opportunity to reach broader patient populations

[1]GlobalData (2022 diagnosed prevalent patient population for US/EU5/JP)

STAT6 Degrader Advantage





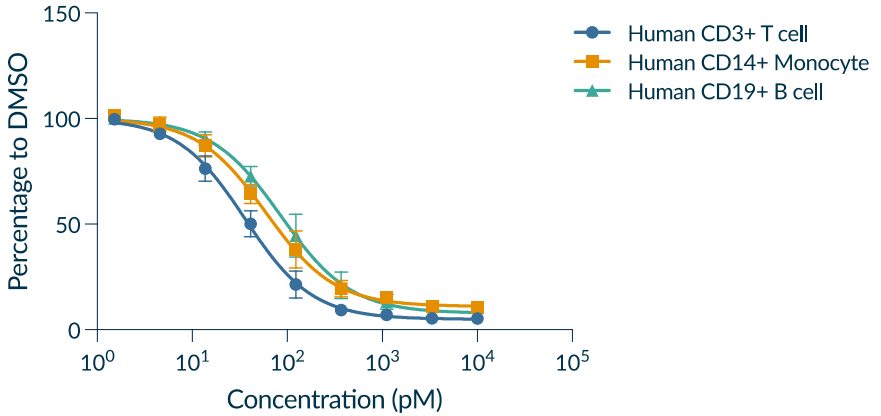
- STAT6 is the specific and essential transcription factor in the IL-4/13 pathway
- Occupancy based approaches (e.g., SMI) unlikely to block pathway fully in a pharmacologically relevant manner
- However, degradation of STAT6 can fully block IL-4/IL-13 signaling *in vitro* and *in vivo*

KT-621: A Picomolar Degrader of STAT6

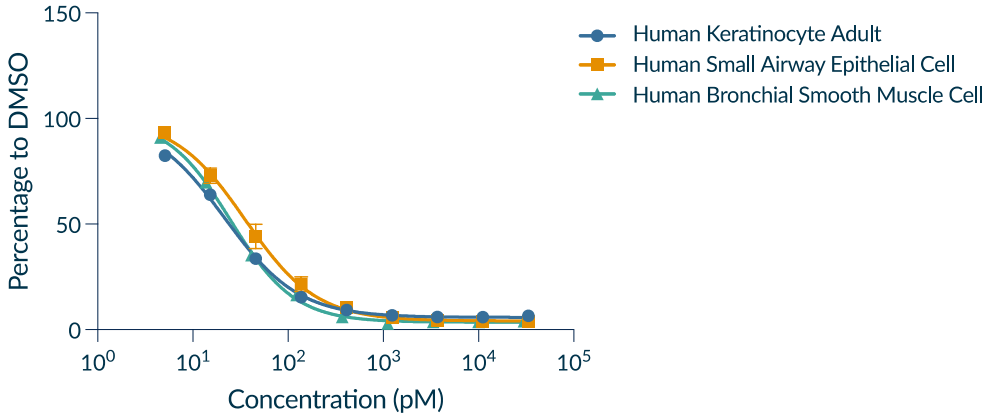
Consistent Degradation Across All Disease Relevant Cell Types Evaluated

	Human Primary Cell Type	KT-621, DC_{50} (pM)
Blood	**Hematopoietic cell (all TH2 diseases)**	
	Human PBMC	13
	Human CD3 T cell	36
	Human CD14 monocyte	60
	Human CD19 B cell	86
	Human eosinophil	99
Skin	**Epithelial cell (AD, CPG, CU, asthma, COPD)**	
	Human keratinocyte (adult)	22
	Human keratinocyte (neonatal)	18
Lungs	Human bronchial tracheal epithelial cell	33
	Human small airway epithelial cell	35
Throat/ Airway	**Smooth muscle cell (asthma, COPD, EoE)**	
	Human bronchial smooth muscle cell	25
	Human esophageal smooth muscle cell	33
Blood Vessels	**Endothelial cell (all TH2 diseases)**	
	Human vascular endothelial cell	46

STAT6 Degradation in Hematopoietic Cells



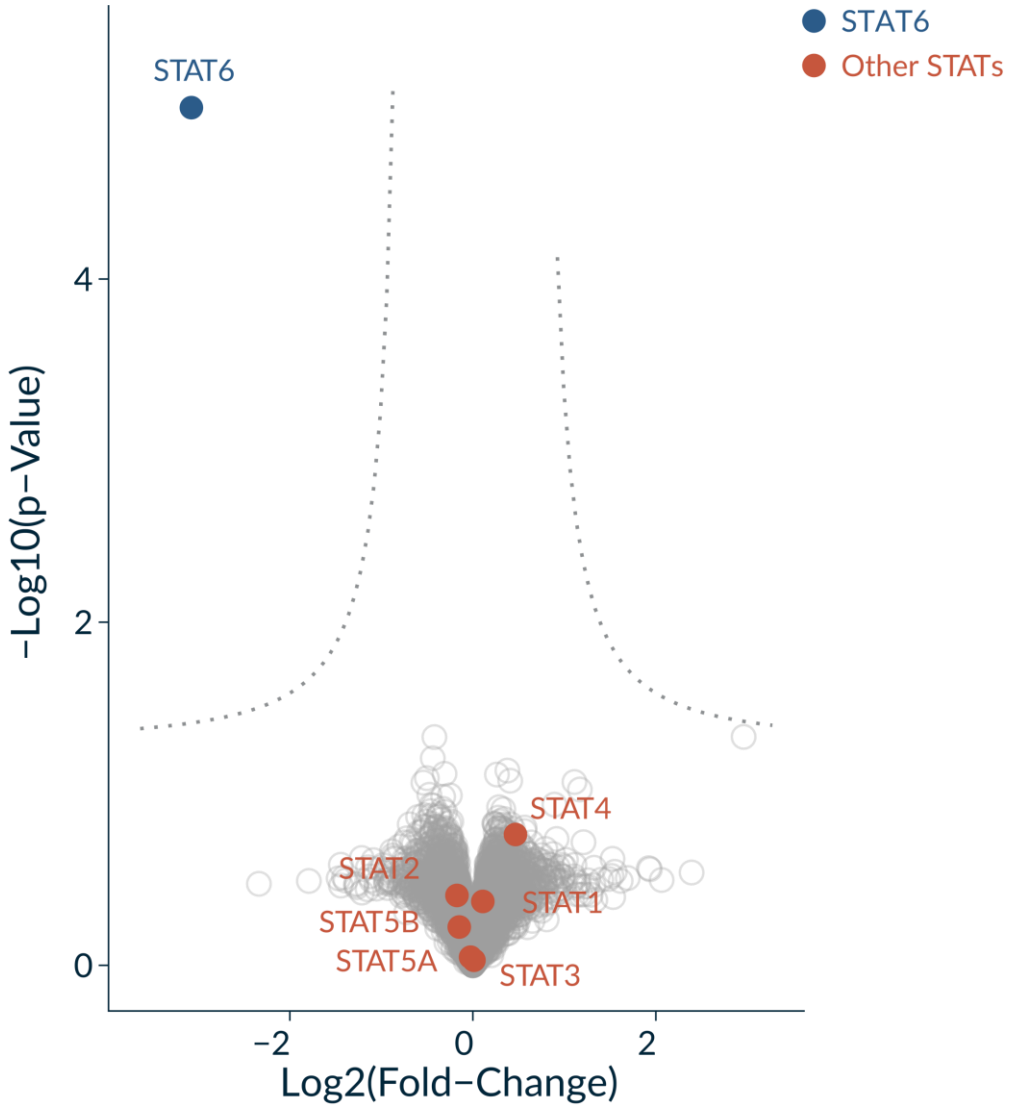
STAT6 Degradation in Tissue Cells



KT-621: Exquisite Degradation Selectivity for STAT6

Complete STAT6 degradation selectivity in human PBMC proteome at 100 x DC_{90}

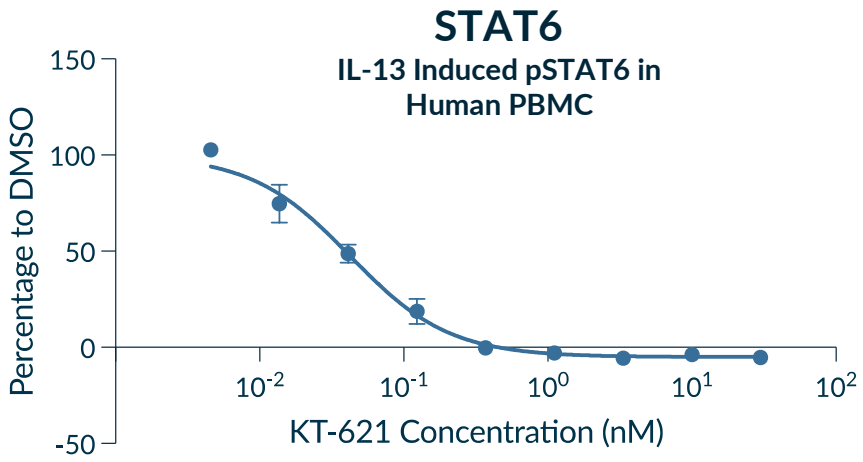
No other STATs are degraded to any extent

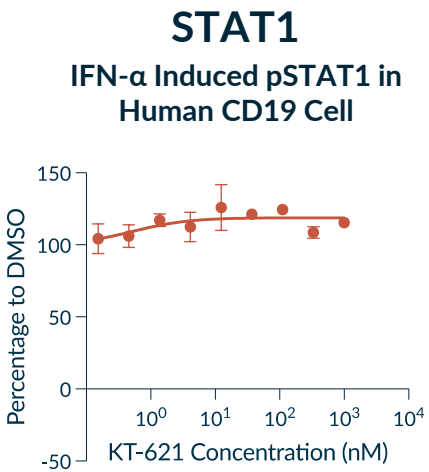


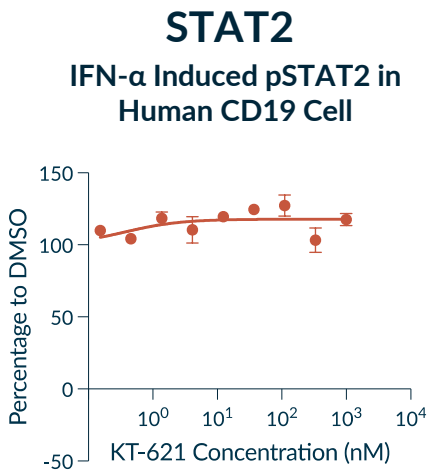
KT-621: Exquisite Pathway Selectivity for STAT6

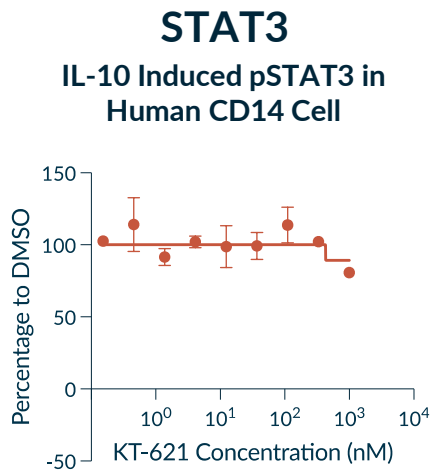
No Impact on Any Other STAT Pathway Observed

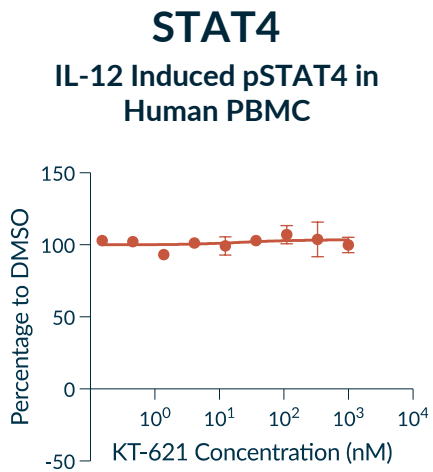
STAT assays	KT-621, IC_{50} (nM)
IFN-α induced pSTAT1	> 1000
IFN-α induced pSTAT2	> 1000
IL-10 induced pSTAT3	> 1000
IL-12 induced pSTAT4	> 1000
IL-2 induced pSTAT5	> 1000
IL-13 induced pSTAT6	0.042

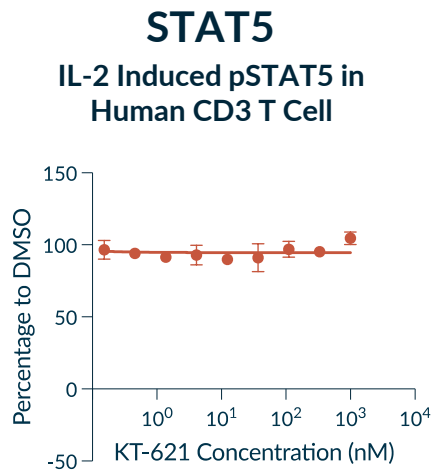








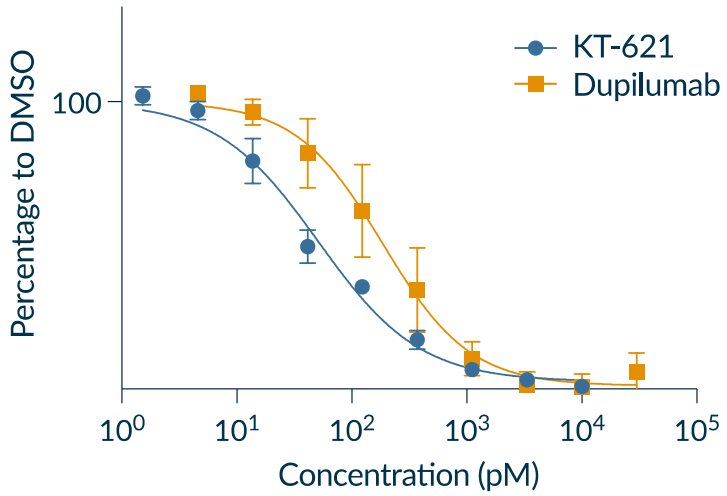




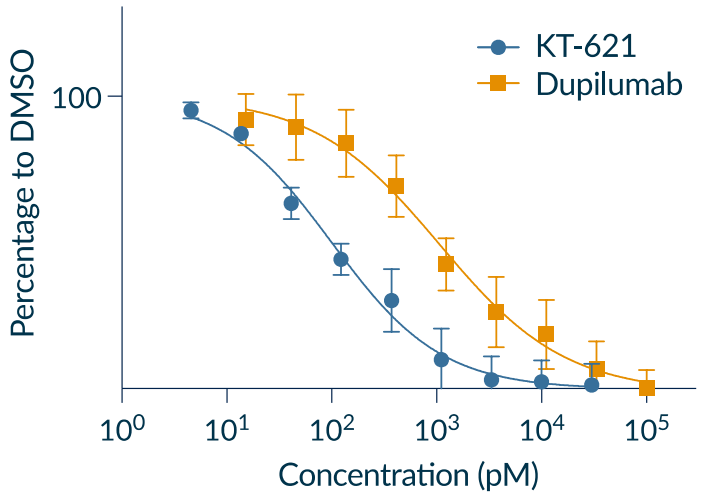
KT-621 Fully Blocks IL-4/13 Pathway in Human TH2 Functional Assays with IC_{50}'s Lower than Dupilumab

		Cellular Functional Assay	KT-621 IC_{50} (pM)	Dupilumab IC_{50} (pM)
TARC	Serum Th2 biomarker, chemoattractant for Th2 cell	IL-4 TARC release in human PBMC	**62**	194
		IL-13 TARC release in human PBMC	**43**	113
CD23	B cell activation marker, correlates with IgE class switch	IL-4 CD23 expression in human CD19 B cell	**125**	354
		IL-13 CD23 expression in human CD19 B cell	**98**	1070
PERIOSTIN	Serum Th2 biomarker and ECM protein associated with tissue remodeling in atopic diseases	IL-13 Periostin release in human bronchial smooth muscle cell	**24**	637
		IL-13 Periostin release in human esophageal smooth muscle cell	**39**	431

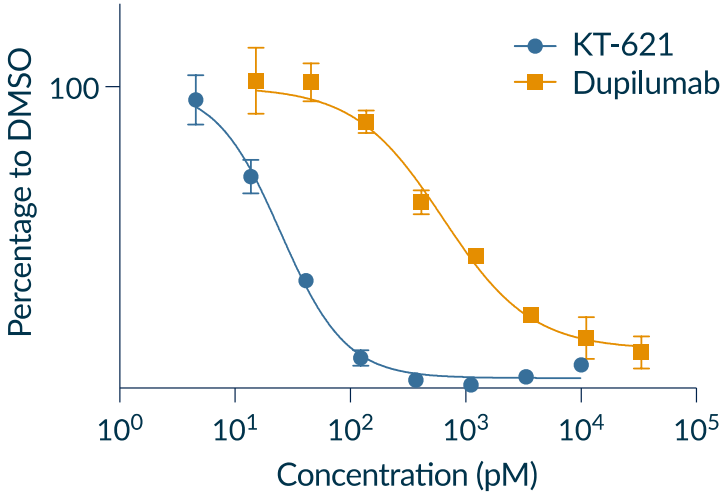
IL-4 Induced TARC Release in Human PBMC



IL-13 Induced CD23 Expression in Human CD19 B Cell



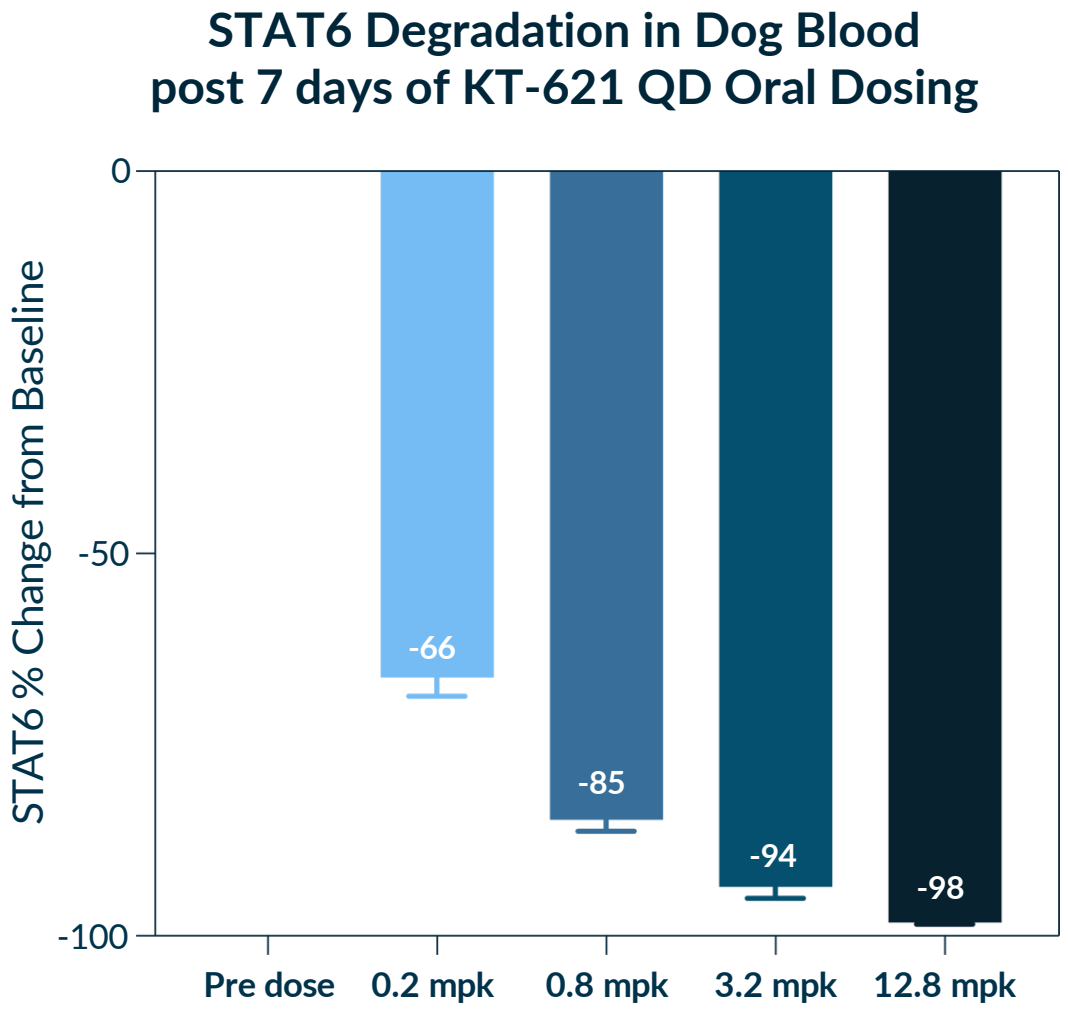
IL-13 Induced Periostin Release in Human Bronchial Smooth Muscle Cell



KT-621 Achieves Dose Dependent Deep Degradation of STAT6 *in vivo* with Low Oral Doses

KT-621 potently degrades STAT6 across multiple preclinical species

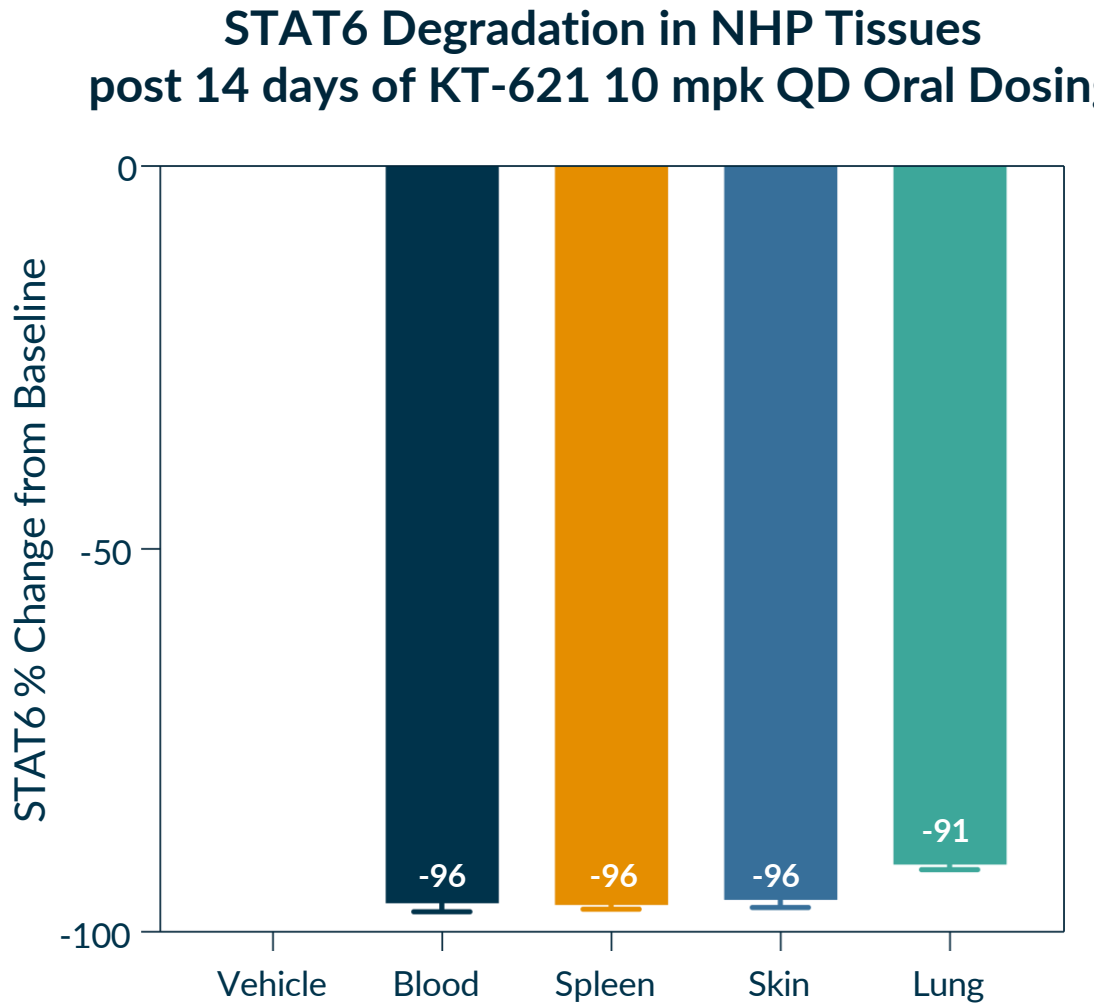
KT-621 can degrade STAT6 to depletion with low oral doses



KT-621 Degrades STAT6 in Disease Relevant Tissues in NHP

Deep degradation of STAT6 in NHP after 14 days of daily oral dosing

STAT6 is degraded in key disease-relevant tissues: blood, spleen, skin and lung

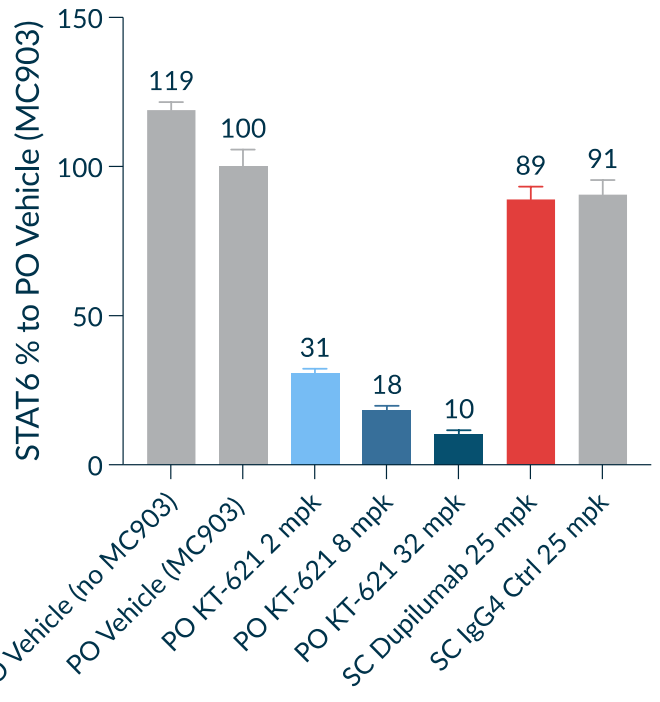


KT-621 Has Comparable *in vivo* Activity to IL-4Rα Saturating Dose of Dupilumab in the MC903 Atopic Dermatitis Model

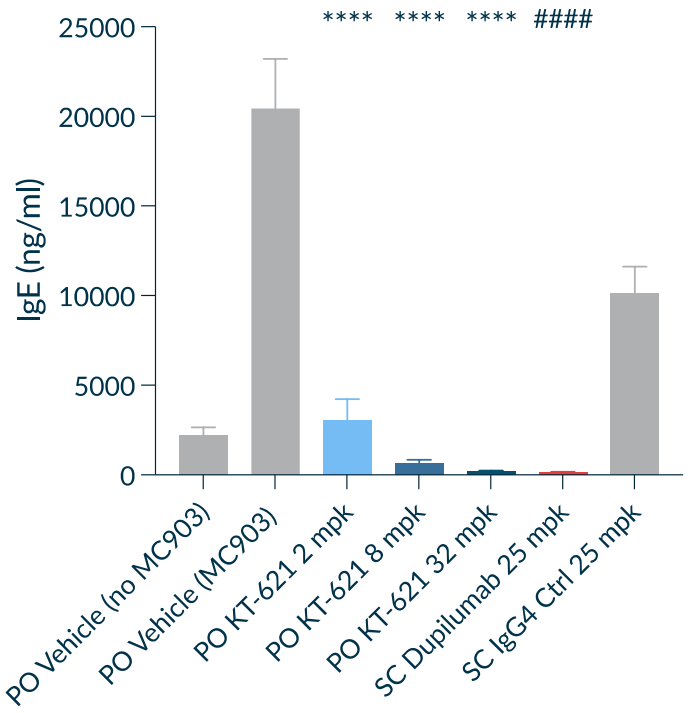
An atopic dermatitis model induced by topical application of low-calcemic vitamin D3 analog MC903 with prominent Th2 inflammation in the IL4/IL4RA humanized mice:

- **KT-621 dosed QD orally for 11 days**
- **Dupilumab dosed 4 times subcutaneously**, 25 mpk twice a week (IL-4Rα saturating dose); **effect equivalent to 300 mg every other week in human**

STAT6 Degradation in Mouse Spleen



Total Serum IgE

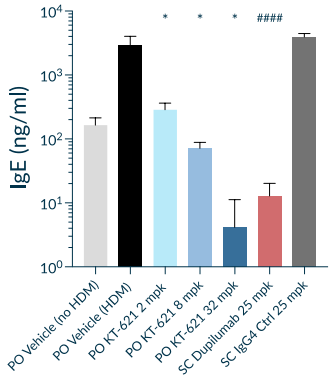


* Significance to PO vehicle (MC903); # Significance to SC IgG4 25 mpk BIW

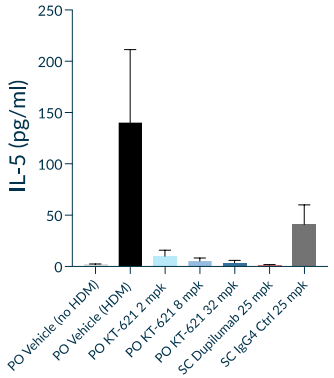
KT-621 Blocks TH2 Inflammation *in vivo* Equally or Better than an IL-4Rα Saturating Dose of Dupilumab in the Intranasal HDM Asthma Model

Serum IgE and Lung Cytokine

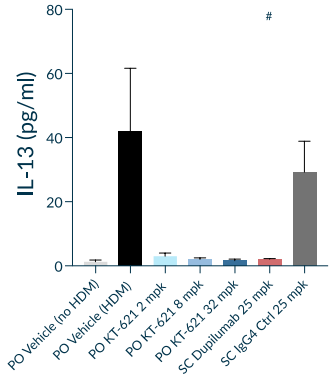
Total Serum IgE



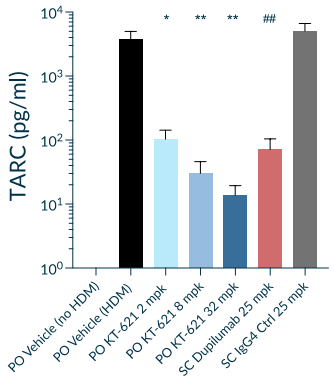
BAL IL-5



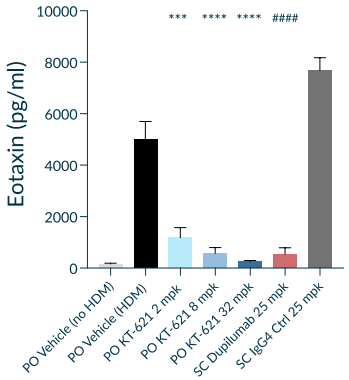
BAL IL-13



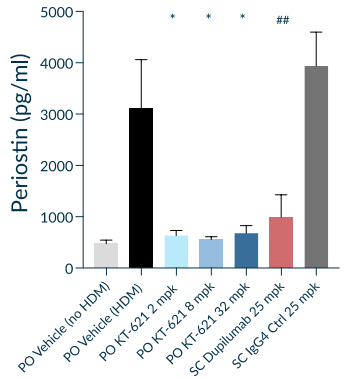
BAL TARC (CCL17)



BAL Eotaxin (CCL11)

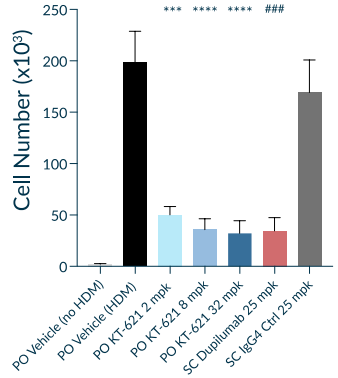


BAL Periostin

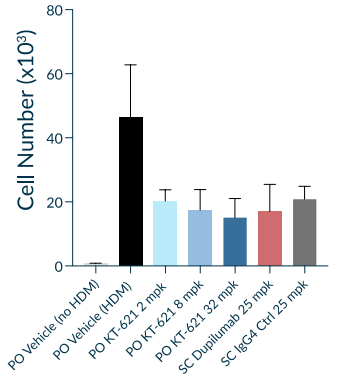


Inflammatory Infiltrate

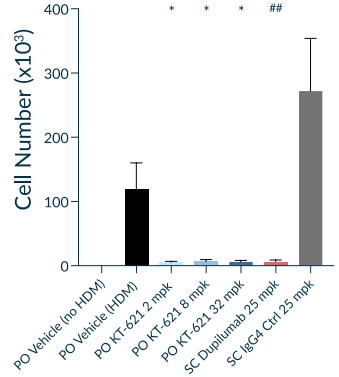
BAL CD4+ T Cell



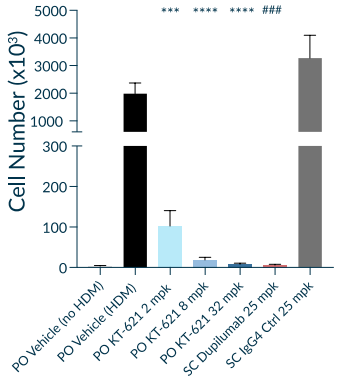
BAL CD8+ T Cell



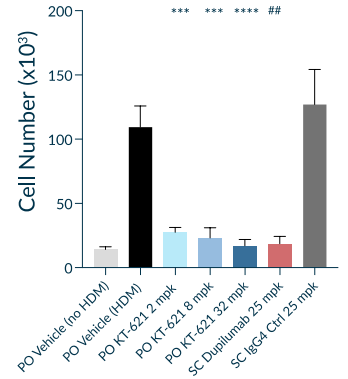
BAL Activated B Cell



BAL Eosinophil



BAL Dendritic Cell



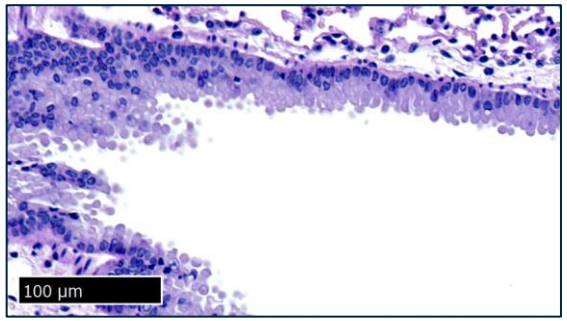
- **KT-621 dosed QD orally for 31 days. 2/8/32 mpk** doses showed **72/85/91% STAT6 degradation** respectively in mouse spleen
- **Dupilumab dosed 9 times subcutaneously**, 25 mpk BIW (IL-4Rα saturating dose), **effect equivalent to 300 mg every other week in human**

A lung inflammation model induced by intranasal house dust mite administration with dominant Th2 inflammation in the IL4/IL4RA humanized mice (Le Floc'h et al. Allergy. 2020);
BAL – bronchoalveolar lavage; *Significance to PO vehicle (HDM); # Significance to SC IgG4 Ctrl 25 mpk.

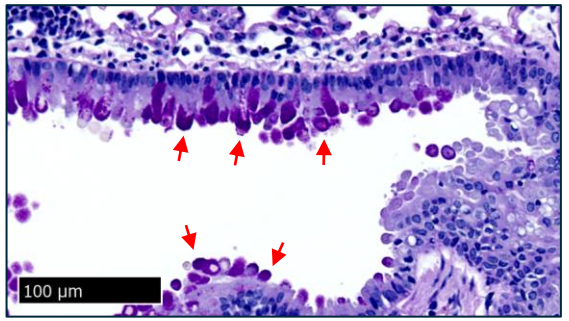
KT-621 Reduced Disease Severity in the Lung in the Intranasal HDM Asthma Model

Lung Remodeling: Goblet Cell Metaplasia (Arrow)

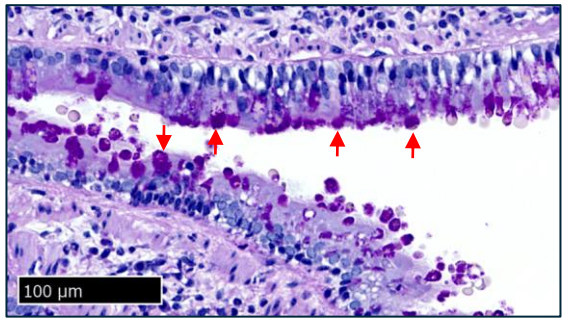
PO Vehicle (no HDM)



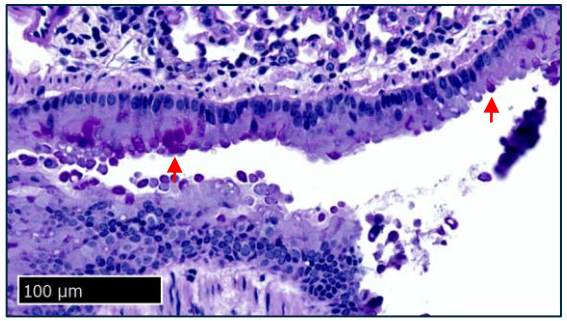
PO Vehicle (HDM)



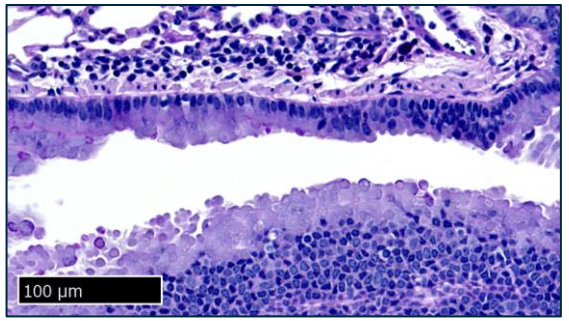
SC IgG4 Ctrl 25 mpk



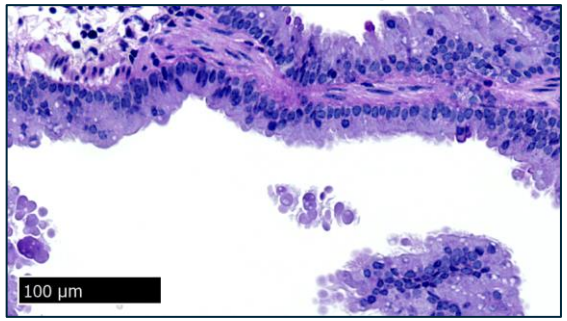
PO KT-621 2 mpk



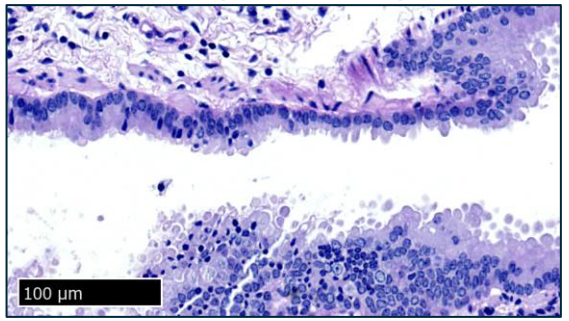
PO KT-621 8 mpk



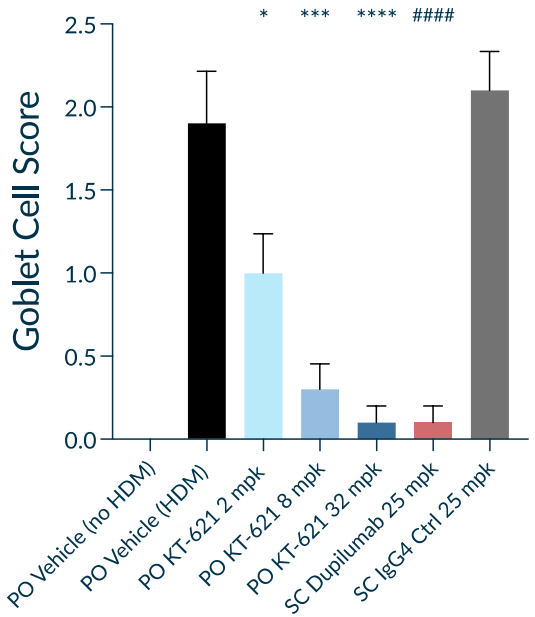
PO KT-621 32 mpk



SC Dupilumab 25 mpk



Lung Goblet Cell Metaplasia



Amelioration of lung remodeling seen after low daily oral doses of KT-621 comparable to dupilumab

A lung inflammation model induced by intranasal house dust mite administration with dominant Th2 inflammation in the IL4/IL4RA humanized mice (Le Floc'h et al. Allergy. 2020);
*Significance to PO vehicle (HDM); # Significance to SC IgG4 Ctrl 25 mpk.

Oral STAT6 Degrader: KT-621

Potential for dupilumab-like activity with oral small molecule profile

Upcoming Presentation: EADV 2024

Validated Biology

Specific and essential transcription factor in IL-4 and IL-13 signaling pathways

Central driver of Th2 inflammation

STAT6 validated by human genetics

Pathway validated by human genetics and dupilumab across multiple indications

Competitive Profile

WW IL-4/IL-13 biologic market currently $10B+ annually

Estimated to grow to $23B+ with expanded indications and new entrants

Mega-blockbuster potential for oral degraders in allergic diseases

Potential to access beyond biologics-eligible patients and much larger population

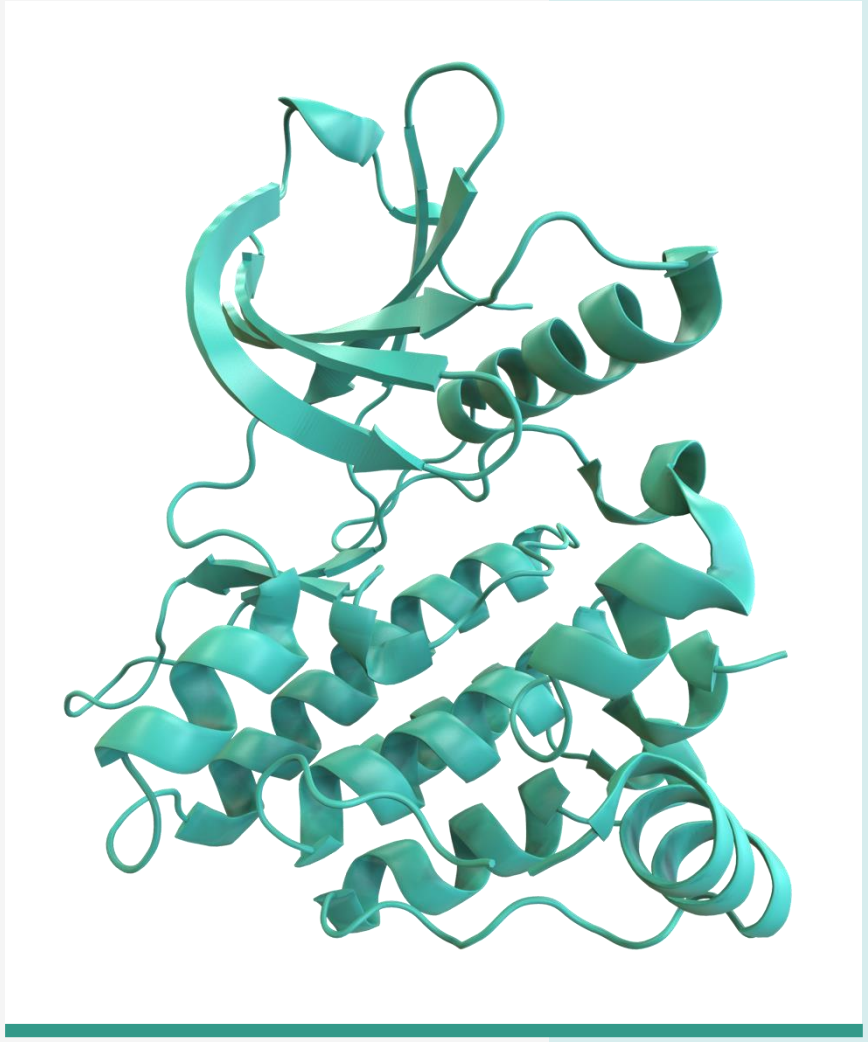
FIH: 2H 2024

Full IL-4 and IL-13 functional inhibition with picomolar IC_{50}'s superior to dupilumab

Robust activity shown in *in vivo* preclinical models of atopic dermatitis and lung inflammation equal or superior to dupilumab

STAT6 degradation was well-tolerated in multiple preclinical safety studies (including GLP-tox) at >40x efficacious concentration

IND enabling studies completed



First-in-Class Oral TYK2 Degrader Program

TYK2 Biology and Target Rationale

Target Biology and Rationale

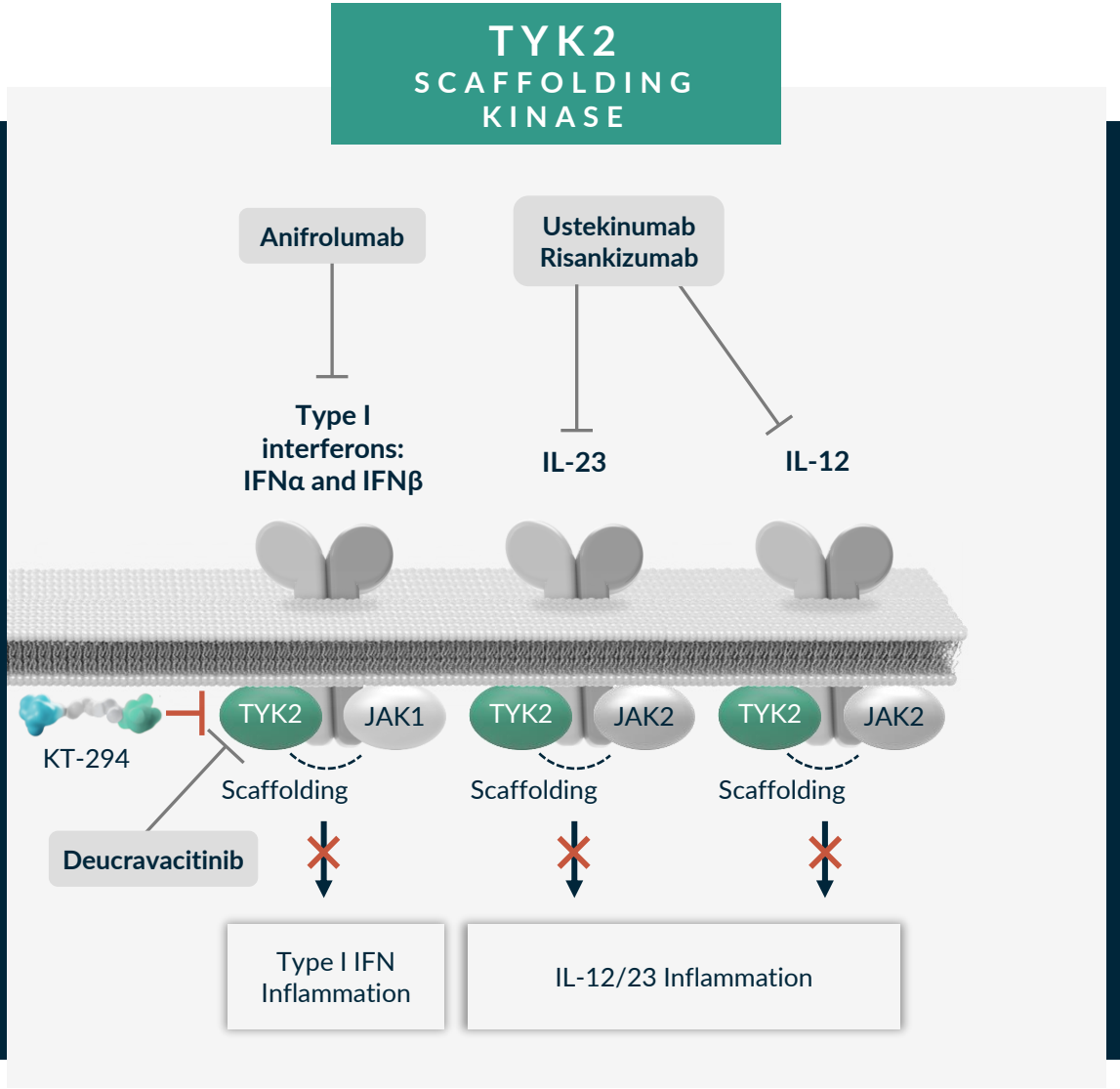
- TYK2 is a member of the JAK family required for Type I IFN, IL-12 and IL-23 cytokine signaling
- TYK2 regulated cytokines are clinically validated targets for autoimmune and inflammatory diseases

Human Genetics

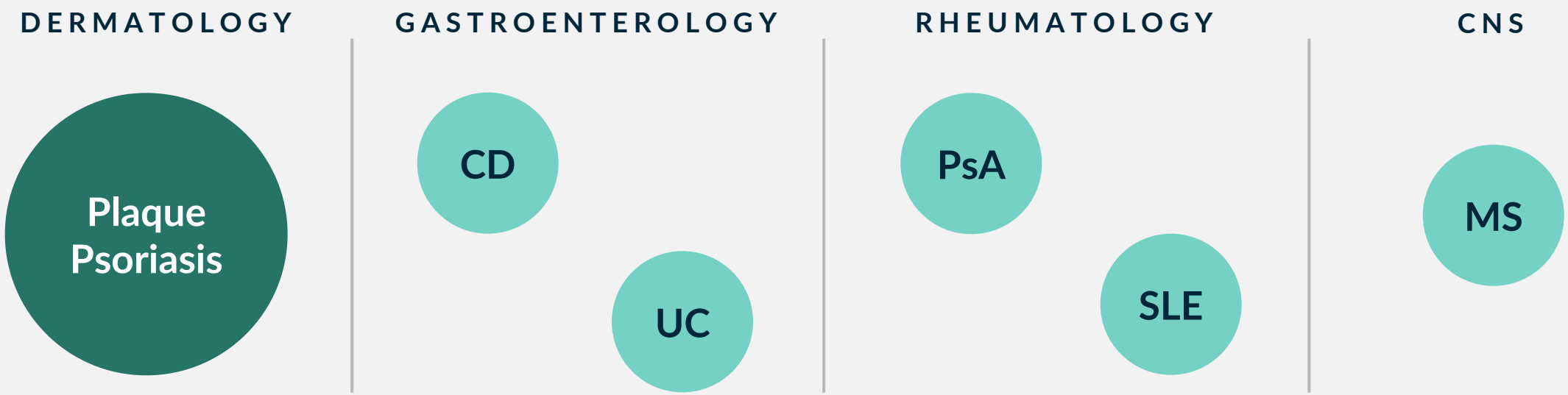
- Loss-of-function variant of TYK2 is protective in autoimmune and inflammatory diseases

Clinical Pathway Validation

- IL-23 (± IL-12)-targeting agents include ustekinumab, risankizumab, guselkumab, and tildrakizumab, with approvals in PsO, PsA, CD, UC
- Type I IFN-targeting agents include anifrolumab with approval in SLE
- TYK2 SMI deucravacitinib recently approved in PsO



Patient Impact of TYK2: Potential Best-In-Class Opportunity in I&I



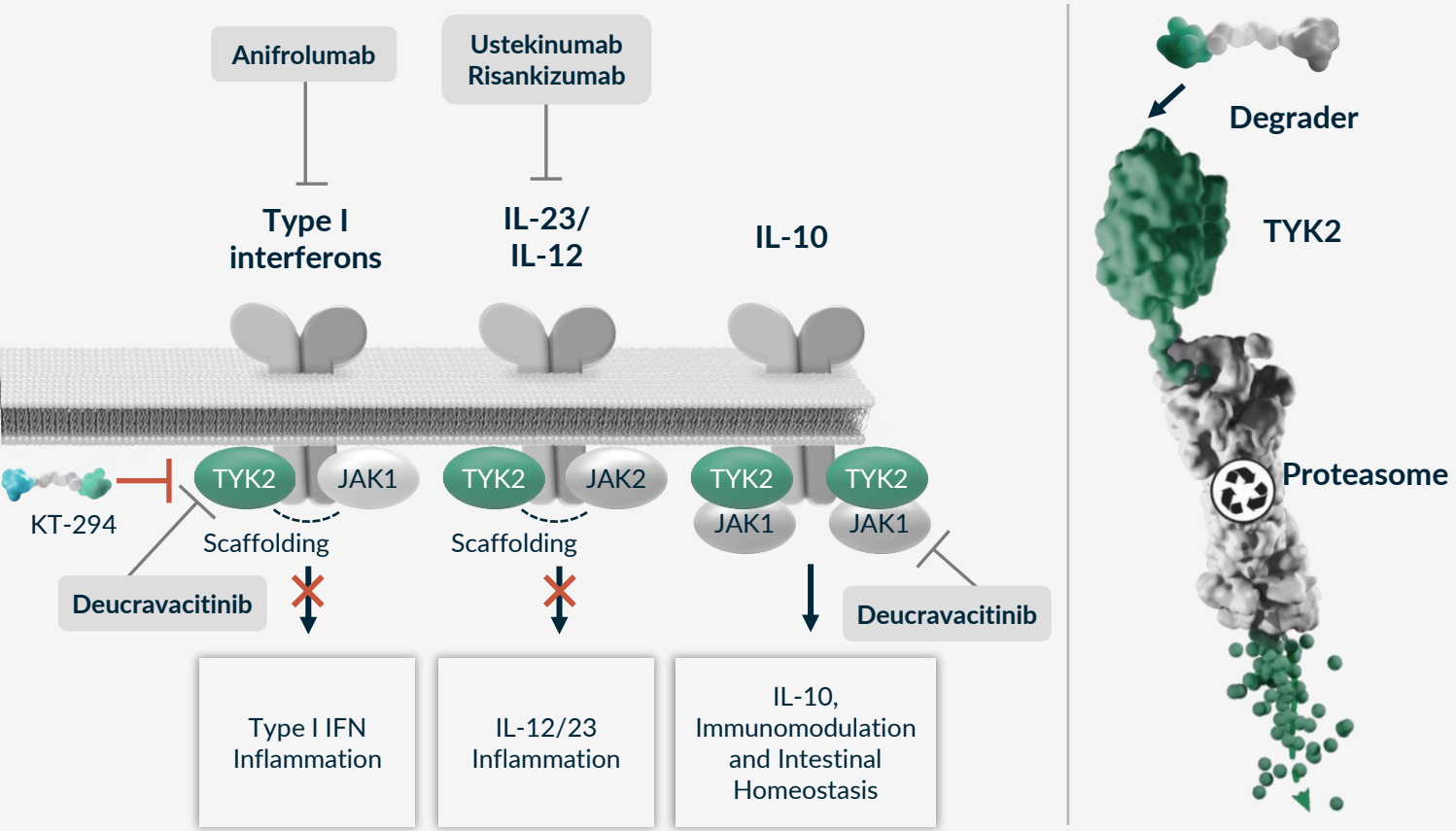
Total Potential Patient Impact[1]: > 20M patients

- Numerous indication opportunities across multiple therapeutic areas de-risked by biologics and deucravacitinib
- TYK2 degradation, differentiated from inhibition, leads to full pathway inhibition with potential to deliver biologic-like activity*
- Oral degrader medicines offer opportunity to reach broader patient populations

[1]GlobalData (2022 diagnosed prevalent patient population for US/EU5/JP)
*Statements regarding TYK2 degrader biology throughout this presentation are based upon preclinical experiments in human cells and preclinical species conducted by Kymera

TYK2 Degrader Advantage

Only TYK2 Degraders Can Reach Biologics-like Activity



- TYK2 has a well-established scaffolding function that is responsible for cytokine receptor surface expression and activation
- Unlike SMIs, only TYK2 degradation recapitulates the human LOF phenotype of full pathway inhibition of Type I IFN, IL-12 and IL-23 and sparing of IL-10
  - Unlike deucravacitinib, which inhibits IL-10 through JAK1, KT-294 does not inhibit IL-10, which is important in IBD
  - Compared to TAK-279, KT-294 fully inhibits Type I IFN
- Full TYK2 degradation demonstrated by KT-294 leads to superior pathway inhibition to existing SMIs and potentially reach biologic-like activity

TYK2 Has Well-Established Scaffolding Function

- TYK2 complete deficiency severely impairs IL-23, Type I IFN, and IL-12 signaling but spares IL-10 in humans
- TYK2 scaffolding functions are demonstrated by differential pathway inhibitions in complete TYK2 deficiency vs a kinase dead variant in humans
- TYK2 deficient humans are generally healthy with only increased risk of some mycobacteria and viral infections that are relatively mild, curable and tend not to recur, de-risking safety for TYK2 degradation

Cytokine Pathway	IL-23	Type I IFN	IL-12	IL-10
WT TYK2	++++	++++	++++	++++
Complete deficiency TYK2 -/-	+	+	+	+++
TYK2 Kinase dead P1104A/P1104A	+	++++	++++	++++

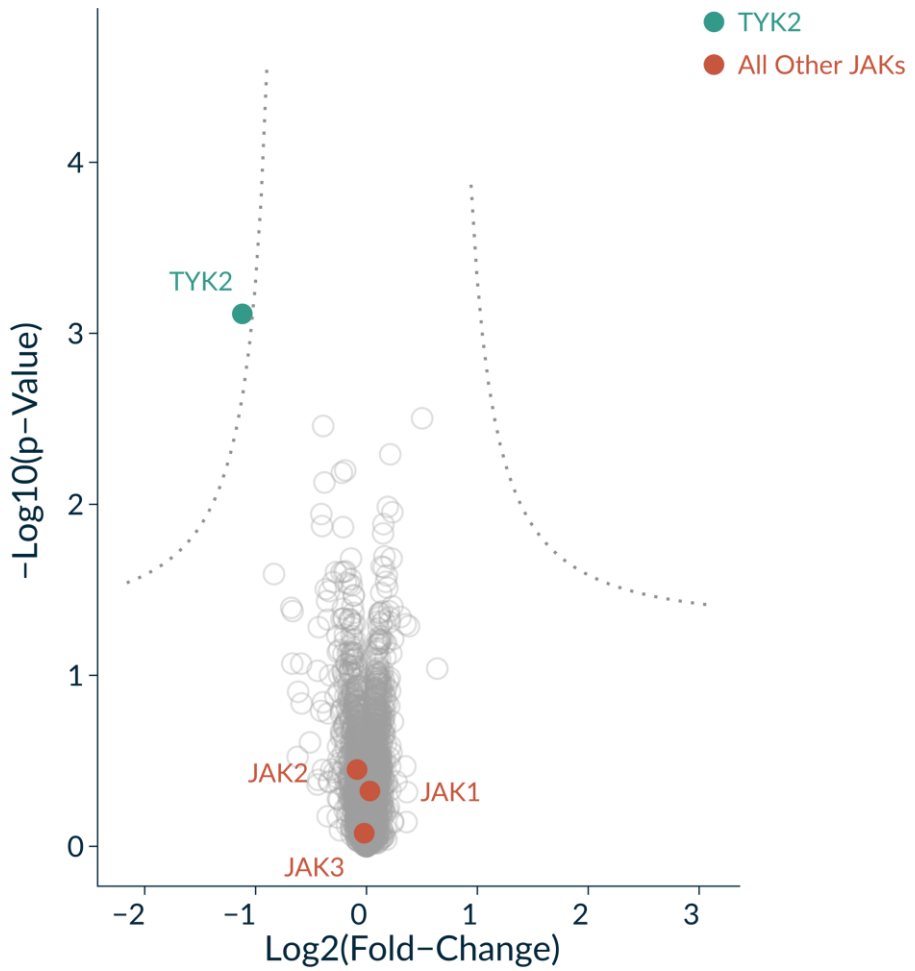
Degrading TYK2 is the only small molecule approach to potentially eliminate all scaffolding and catalytic functions of TYK2, fully recapitulating the human TYK2-/- biology

Ogishi et al. JEM. 2022

KT-294, a Highly Selective Picomolar TYK2 Degrader, Recapitulates TYK2 Human Deficiency Biology

Fully Inhibits of Type I IFN and IL-12/23 and Spares IL-10/22

Selective TYK2 Degradation by KT-294 in hPBMC Proteome at 10x DC_{90}



Cellular Degradation/Functional Assay	KT-294 DC_{50}/IC_{50} (nM)
Human PBMC degradation	**0.08**
Human keratinocyte (neonatal and adult)	**0.07**
IL-23 pathway	
IL-23 pSTAT4 in human PBMC	**0.7**
IL-23 pSTAT3 in human CD3+CD161high TH17 cell	**2.1**
IL-23/IL-1β IFN-γ release in human PBMC	**2.4**
Type I IFN pathway	
IFN-α pSTAT1 in human CD19 B cell	**13**
IFN-α pSTAT2 in human CD19 B cell	**15**
IFN-α IP10 release in human PBMC	**4.9**
IL-12 pathway	
IL-12/IL-18 pSTAT4 in human PBMC	**1.3**
IL-12/IL-18 IFN-γ release in human PBMC	**10**
IL-10 and IL-22 pathways	
IL-10 pSTAT3 in human CD14 monocyte	**> 1000**
IL-22 pSTAT1 in HT29 cell	**> 1000**
IL-22 pSTAT3 in HT29 cell	**> 1000**

KT-294, Unlike Allosteric TYK2 Inhibitor Deucravacitinib, Does not Inhibit IL-10

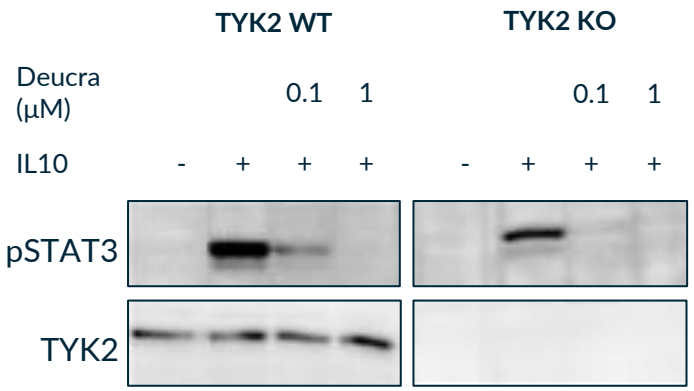
IL-10 has essential roles in intestinal homeostasis

- Loss of function mutations of the IL-10 pathway cause early onset refractory colitis in humans

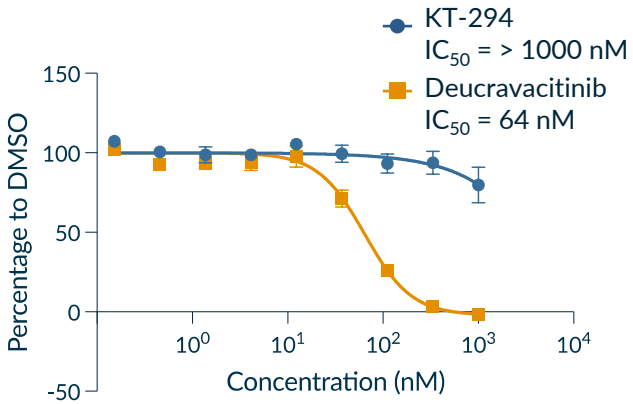
Deucravacitinib inhibits IL-10 because of its anti-JAK1 activity; KT-294 spares JAK1 and as a result IL-10

- Deucra JAK1 Ki = 0.33 nM (Burke et al. Sci Transl Med. 2019)
- KT-294 JAK1 Ki = > 1000 nM

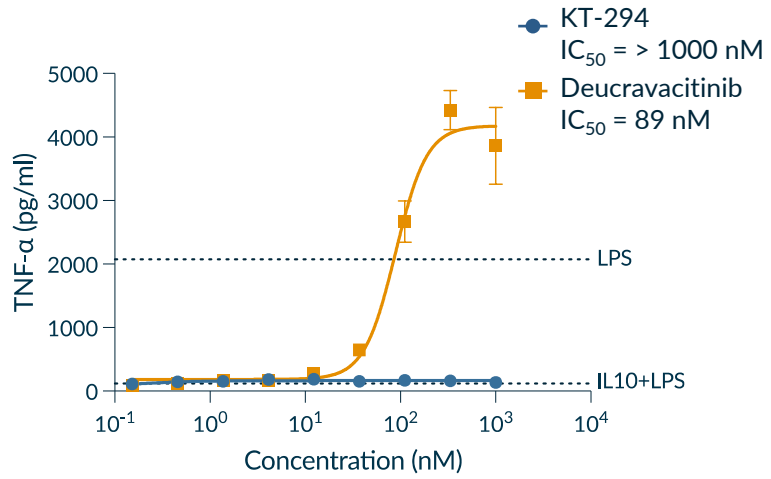
Deucravacitinib Inhibited IL-10 induced pSTAT3 in TYK2 KO EBV B Cell



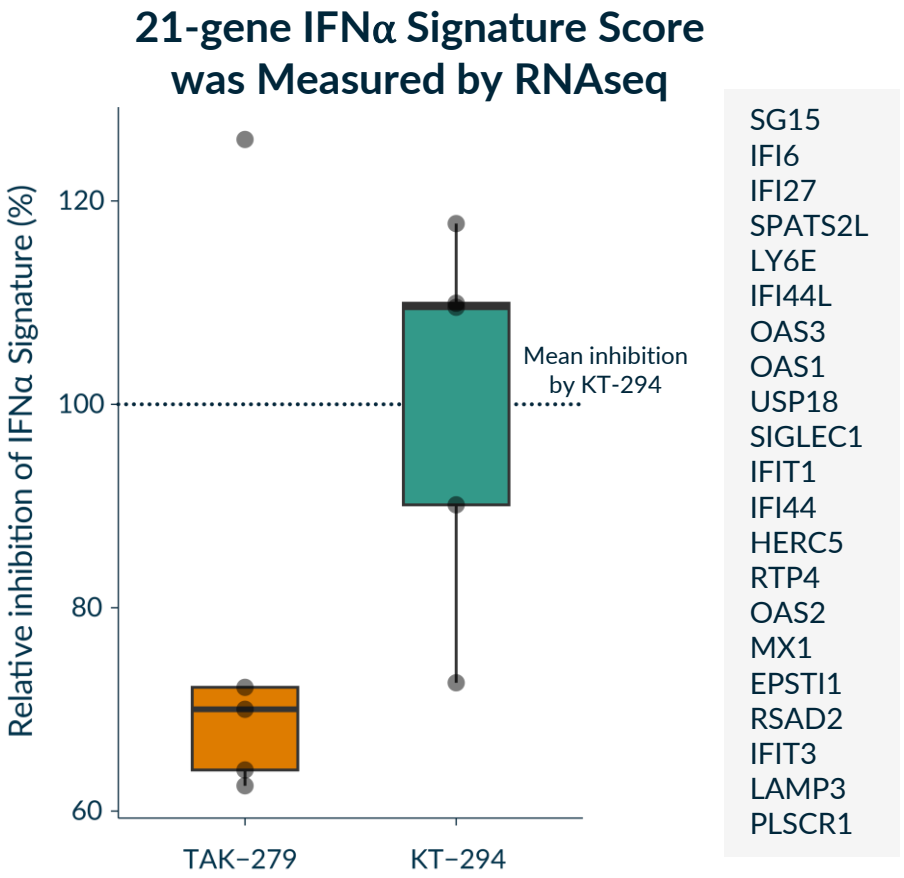
Deucravacitinib Inhibited IL-10 Induced pSTAT3 in Human CD14 Monocyte

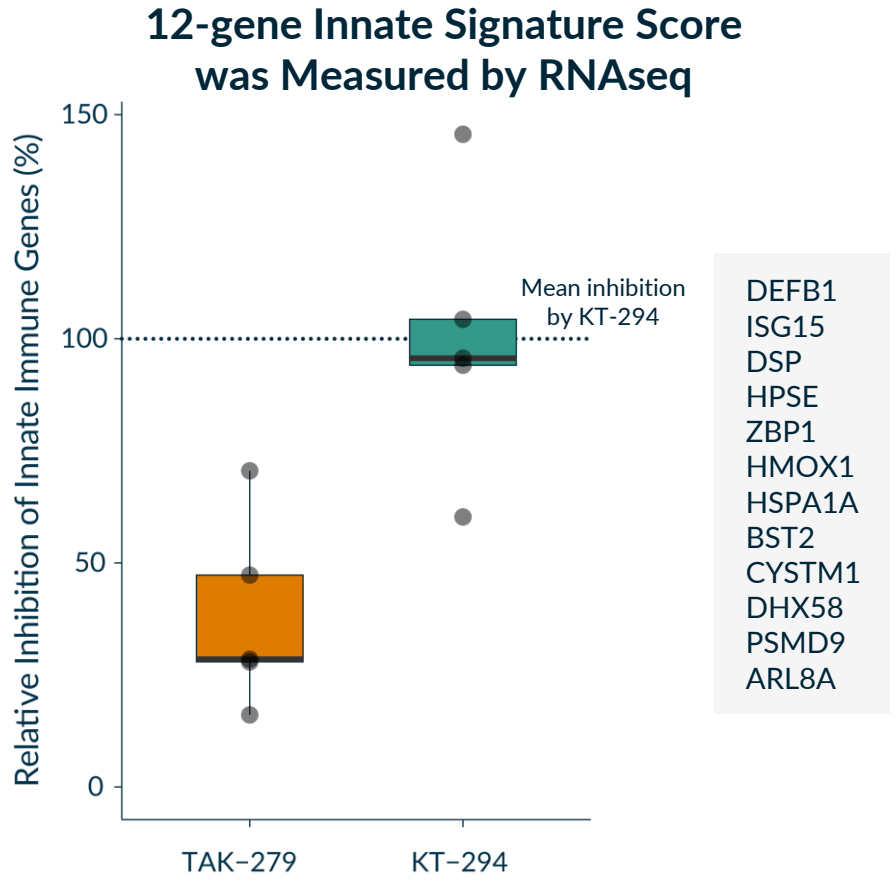


Deucravacitinib Inhibits IL-10's Function of Suppressing LPS Induced TNF-α Release in Human CD14 Monocyte



Superior Inhibition of Type I IFN Pathway and Innate Immunity by KT-294 vs TAK-279





Doses Used:

- TAK-279 = 422nM (IFNα stimulated pSTAT2 IC_{95}). Clinical exposure Cmax (free) at 35mg[1] = ~ 77 nM
- KT-294 = 56nM (IFNα stimulated pSTAT2 IC_{95})

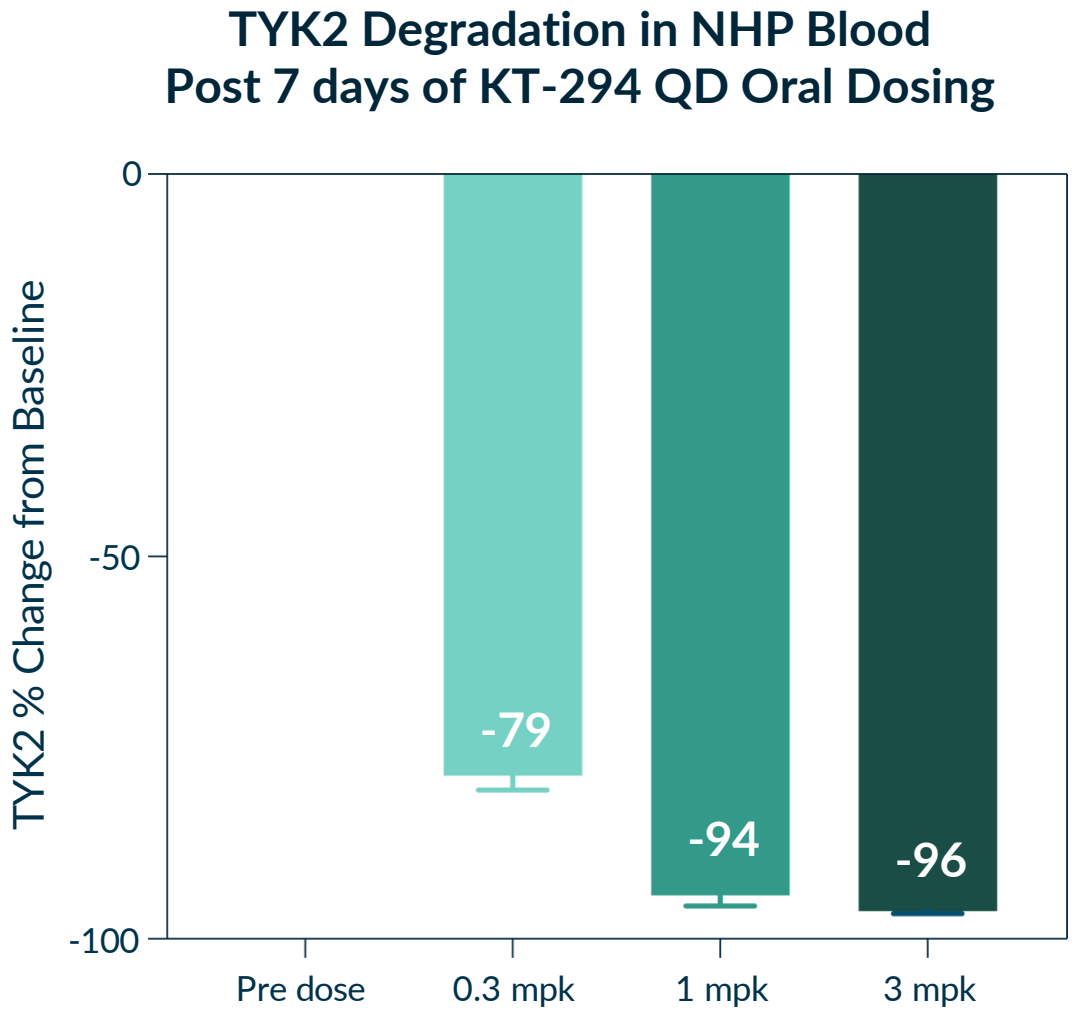
At concentrations where TAK-279 and KT-294 block pathway 95%, degrader demonstrates superior biological effect. (TAK-279 does not reach these exposures in clinic)

[1]Gangolli et al., SID 2022

KT-294 Achieved Dose Dependent Deep Degradation of TYK2 *in vivo* with Low Oral Doses

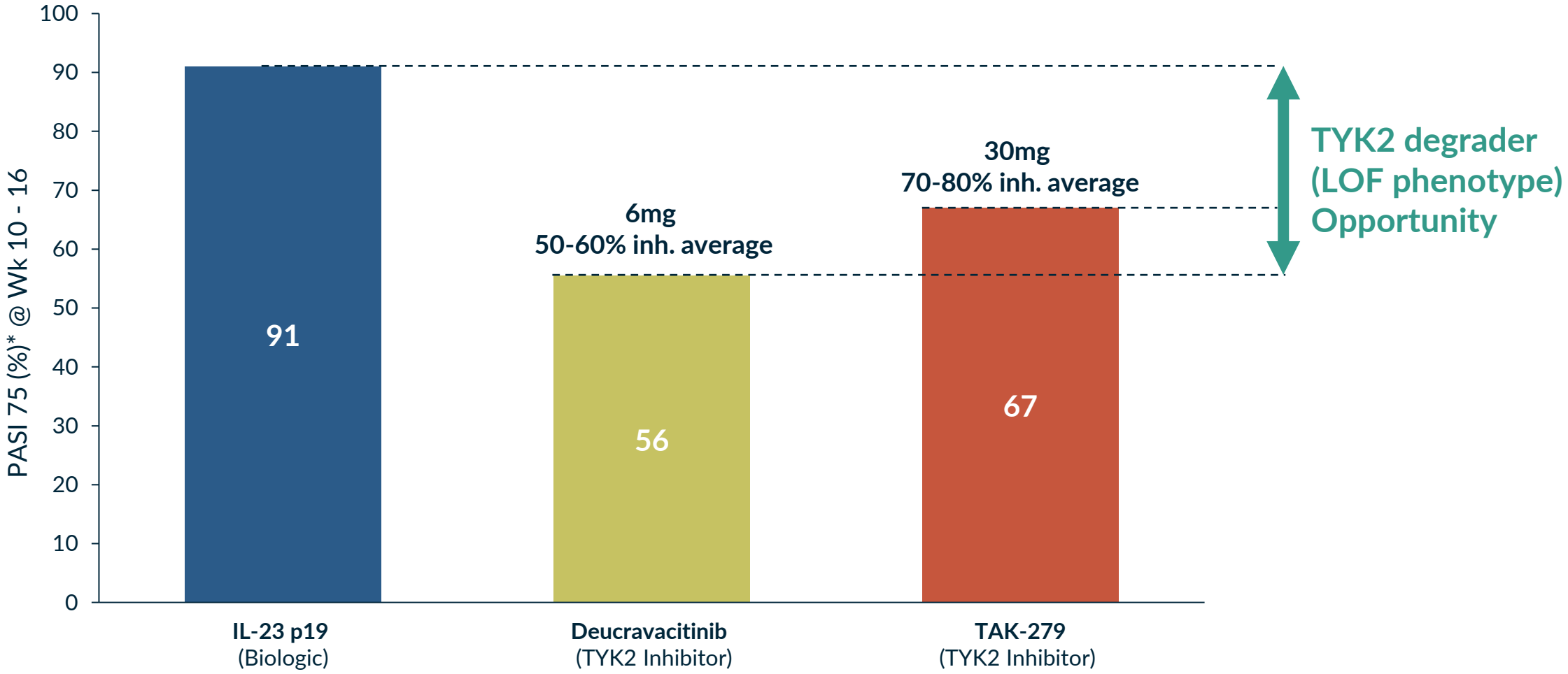
KT-294 potently degrades TYK2 across multiple preclinical species

In NHP, KT-294 can degrade TYK2 to depletion with low oral doses



TYK2 SMI's Do Not Reach Maximal Target Engagement

Clinical Efficacy In Psoriasis is Target Engagement Dependent



Company presentations and package inserts; * total observed response rate for primary endpoint cut-off ranges from Wk 10 to Wk 16.

Biological and Clinical Differentiation

TYK2 Clinical Opportunities	Deucravacitinib IL12/23, IFN, IL10	TAK-279 IL12/23, ~IFN	KT-294 IL12/23, IFN	*KT-294, unlike TYK2 SMI, can replicate the TYK2 deficient phenotype and result: potent Type I IFN, IL-12/23 inhibition fully while sparing IL-10* **WITH FOLLOWING EXPECTED CLINICAL DIFFERENTIATION:**
Psoriasis	++	++	+++	**>90% degradation vs 70-80% inhibition at steady state (best anti-IL23 profile)**
Psoriatic Arthritis	++	++	+++	**>90% degradation vs 70-80% inhibition at steady state (best anti-IL23 profile)**
IBD	-	++	+++	**>90% degradation vs 70-80% inhibition at steady state (best anti-IL23 profile), + sparing IL-10**
Lupus & interferonopathies	++	+	+++	**>90% degradation vs 70-80% inhibition at steady state (best anti-IL23 profile) + best anti-IFN profile**

Oral TYK2 Degrader: KT-294

Potential Best-in-Class Opportunity with Biologics-like Profile

Validated Biology

TYK2 is a member of the JAK family required for Type I IFN, IL-12 and IL-23 cytokine signaling

Pathway validated by upstream biologics (i.e. ustekinumab) and TYK2 SMI across many diseases

TYK2 validated by human genetics

Competitive Profile

IL-23 and Type 1 IFN-based biologic market currently ~$18B annually

Estimated to grow to ~$27B with expanded indications and new entrants

TYK2 SM inhibitors have limitations due to selectivity (deucravacitinib) or lack of potent IFN-α activity (TAK-279) and limited clinical target engagement (both)

Mega-blockbuster potential for oral degrader with biologics-like activity that is superior to TYK2 SMI

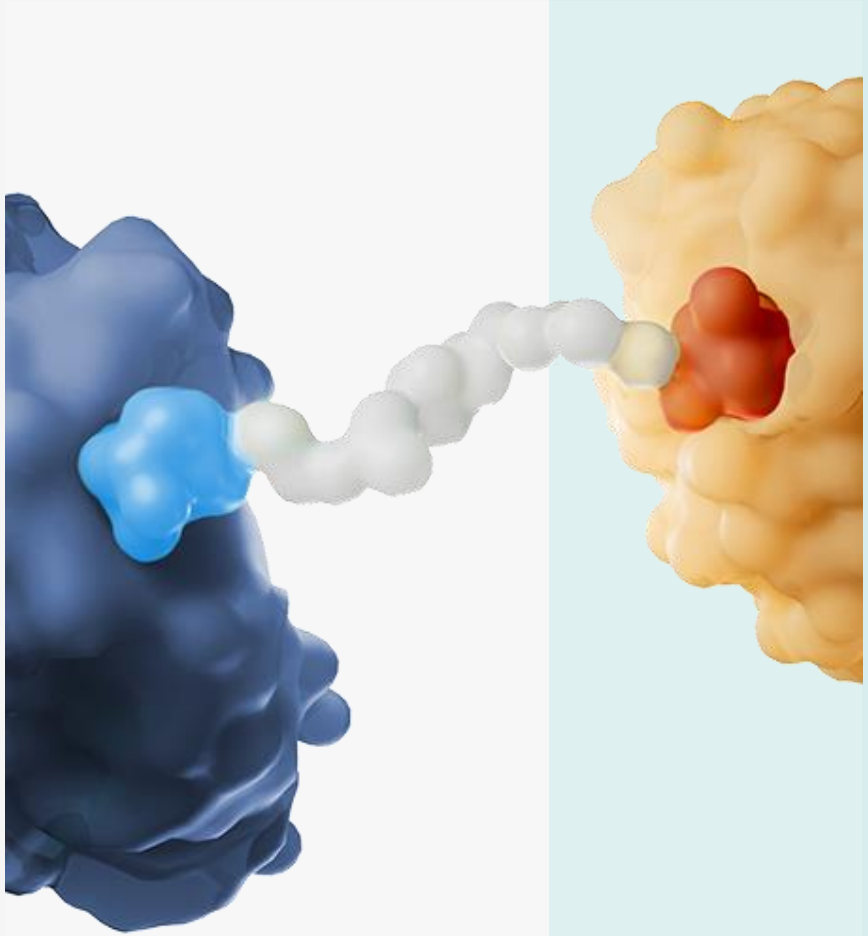
FIH: 1H 2025

Degrades TYK2 in human cells with pM potency

Recapitulates the phenotype of TYK2 human deficiency showing potent IFN-α, IL-12 and IL-23 inhibition and sparing IL-10

Dosed orally, shows complete TYK2 degradation in NHP providing a path to full target engagement in clinic, unlike current SMI

Currently in IND enabling studies



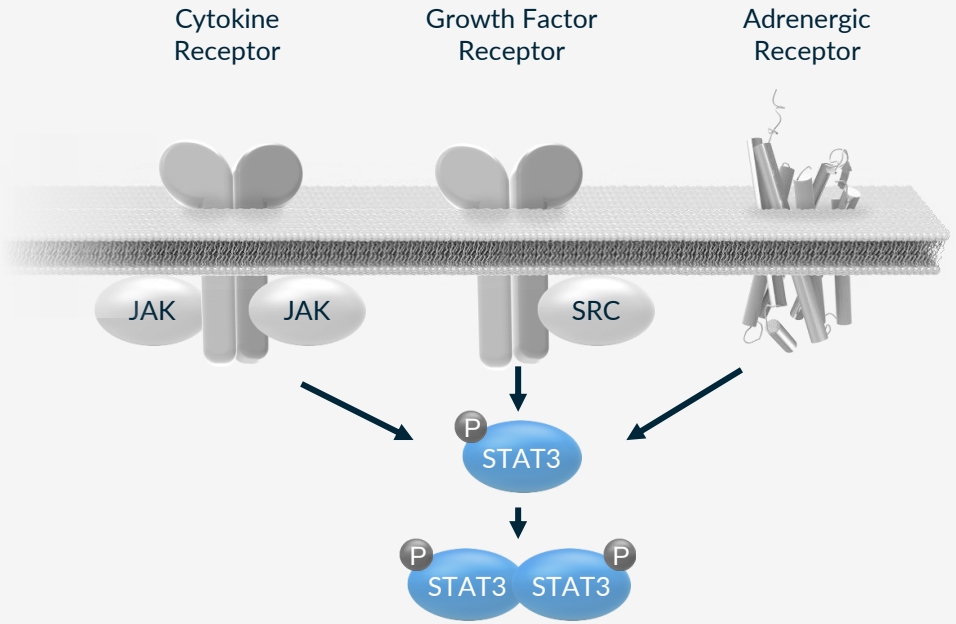
Kymera's Oncology Pipeline

MDM2, STAT3

Kymera Oncology Degrader Portfolio

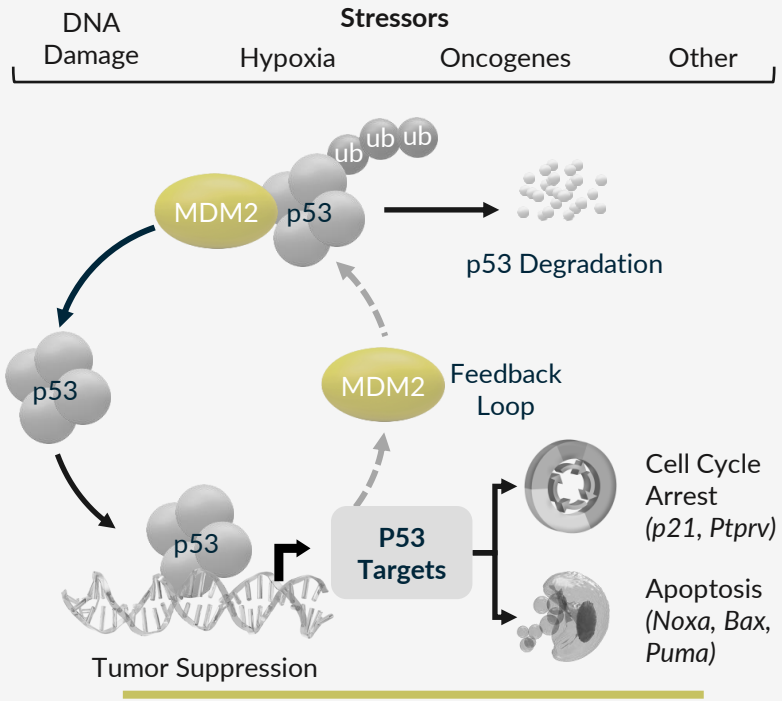
Targeting undrugged or poorly drugged targets in areas with large clinical and commercial impact, with focus on mechanisms that can address both liquid and solid tumors

STAT3
TRANSCRIPTION FACTOR

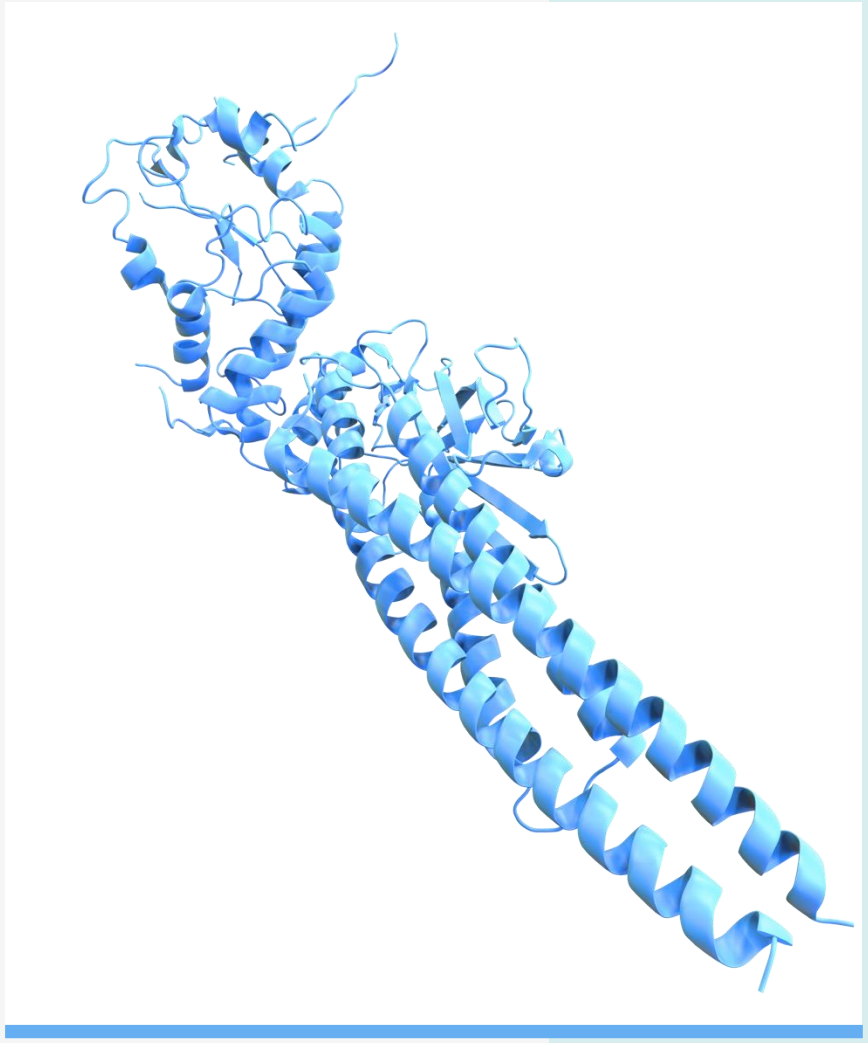


STAT3 is a **traditionally undrugged transcription factor** within a clinically validated pathway with unique tumor cell intrinsic and extrinsic mechanisms

MDM2
p53 MODULATOR



MDM2 is a poorly drugged (by SMI) E3 ligase that modulates p53, the **largest tumor suppressor**



First-in-Class
STAT3 Degrader Program

STAT3 Biology and Target Rationale

Target Biology and Rationale

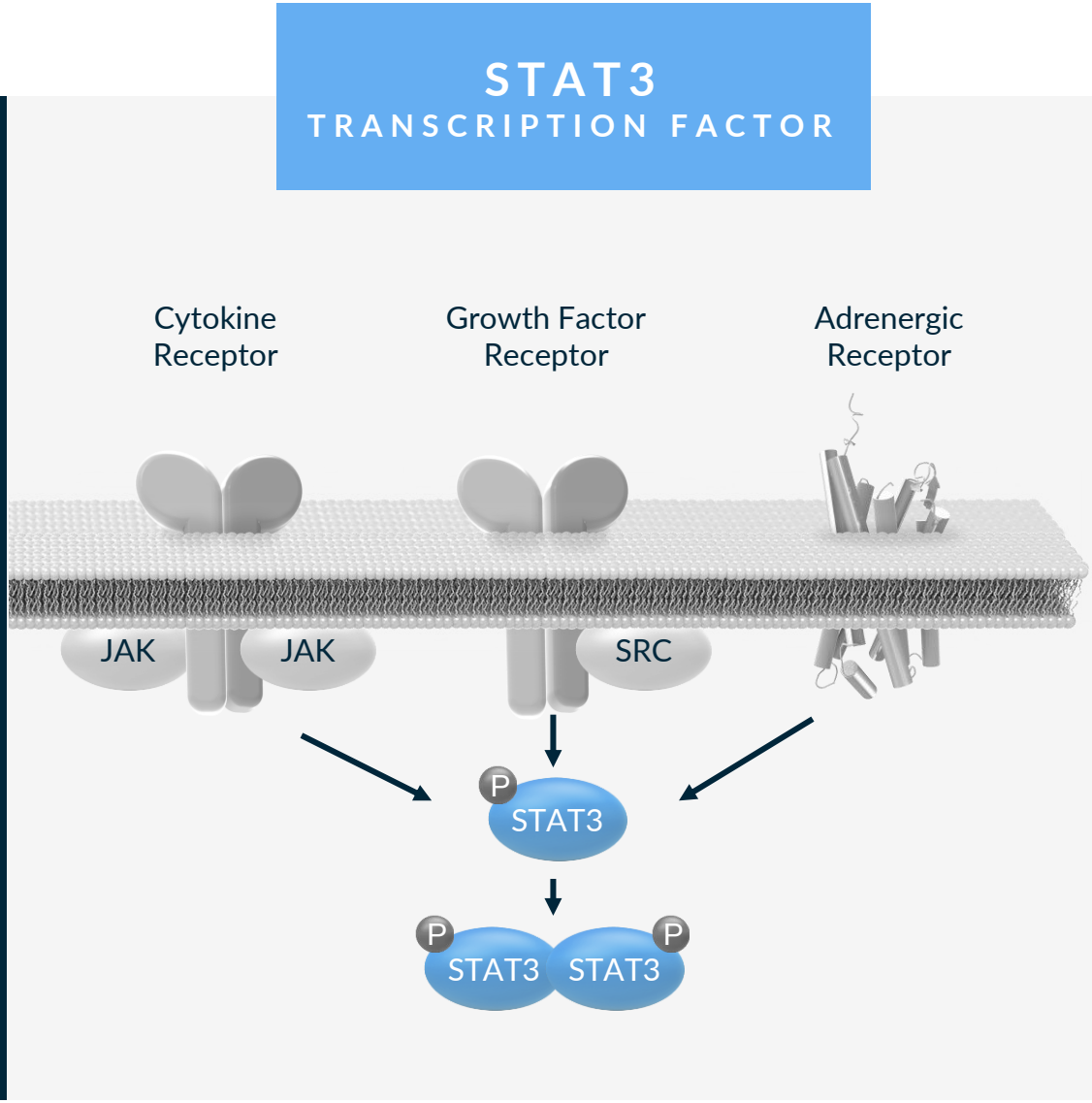
- STAT3 is a largely undrugged transcription factor activated through cytokine and growth factor receptors via JAKs and non-JAK mediated mechanisms
- STAT3 plays a role in tumor biology, evasion of immune surveillance and inflammation/fibrosis
- No known drugs selectively block STAT3 broadly across all relevant cell types or address both phosphorylation-dependent and –independent functions of STAT3

Clinical Pathway Validation

- Multiple drugs approved that target upstream effectors signaling through STAT3 (ruxolitinib [JAK1/2], tocilizumab [IL-6R], belumosudil [ROCK-2])

Human Genetics

- T cell lymphomas/leukemias responsive to JAK inhibition have STAT3 and/or JAK mutations and STAT3 pathway hyperactivation
- cHL responsive to anti-PD-1 and JAK inhibition has 9p24.1 JAK2/PD-L1/L2 amplicon and STAT3 activation



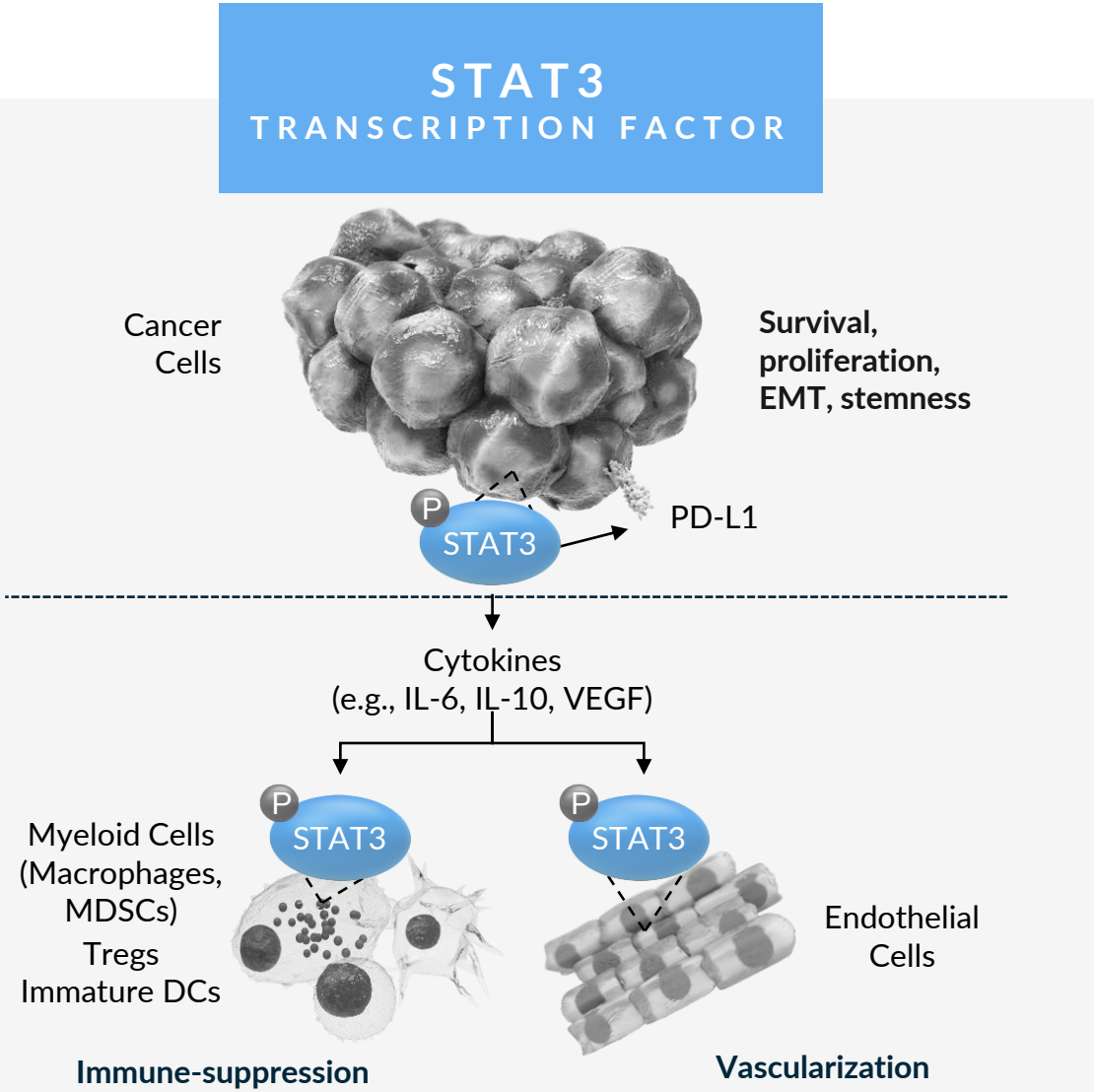
STAT3 Has Unique Tumor Cell Intrinsic and Extrinsic Mechanisms

Tumor Intrinsic

- Hyperactivation of STAT3 via dysfunctional receptor signaling or genomic aberrations lead to tumorigenic processes.
- Therapeutic opportunities lie in STAT3-dependent malignancies (e.g., T cell malignancies and cHL) & in mitigation of resistance mechanisms driven by STAT3 signaling (e.g., TKI; KRAS G12Ci resistance)

Tumor Extrinsic

- STAT3 plays pivotal role in generation and maintenance of an immunosuppressive tumor microenvironment.
- Opportunities in anti-PD-1 sensitive tumors (e.g., cHL) and multiple heme and solid tumor indications poorly sensitive to immune checkpoint inhibitors that can be sensitized by TME remodeling (e.g., NSCLC with inactivating mutations in STK11, others)



KT-333: First-in-Class STAT3 Degrader

Multiple Monotherapy and Combination Development Opportunities in Liquid and Solid Tumors

	Hematological Malignancies	Solid Tumors
Pre-Clinical	• **Durable single agent antitumor activity** across multiple T-cell lymphoma models (ALCL and CTCL) • **PD-L1 and JAK2 overexpression in cHL** due to 9p24.1 amplicon with associated **high pSTAT3 expression**	• **TME remodeling with induction of IFN-γ signature** in solid tumor models leading to **sensitization to anti-PD-1**
Clinical	• Antitumor activity in ongoing Phase 1a study in **cHL, CTCL and NK-Cell Lymphoma** with **multiple PRs/CRs**	• **IFNγ signature response** in blood and tumor in ongoing Phase 1a study indicates **remodeling of TME**
Development Opportunities	• **Monotherapy opportunities with accelerated registration path** across several high unmet need lymphoma indications	• Opportunities in **combination with anti-PD-1** across different CPI-sensitive indications, and possible **monotherapy and combo opportunities in certain genotype-defined sensitive patient populations**

	U.S. Incidence	R.O.W. Incidence
Classical Hodgkin Lymphoma (cHL)	~8.8k	~11.4k
Peripheral T-cell lymphoma (PTCL)	~3.6k	~4.5k
Cutaneous T-cell lymphoma (CTCL)	~3.6k	~2.5k
Large granular lymphocyte leukemia (LGL-L)	<1k	<1k

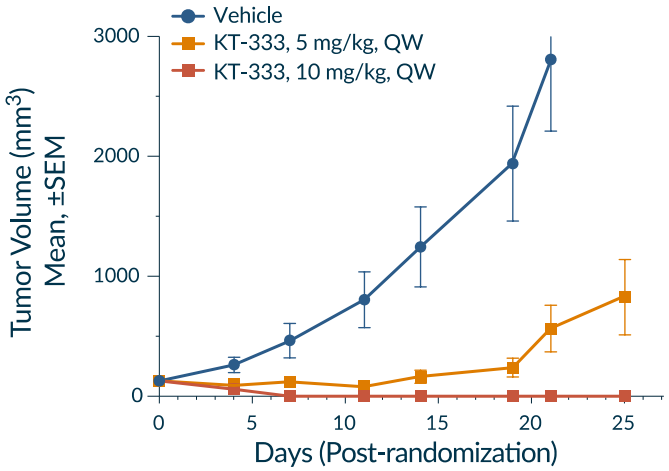
Potential Patient Impact

Combination potential to re-sensitize solid tumors to CPI therapy and/or enhance the response rates of CPI therapies across approved solid tumor indications, including NSCLC, SCLC, melanoma, SCCHN, RCC, UC, TNBC, MSI-H CRC, dMMR endometrial

Mono- and combination therapy potential in **biomarker-selected NSCLC, breast, pancreatic, cervical, others**

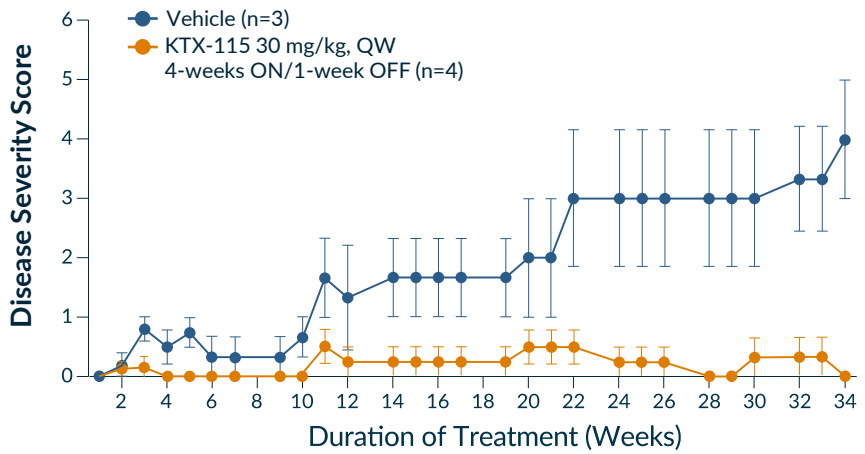
Sources: GlobalData, NORD. Note: R.O.W = France, Germany, Italy, Spain, UK, and Japan.

Durable Antitumor Activity of STAT3 Degradation as a Single Agent in Preclinical Models of T cell Lymphoma



ALK+ ALCL
SU-DHL-1

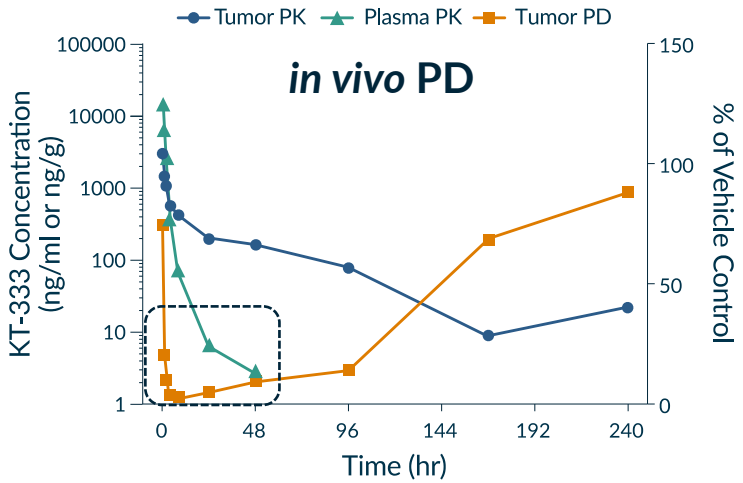
64th ASH® Annual Meeting and Exposition



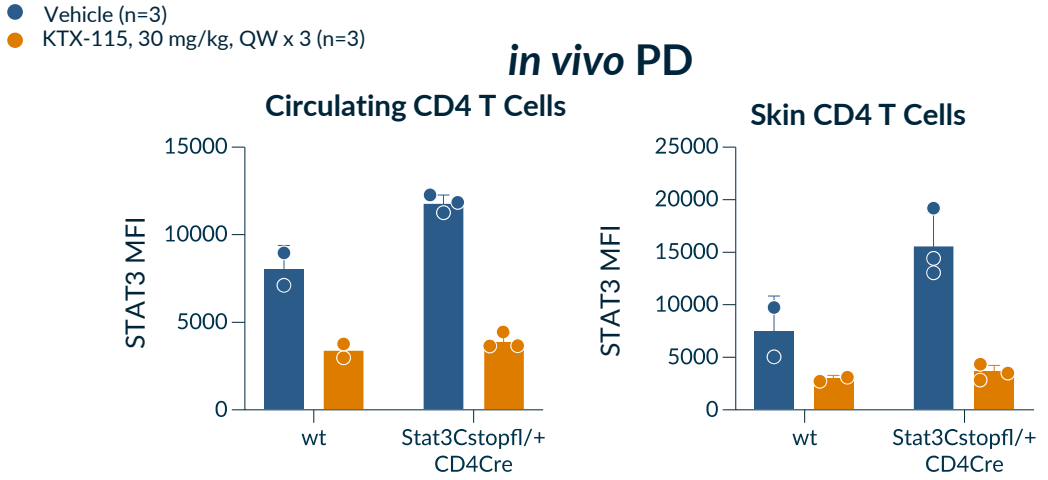
CTCL
GEMM *Fanok et al. (2018)*
Collaboration with NYU

64th ASH® Annual Meeting and Exposition

Complete Tumor Regressions Associated with >90% STAT3 KD for ~48h Achieved with Intermittent Dosing of KT-333



STAT3 Degradation Results in Disease Amelioration in a CTCL Preclinical Model with Potent Degradation of STAT3 in CD4+ T Cell-of-Origin



Genetic and Clinical Validation for Targeting STAT3 in cHL

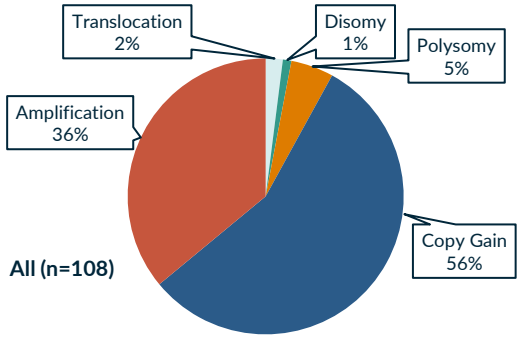
Genetic Basis for Anti-PD-1 Activity in cHL

Chromosome *9p24.1/PD-L1/PD-L2* Copy Number Alterations a Defining Feature in Newly Diagnosed Hodgkin Lymphoma

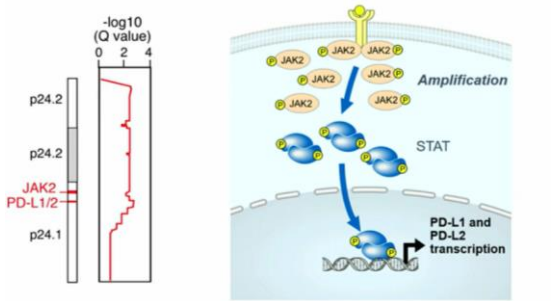
Cases were classified by the highest observed level of 9p24.1 alteration

107/108 cases had 9p24.1 alterations

Genetic basis for sensitivity to PD-1 blockade?



9p24.1 Amplicon Block in CHL and PMBL

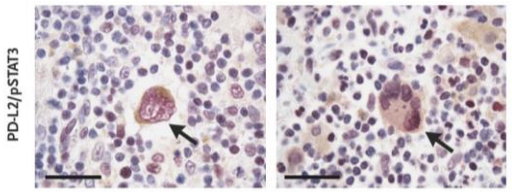


PD-L1 and PD-L2 Copy Gain and Further Induction via JAK2/STAT Signaling

Green et al., *Blood* (2010)

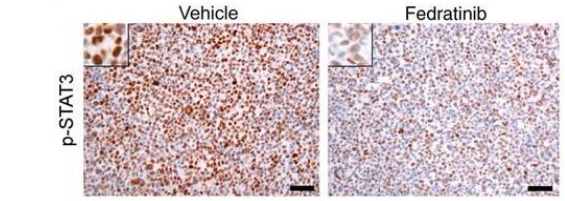
- Anti-PD-1 drugs nivolumab and pembrolizumab highly active and approved for R/R cHL

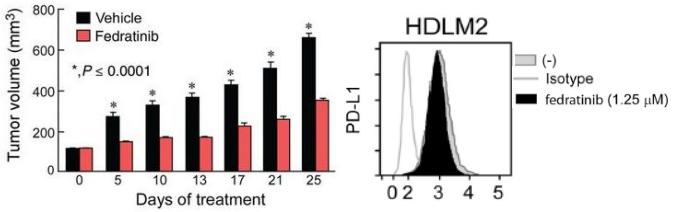
STAT3 Activation in cHL and Impact of JAK-STAT Inhibition



Patient No.	Polysomy 9p	PDL1/2 Gain	PDL1/2 Amplification	PD-L1	PD-L2	IHC-positive HRS cells	Nuclear pSTAT3	EBER
1	+	–	–	+	+	+	–	
2	+	–	–	+	+	+	–	
3	+	–	–	+	+	+	–	
4	+	+	–	+	+	+	–	
5	+	+	–	+	+	+	–	
6	+	+	–	+	+	+	+	
7	+	+	+	+	+	+	–	
8	+	+	+	+	+	+	–	
9	–	+	+	+	+	+	–	
10	–	–	+	+	+	+	–	

Ansell *et al. NEJM* (2015)

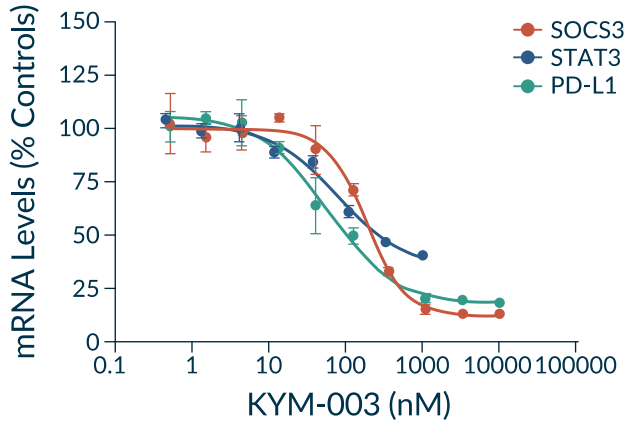


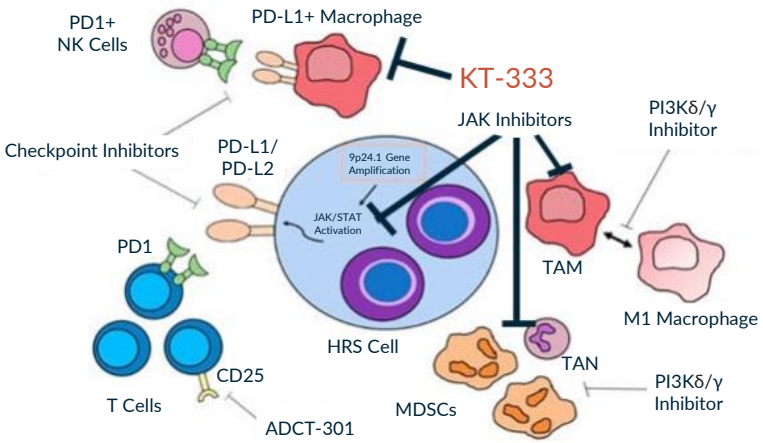


Hao et al., *Clin Cancer Res* (2014)

STAT3 Degrader: Potential to Impact JAK-STAT *and* PD-L1/L2 Pathways

PD-L1 Downregulation by STAT3 Degrader





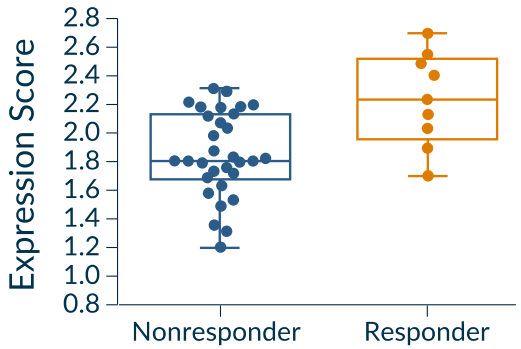
STAT3 Degradation Elicits an IFNγ Gene Signature in TME and Sensitizes Solid Tumor Mouse Models to PD-1 Inhibition

IFNγ mRNA Signature Predictive of Clinical Responses to Anti-PD-1 (Pembrolizumab)

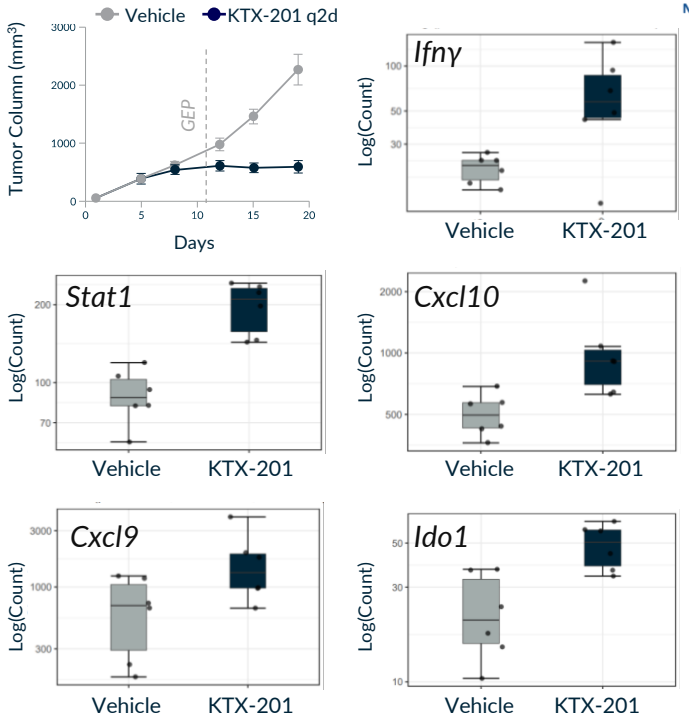
IFNγ, and Expanded Immune Gene Signature

IFN-γ
IDO1
CXCL10
CXCL9
HLA-DRA
STAT1
IFNG

IFNγ Signature



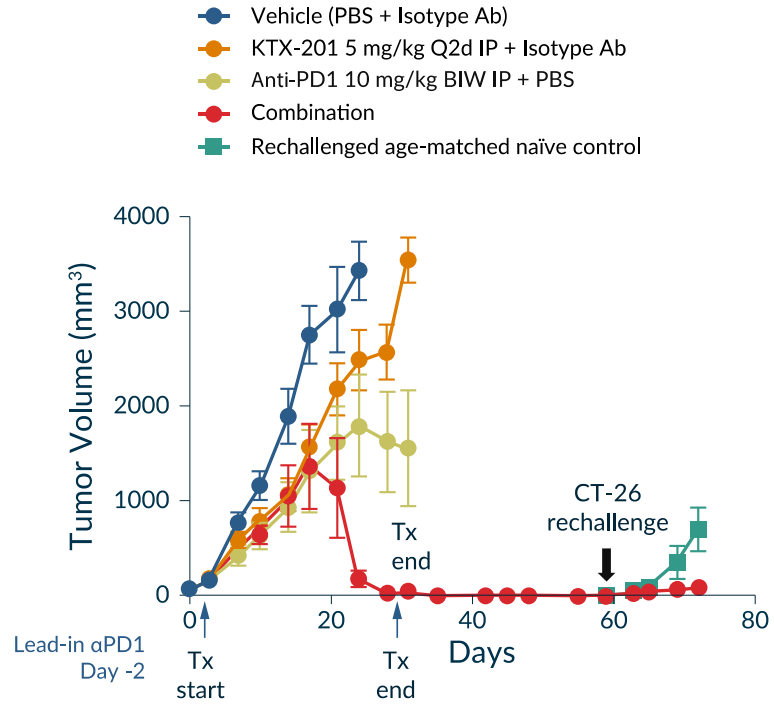
IFNγ mRNA Signature in TME Elicited by STAT3 Degradation in CT-26 Preclinical Model



On treatment - Day 11; n=6/grp

STAT3 Degrader Sensitizes CT-26 Model to Anti-PD-1 via Activation of Antitumor Immunity

CT-26



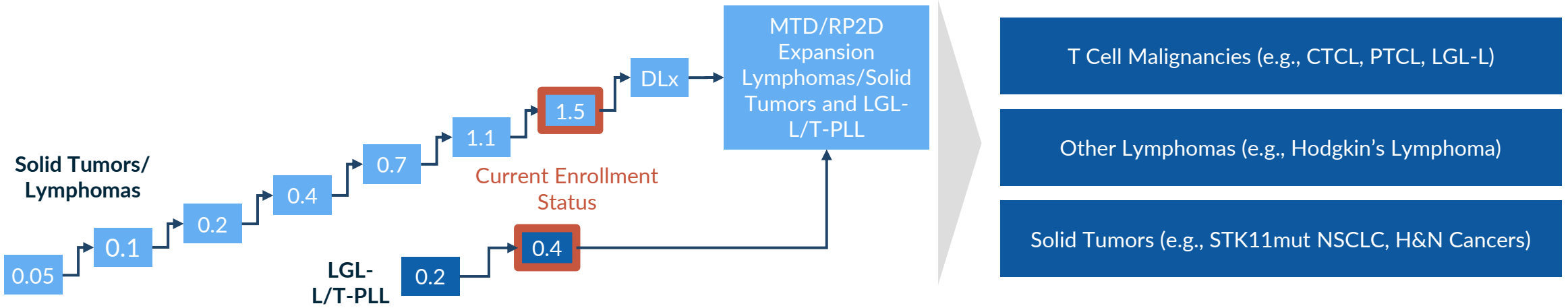
KT-333: Phase 1, Multicenter, Dose-Escalation and Expansion Trial to Evaluate KT-333

Adult Patients with Lymphomas, Leukemias and Solid Tumors

Phase 1a
Dose Escalation & MTD/RP2D Expansion

Phase 1b
Dose Expansion Opportunities

KT-333 IV Weekly in 28-day Cycles



Key Objectives	Phase 1a	Phase 1b
Primary	• Safety/Tolerability and MTD and RP2D	• Safety/Tolerability at RP2D in Patients with Lymphoma/Leukemia and Solid Tumors
Secondary	• PK Parameters of KT-333 • Preliminary Estimates of Activity	• Preliminary Clinical Activity (ORR, DoR, PFS, DCR, OS) • PK Parameters of KT-333
Exploratory	• PD Effects of KT-333	• PD Effects of KT-333

MTD: Maximum Tolerated Dose. RP2D: Recommended Phase 2 Dose. ORR: Overall Response Rate

Phase 1a Enrollment

	Dose Level 1 0.05 mg/kg (n=4)	Dose Level 2 0.1 mg/kg (n=4)	Dose Level 3 0.2 mg/kg (n=8)	Dose Level 4 0.4 mg/kg (n=14)	Dose Level 5 0.7 mg/kg (n=8)	Dose Level 6 1.1 mg/kg (n=6)	Dose Level 7 1.5 mg/kg (n=3)	Overall (N=47)
Age (years)								
Median (min, max)	64.5 (57, 70)	63.5 (59, 74)	70.5 (40, 76)	63.5 (42, 81)	66.0 (30, 75)	45.5 (24, 73)	61.0 (50, 65)	65.0 (24, 81)
Sex (n, (%))								
Male	3 (75.0)	1 (25.0)	4 (50.0)	12 (85.7)	6 (75.0)	2 (33.3)	-	28 (59.6)
ECOG								
0	1 (25.0)	-	4 (50.0)	5 (35.7)	4 (50.0)	4 (66.7)	1 (33.3)	19 (40.4)
1	3 (75.0)	4 (100)	4 (50.0)	9 (64.3)	4 (50.0)	1 (16.7)	2 (66.7)	27 (57.4)
2	-	-	-	-	-	1 (16.7)	-	1 (2.1)
Prior Systemic Therapy Regimens								
≥4	2 (50.0)	4 (100.0)	5 (62.5)	7 (50.0)	3 (37.5)	4 (66.7)	2 (66.7)	26 (55.3)
Tumor Type								
Solid Tumor‡	3 (75.0)	2 (50.0)	5 (62.5)	7 (50.0)	3 (37.5)	-	1 (33.3)	21 (44.7)
CTCL	1 (25.0)	1 (25.0)	-	3 (21.4)	2 (25.0)	4 (66.7)	-	11 (23.4)
T-Cell LGL-L	-	-	2 (25.0)	-	2 (25.0)	-	-	4 (8.5)
Hodgkin's	-	-	-	2 (14.3)	-	2 (33.3)	-	4 (8.5)
PTCL	-	1 (25.0)	-	1 (7.1)	-	-	1 (33.3)	3 (6.4)
T-PLL	-	-	1 (12.5)	1 (7.1)	-	-	-	2 (4.3)
NK-Cell Lymphoma	-	-	-	-	-	-	1 (33.3)	1 (2.1)
B-Cell Lymphoma	-	-	-	-	1 (12.5)	-	-	1 (2.1)

- As of June 3, 2024, 47 patients enrolled across Dose levels 1-7 (0.05–1.5 mg/kg)
- Patients with leukemias (T-cell LGL and T-PLL) are evaluated with leukemia-specific DLT criteria and separated out into separate dose escalation based on DLTs observed during dose escalation

‡ = colorectal (4); head and neck (3); pancreatic (2); anal; appendiceal; cervical; cholangiocarcinoma; colon adenocarcinoma; duodenal; endometrial; gallbladder; ovarian, peritoneal, rectal and renal (n=1 each)

KT-333 Safety Summary: DL1-7

Data cut-off date of June 3, 2024

- Overall, KT-333 well-tolerated with primarily Grade 1-2 AEs
- Most common AEs related to KT-333 in >10% of all patients (n=47):
  - Stomatitis (38%)
  - Fatigue (17%)
- Related Grade 3 AEs were stomatitis, n=2; arthralgia, n=1; fatigue, n=1; weight decreased, n=1 (there were no >Grade 3* AEs considered related to KT-333)
- Related SAEs were Grade 2 pyrexia (n=1) in a patient with NK-Cell lymphoma and Grade 3 stomatitis in a patient with LGL-L (was also a DLT)
- Two DLTs observed in LGL-L patients, Grade 3 stomatitis and arthralgia, at DL5; one DLT observed in a lymphoma patient, Grade 3 fatigue, at DL7

* Two Grade 4 events were observed: DL4: CTCL patient with Grade 4 Toxic epidermal necrolysis and an LGL-L patient in DL5 with Grade 4 Neutropenia, both considered not related to KT-333. No Grade 5 events.

Responses Observed Across Multiple Tumor Types During Dose Escalation of KT-333

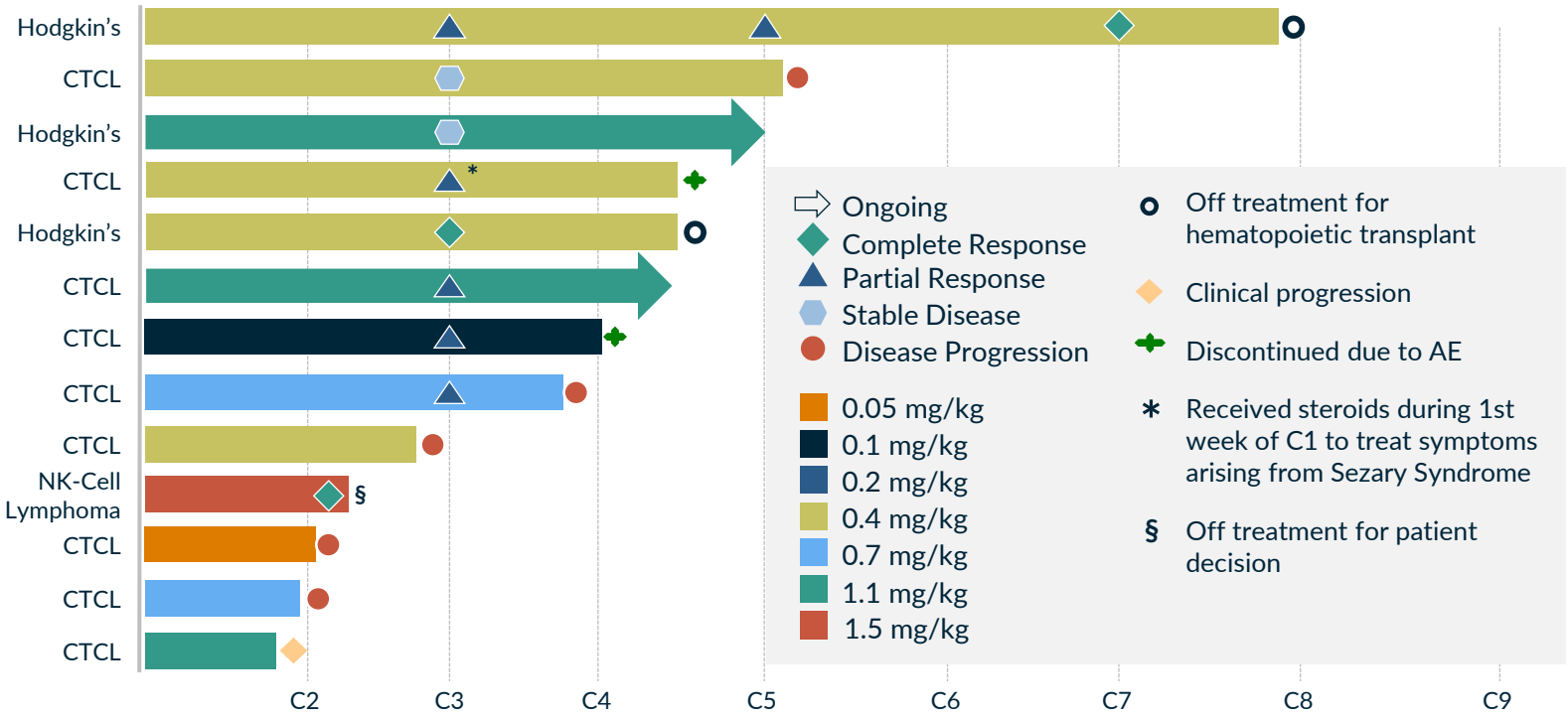
Data cut-off date of June 3, 2024

Clinical Responses

	Best Overall Response[1]				
	Hodgkin's Lymphoma (n=3)	NK-Cell Lymphoma (n=1)	CTCL[3] (n=9)	Solid Tumor (n=14)	Other Hematologic Malignances[4] (n=5)
Complete Response	2	1[2]	-	-	
Partial Response	-	-	4	-	
Stable Disease	1	-	1	4	
Progressive Disease	-	-	4[5]	10	5

[1]The patient totals listed above represent the number of patients enrolled that were disease evaluable for response assessment at the time of cut-off; [2]PET-CR; [3]Cutaneous T-Cell lymphoma; [4]Includes two patients with peripheral T-Cell lymphoma and one each of B-Cell NHL, LGL-L and T-PLL; [5]Includes one patient with clinical progression

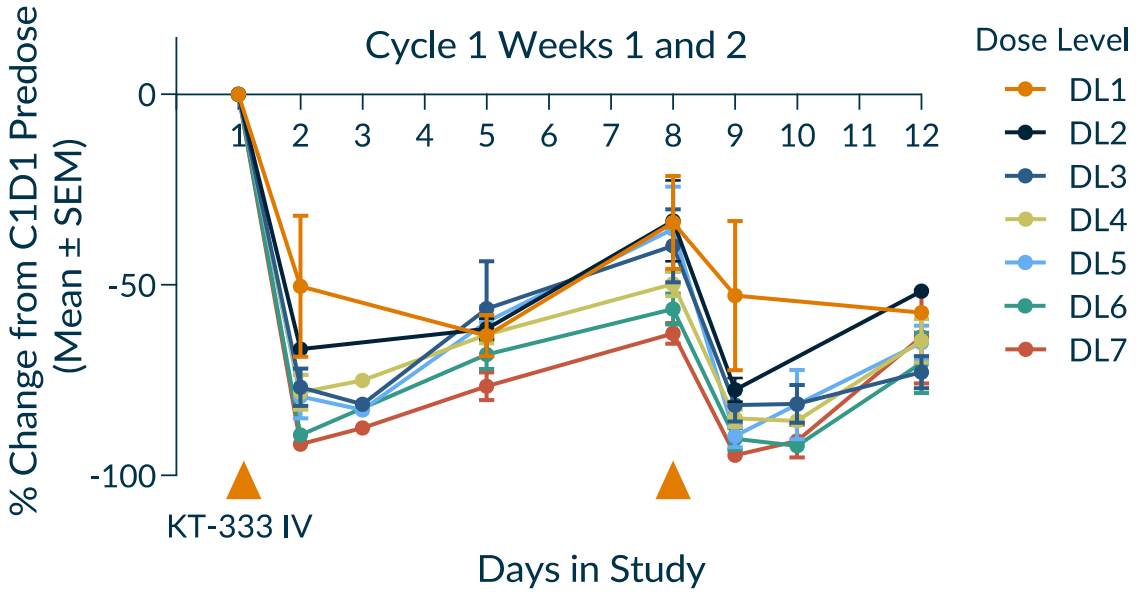
Duration of Time on Treatment: Disease Evaluable CTCL, Hodgkin's and NK-Cell Lymphoma Patients



Antitumor activity observed across multiple hematological malignancies, including complete responses in two patients with Hodgkin's lymphoma moving to potentially curative stem cell transplants after treatment

Robust STAT3 Degradation in PBMCs

Timecourse of STAT3 Degradation in PBMCs



- Strong proof-of-mechanism demonstrated for KT-333 with up to 95% mean maximum degradation of STAT3 in PBMCs at DL7

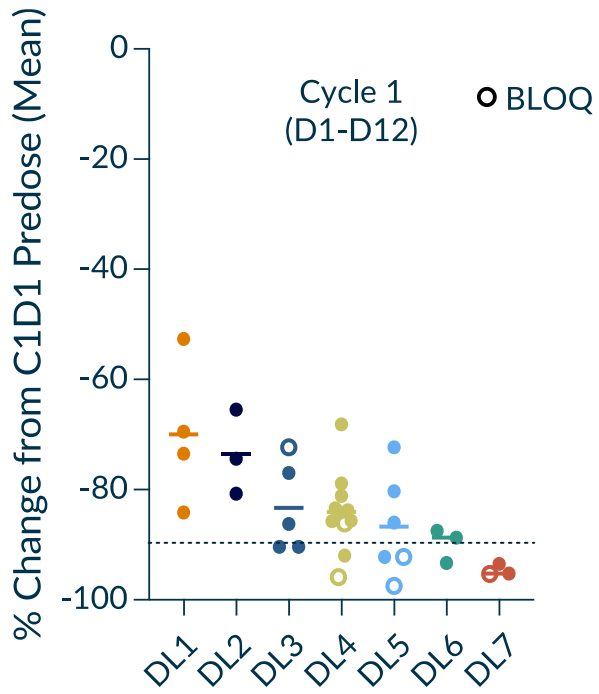
Maximum Degradation of STAT3 in PBMCs

Per Cohort (min, max; n)

Dose Level	Cycle 1 D1-D12
0.05 mg/kg	-69.9% (-52.6%, -84.1%; 4)
0.1 mg/kg	-73.5% (-65.5%, -80.7%; 3)
0.2 mg/kg	-83.3% (-72.3%*, -90.4%; 5)
0.4 mg/kg	-84.0% (-68.1%, -95.9%*; 11)
0.7 mg/kg	-86.8% (-72.3%, -97.5%*; 6)
1.1 mg/kg	-89.8% (-87.5%; -93.3%; 3)
1.5 mg/kg	-94.7% (-93.5%, -95.3%*; 3)

*BLOQ

Per Patient (min, max; n)

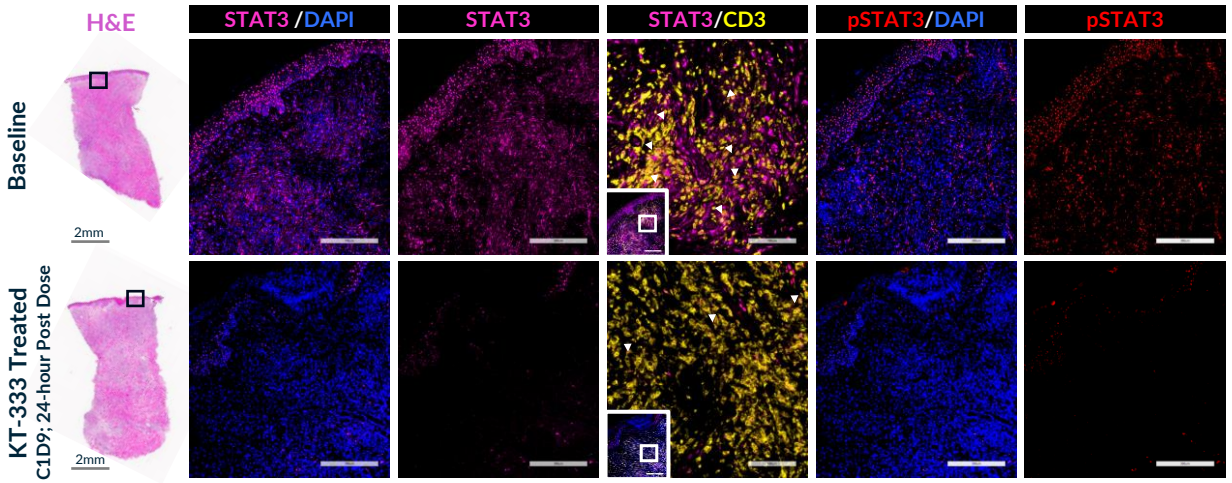


Maximum STAT3 Degradation was > 90% in 9 Patients in Cycle 1 of DL3 through DL7

Shastri et al., *EHA* (2024)

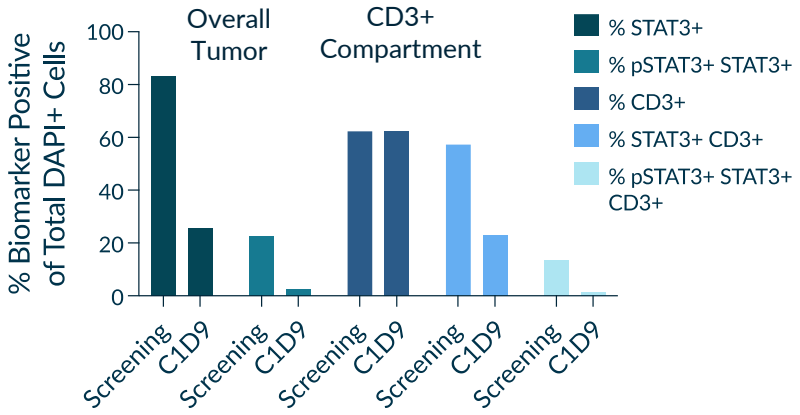
Robust STAT3 Knockdown and Induction of Antitumor IFN-γ Response in Tumor Biopsies

KT-333 Leads to Marked Reductions in STAT3, pSTAT3 in Tumor Tissue from a CTCL Patient

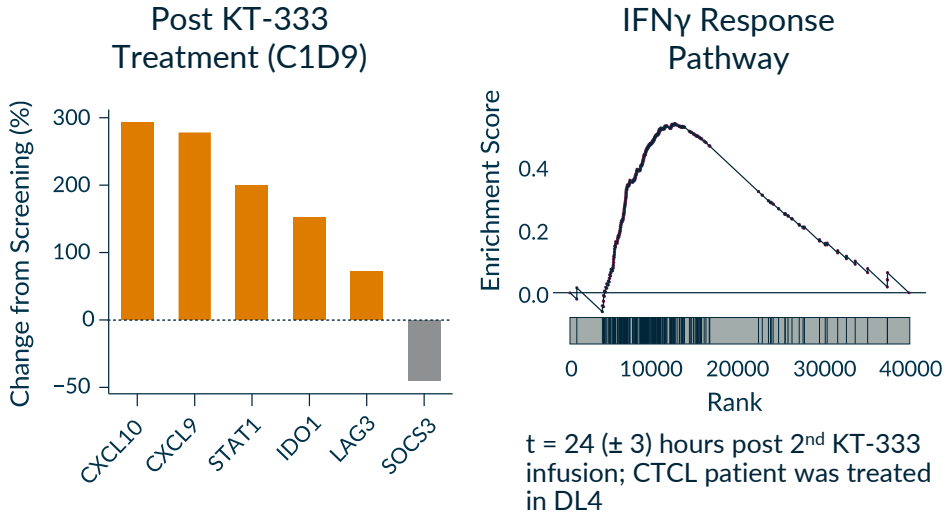


STAT3 and pSTAT3 % Positive Cells are Reduced

- 69% & 87% respectively in the post treatment tumor biopsy compared to screening



KT-333 Leads to Induction of IFNγ Pathway Response and Downregulation of SOCS3 in a CTCL Tumor



t = 24 (± 3) hours post 2nd KT-333 infusion; CTCL patient was treated in DL4

- KT-333 resulted in robust reduction of STAT3 and pSTAT3 expression by 69% and 87% in a CTCL tumor biopsy in DL4
- Induction of IFN-γ signature in tumor by KT-333 consistent with preclinical findings where effect in syngeneic solid tumor model associated with enhanced response to anti-PD-1

Shastri et al., *EHA* (2024)

STAT3 Degrader: KT-333

First-in-class opportunity to address STAT3 driven pathology across broad indications

Recent Clinical Data*

Strong PD effect in blood with mean maximum STAT3 degradation of 90-95% at DL6-7 and maximum degradation up to 98%

STAT3 and pSTAT3 positive cells reduced by 69% and 87% in tumor at DL4; IFN-γ response observed in tumor and blood

KT-333 safe and well-tolerated at top dose levels in lymphomas and solid tumors

CRs achieved in 2 of 3 cHL patients who progressed after prior BV and CPI enabling HSCT in both

PRs achieved in 4 of 9 CTCL patients; CR in $STAT3^{mut}$ NK-Cell Lymphoma

Significant Opportunity

Activity in cHL identifies potential 3L monotherapy and 2L anti-PD1 combination development pathways

CTCL activity shows potential in R/R disease that could be further enhanced through combinations

Response in $STAT3^{mut}$ lymphoma further highlights potential in pts with STAT3 pathway hyperactivation

Opportunity for expansion into solid tumors in combination with immune checkpoint inhibitors (e.g., anti-PD1) and targeted therapy (e.g., KRAS inhibitors)

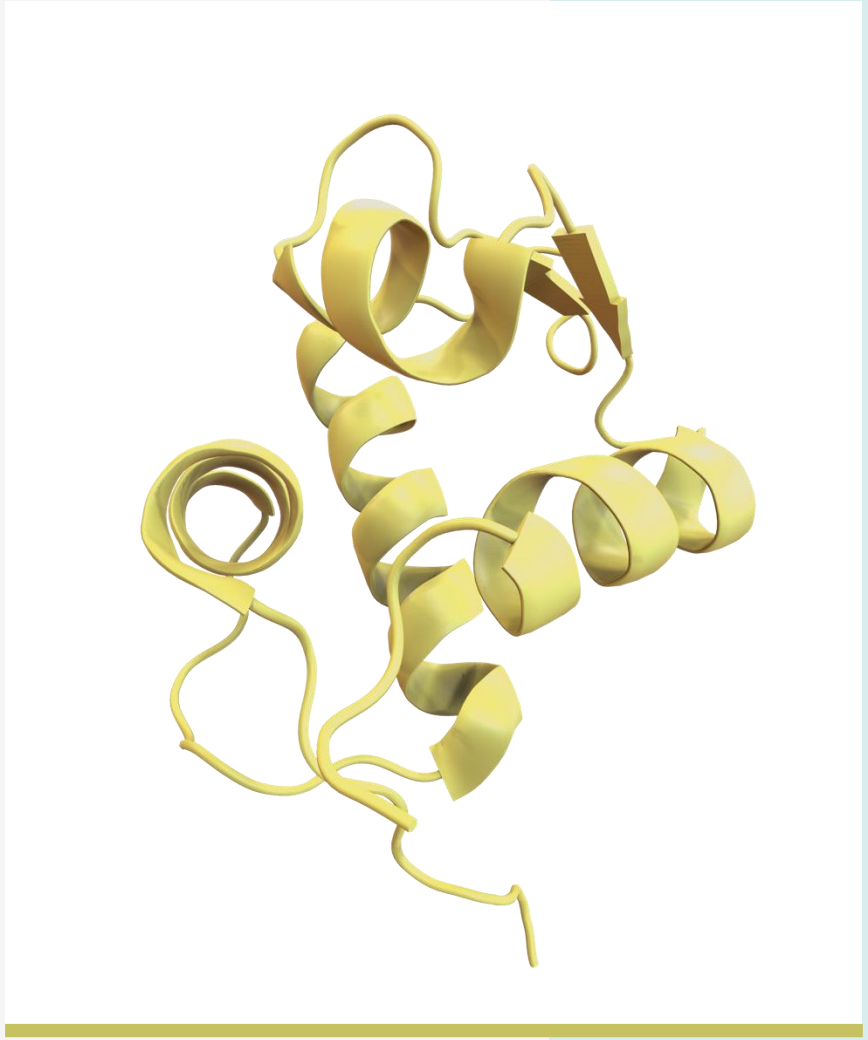
Complete Recruitment & Phase 1 Data: 2H24

Completion of enrollment in the Phase 1a dose escalation study and data set to be shared in the second half of 2024, with remaining enrollment focused on cHL

Evaluate next steps including potential Ph1b expansions in cHL and CTCL and evaluation of anti-PD1 combination in cHL

Explore opportunities for evaluation of combination with anti-PD1 in solid tumors

*As of June 3, 2024, data cut-off date.



First-in-Class MDM2 Degrader Program

MDM2 Biology and Target Rationale

Target Biology and Rationale

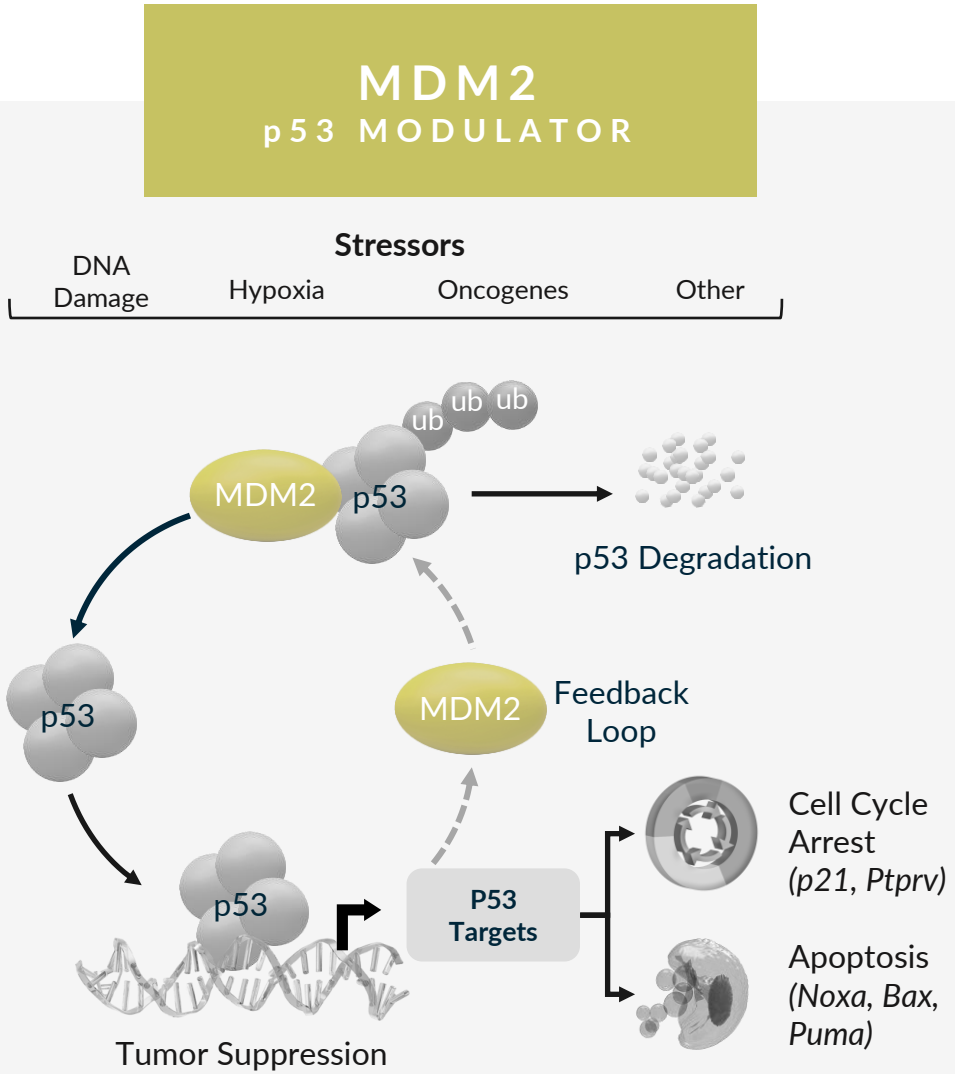
- MDM2 is the E3 ligase that modulates p53, the largest tumor suppressor
- MDM2 overexpression and amplification can inactivate p53 in the 50% of tumors that are p53 WT
- Activity of small molecule inhibitors of MDM2 limited by p53-MDM2 feedback loop that interferes with pharmacologic effect of SMIs

Clinical Pathway Validation

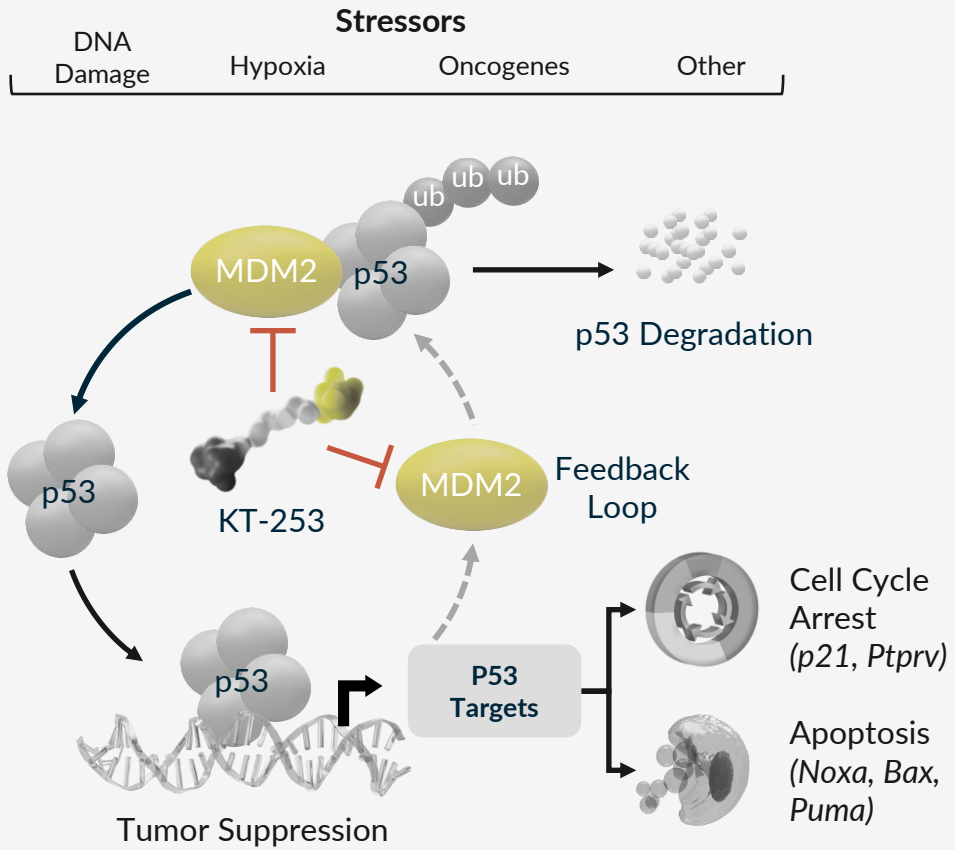
- MDM2 SMIs have demonstrated p53 pathway activation (e.g. plasma GDF-15 elevation) and modest monotherapy clinical activity in AML as well as activity in Merkel Cell Carcinoma and Myelofibrosis

Human Cancer Genetics

- DepMap demonstrated MDM2 dependency across multiple p53 WT cell lines
- MDM2 degradation has potential to phenocopy impact of genetic deletion in p53 WT tumors



MDM2 Degrader Advantage



- Unlike small molecule inhibitors, degraders remove the protein, which can overcome the p53-dependent feedback loop that upregulates MDM2 production, enabling an acute apoptotic response
- Induction of acute apoptotic response in tumors allows time for recovery of normal cells and an increase TI vs SMI
- Emerging gene signature of sensitivity to MDM2 degrader mechanism to be leveraged to prospectively select patients in Phase 1b and beyond

KT-253: Potential Best-in-Class p53 Stabilizer

Potential to Treat Numerous p53WT Tumors

	Hematological Malignancies	Solid Tumors
Pre-Clinical	• As monotherapy, **robust responses in AML/ALL models**, including venetoclax-resistant AML, and **strong combinatorial effect seen with venetoclax** in venetoclax-resistant AML models	• **Preclinical activity across variety of solid tumors**, including Merkel cell carcinoma (MCC), pediatric tumors and subsets of common adult tumors • **Gene signature of sensitivity** to degrader mechanism emerging from adult solid tumor models
Clinical	• Recently initiated AML enrollment with early evidence of p53 pathway activation	• **PR in MCC patient at DL1** in ongoing Phase 1a study shows translation of preclinical sensitivity to the clinic
Development Opportunities	• Monotherapy and combination opportunities in **AML,** and potential opportunities across **Myelofibrosis, MDS, ALL and TP53^{WT} lymphomas**	• As monotherapy across a **subset of adult and pediatric solid tumors**, to be **informed by emerging gene signature** with potential for tumor agnostic development path

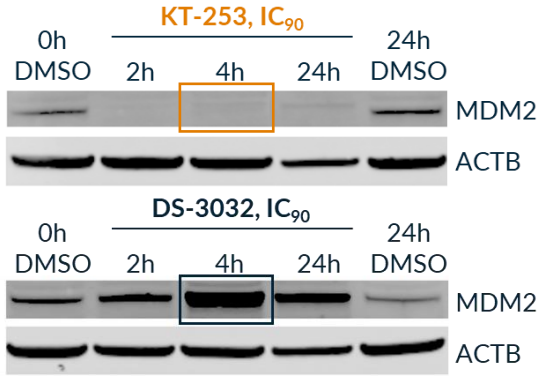
	U.S.	R.O.W.
	Incidence	Incidence
Acute Myeloid Leukemia (AML)	~21k	~21k
Myelodysplastic Syndromes (MDS)	~41k	~58k
Myelofibrosis (MF)	~2k	~3k

	Potential Patient Impact
Solid Tumors	Subsets of various p53 functional adult solid tumors **(melanoma, colorectal, lung, gastric, breast)** selected based on emerging gene signature of sensitivity, and majority of **Merkel cell carcinoma, rhabdomyosarcoma, neuroblastoma, Ewing sarcoma**

Note: R.O.W = France, Germany, Italy, Spain, UK, and Japan; Source: GlobalData

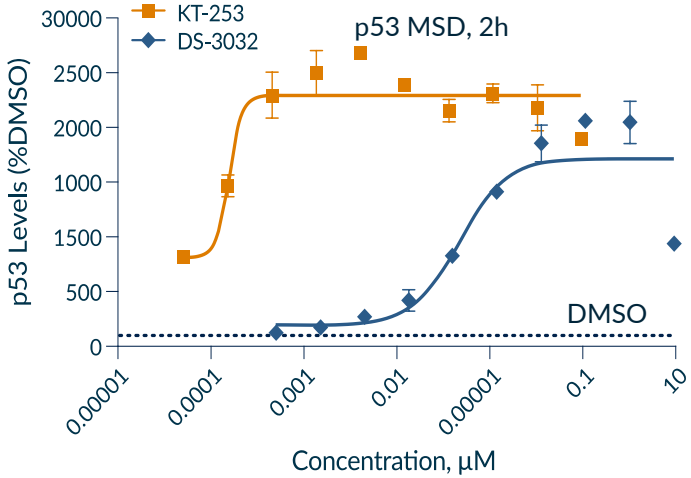
KT-253's Potent p53 Stabilization with Brief Exposures Drives Apoptosis in Cancer Cells

KT-253 Keeps MDM2 Levels Undetectable, Stabilizing p53

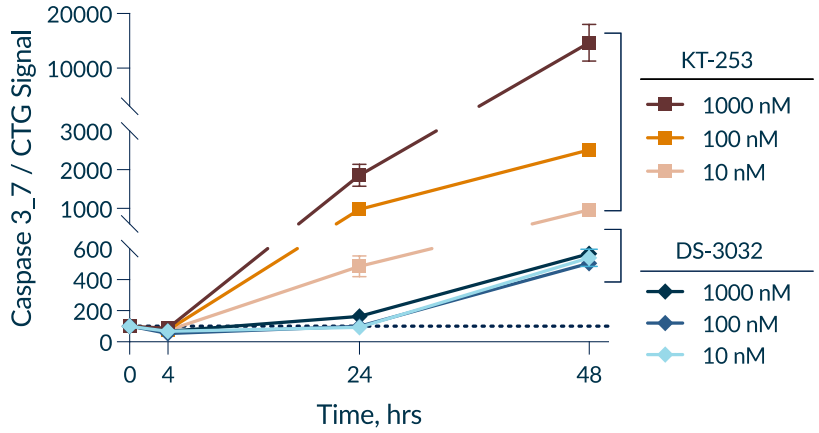


MDM2 levels are increased by the small molecule inhibitor (feedback loop), impairing p53 stabilization

KT-253 Strongly Stabilizes p53



4hr Target Coverage by KT-253 Is Sufficient to Induce Apoptosis

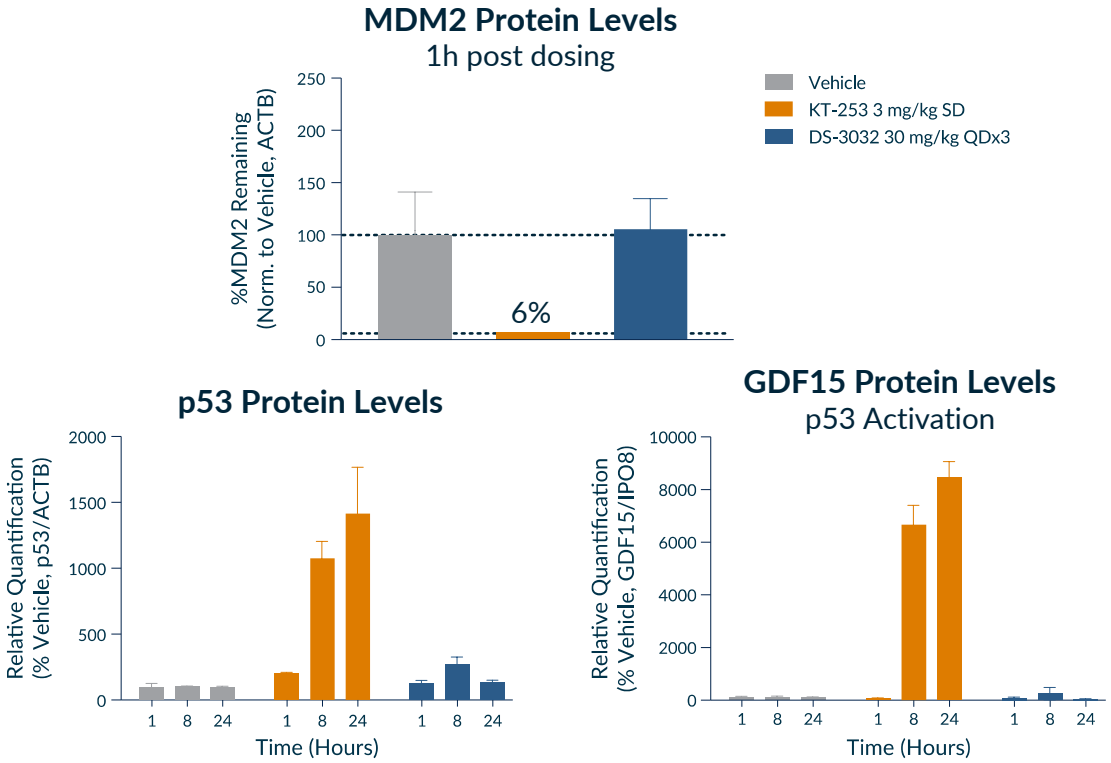


Compound	KT-253	DS-3032	AMG-232
Company	Kymera	Sankyo/Rain	Amgen/Kartos
Clinical stage	Phase I	Completed/Terminated	Multiple Ph II; combo AML
RS4;11 IC_{50} (nM) (Cell Viability)	0.3	67	280
MDM2-HiBiT, DC_{50} (nM) (Degradation)	0.4	-	-

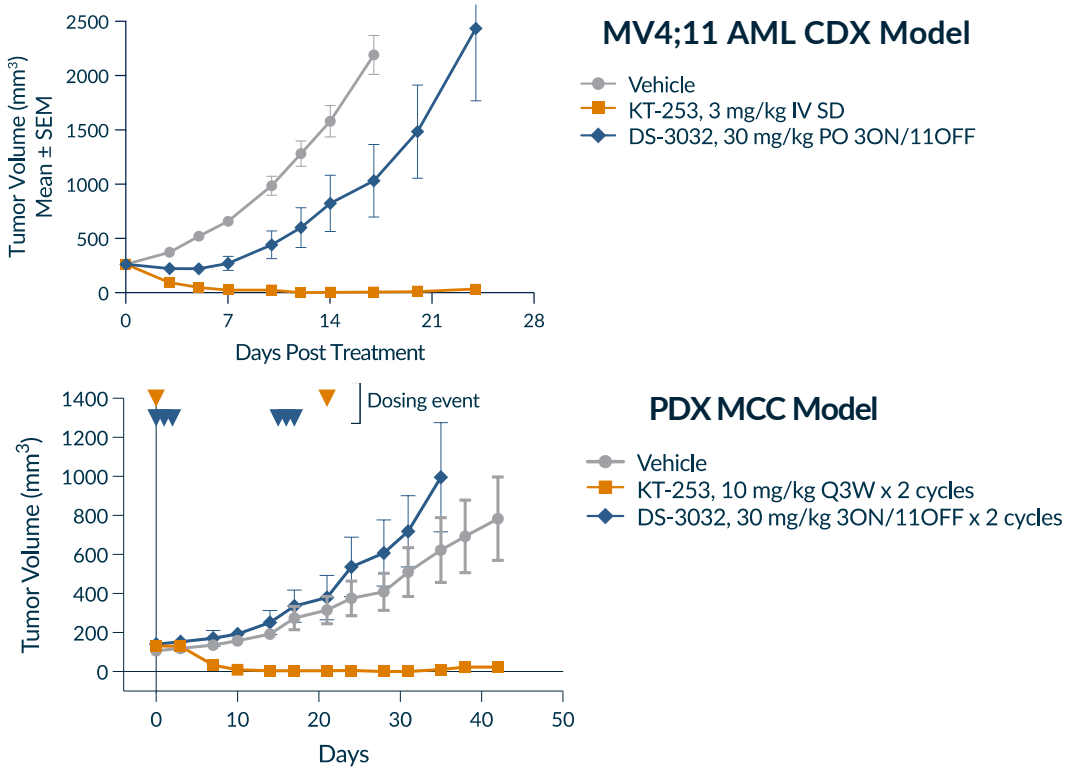
- KT-253 is **>200-fold more potent** in tumor cell viability assays than SMI's
- Data supports intermittent dosing schedule of KT-253 can drive efficacy while increasing therapeutic index

KT-253 Potently Degrades MDM2 Leading to Pathway Impact and Antitumor Activity Superior to SMI in AML and MCC Models

MDM2 Degradation Leads to Superior P53 Upregulation vs SMI



MDM2 Degradation Leads to Superior Antitumor Responses in AML and MCC Preclinical Models



- Targeted proteomic analysis of RS4;11 tumors demonstrates robust degradation of MDM2 one hour post dosing and associated pathway activation biomarkers including p53 and GDF15

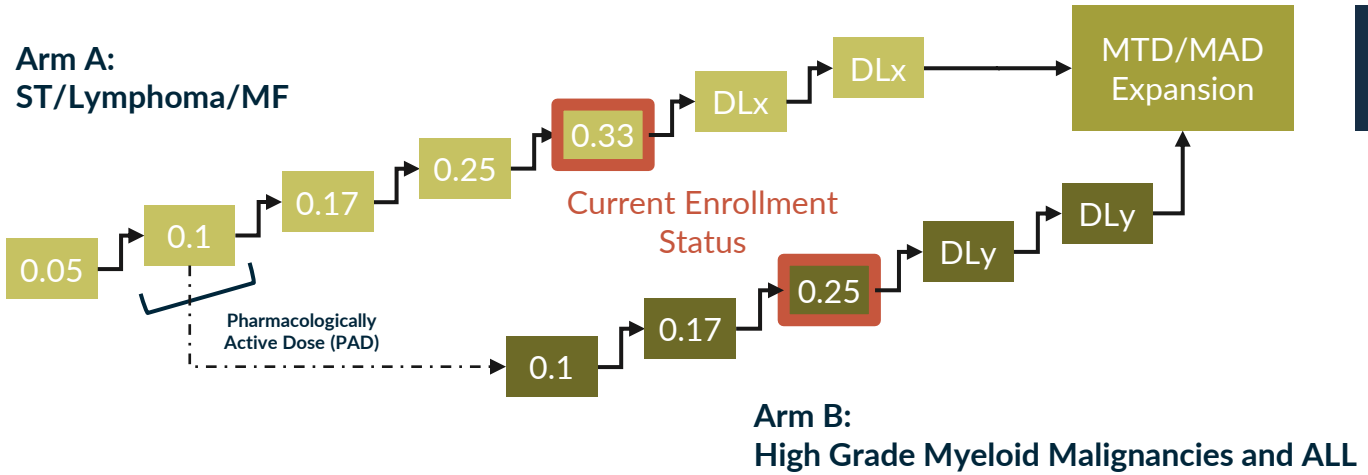
- Sustained tumor regressions in MV4;11 (AML) CDX models after a single 3 mg/kg KT-253 dose
- KT-253 demonstrated robust antitumor activity in Merkel Cell Carcinoma
- No antitumor activity observed with clinically relevant dosing regimen of SM (DS-3032)

KT-253 Phase 1a: Study Design

Phase 1a

Arm A: R/R Lymphoma, Solid Tumors or Myelofibrosis (MF); Arm B: High Grade Myeloid Malignancies and ALL

Regimen: Single Agent KT-253 mg/kg Intravenous (IV) Infusion Every 3 Weeks



Phase 1b
AML
R/R p53^{wt} AML

Exploratory Expansion p53^{wt}
Solid Tumor
n=20

p53^{WT} R/R AML at
MTD/MAD
n = 20

p53^{WT} R/R AML at
Dose lower than MTD/MAD
n = 20

Key Objectives	Phase 1a
Primary	• Safety, MTD and/or RP2D
Secondary	• PK • Preliminary Efficacy
Exploratory	• PD

Clinical Trial Status*

- Arm A: R/R Solid Tumors, Lymphomas and Myelofibrosis
  16 patients enrolled across first 5 dose levels
- Arm B: R/R High-Grade Myeloid Malignancies/ALL
  8 patients enrolled at first 3 dose levels

*As of April 9, 2024, data cut-off date.

KT-253 Safety Summary: Arm A DL1-5 and Arm B DL1-3

Data cut-off date of April 9, 2024

- KT-253 was well-tolerated with no neutropenia or thrombocytopenia typical of MDM2 small molecule inhibitors observed
- Most common AEs related to KT-253 observed in >15% patients (n=24), n (%):
  - Nausea 8 (33.3%)
  - Fatigue 6 (25%)
  - Decreased appetite 4 (16.7%)
- One DLT observed of AEs leading to discontinuation that included Grade 2 fatigue and arthralgia in Arm A DL4
- Arm A: KT-253 related SAEs included Grade 3 hypotension in one patient with decreased oral intake at DL1 and Grade 3 ventricular tachycardia leading to treatment discontinuation in one patient at DL3
- Arm B: No SAEs were observed

Responses Observed Across Multiple Tumor Types During Dose Escalation of KT-253

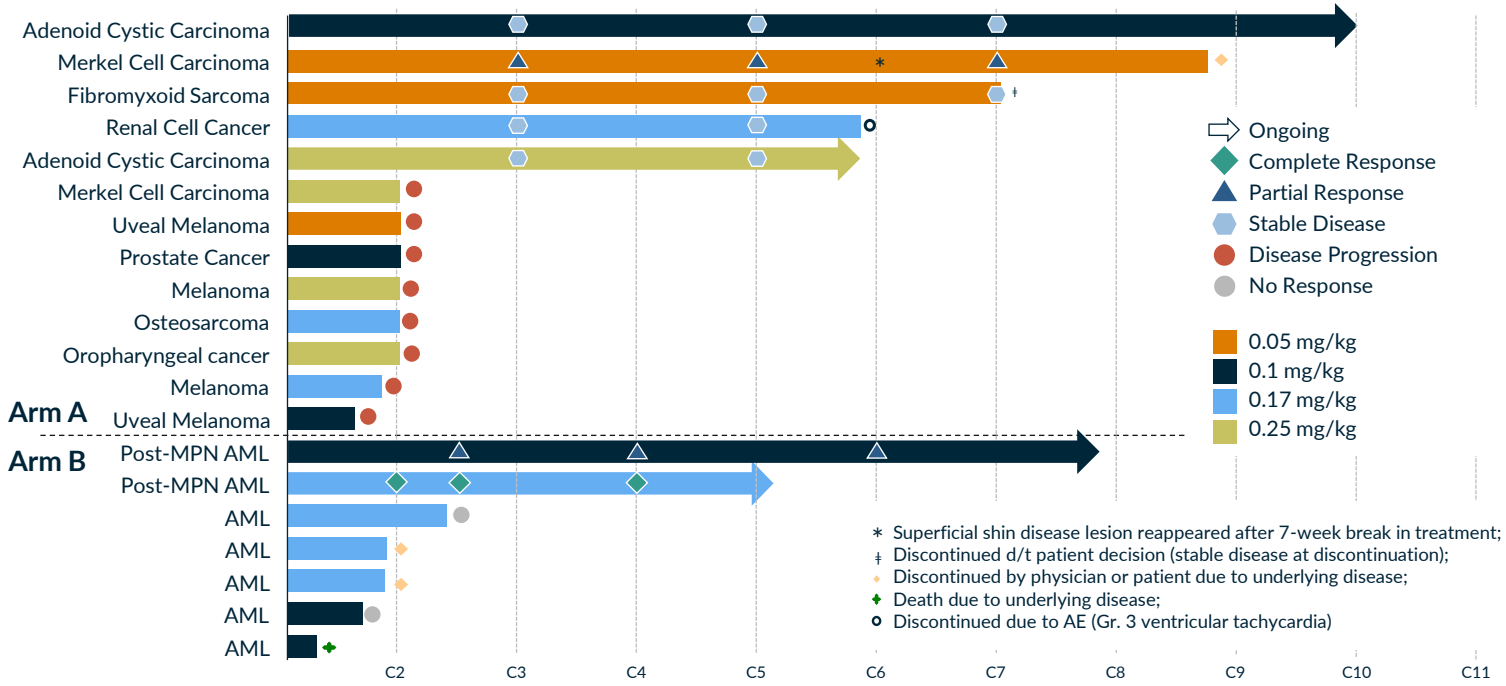
Data Cutoff Date of April 9, 2024

Clinical Responses

Best Overall Response by Arm	
ARM A (n=13[1], n (%))	
Complete Response	-
Partial Response	1[2] (7.7)
Stable Disease	4[3] (30.8)
Progressive Disease	8[4] (60.2)
ARM B (n=7[1], n (%))	
Complete Response	1[5] (14.3)
Partial Response	1[5] (14.3)
No Response	2 (28.6)
Treatment Failure-Refractory Disease	-
Non-Evaluable	3[6] (42.9)

[1]Thirteen of the sixteen Arm A and seven of eight Arm B patients enrolled were evaluable for response assessment at the time of cut-off; [2]MCC; [3]Fibromyxoid sarcoma (n=1), adenoid cystic carcinoma (n=2); renal (n=1); [4]Includes one patient with uveal melanoma assessed as clinical progression; [5]Post-MPN AML; [6]Off treatment from death due to underlying disease (n=1) or clinical deterioration (n=2) prior to first response assessment; Arm A responses assessed per RECIST 1.1; Arm B by ELN 2022

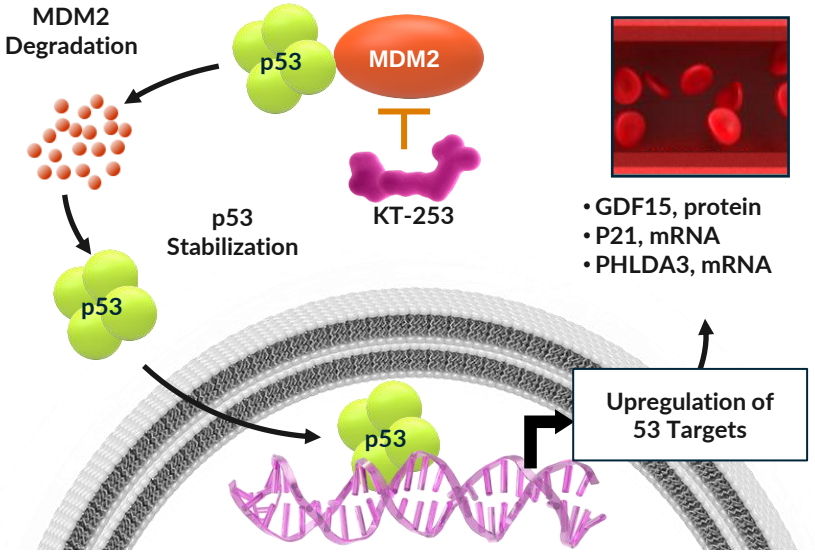
Duration of Time on Treatment – Disease Evaluable Patients



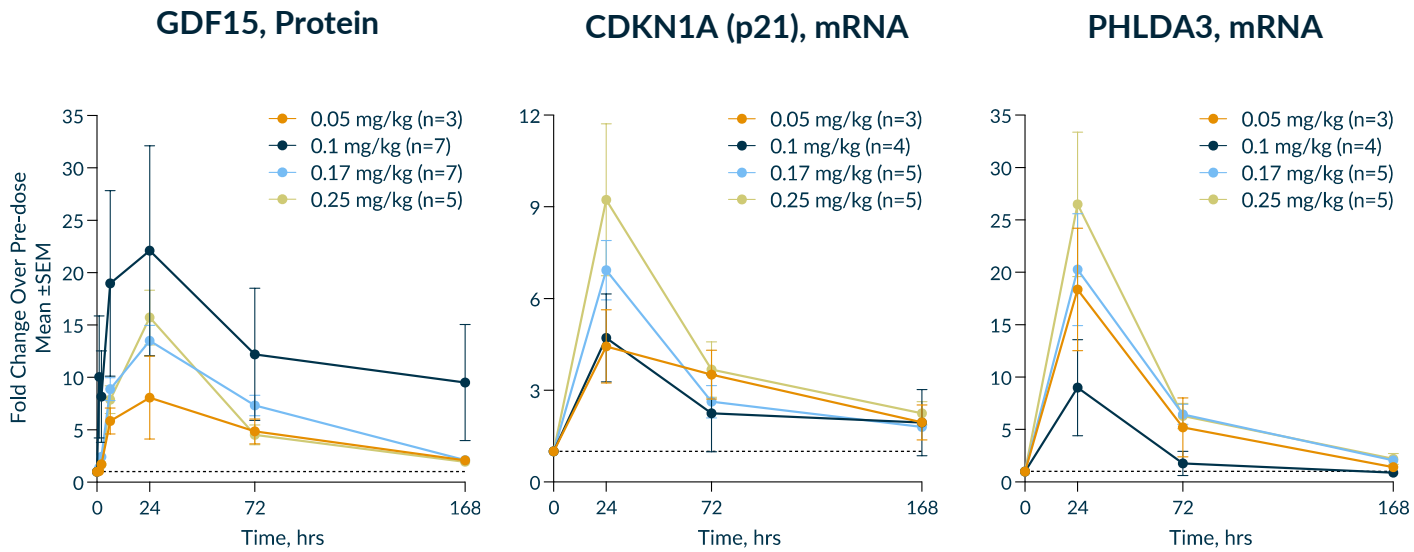
Preliminary signs of efficacy observed in both solid tumors and AML, with responses observed in Merkel Cell Cancer and in 2 of 2 Post-MPN AML patients

Potent Upregulation of p53 Biomarkers Shows Target Engagement by KT-253

Upregulation of PD Biomarkers by MDM2 Degradation-mediated p53 Pathway Activation



Rapid Upregulation of Plasma GDF-15 Protein and Upregulation of CDKN1A and PHLDA3 mRNA Levels in Blood



Fold-change over pre-dose baseline for Cycle 1. Pre-dose baseline indicated by dotted line

Strong proof-of-mechanism with evidence of target engagement and upregulation of p53 pathway biomarkers even at the lowest dose levels in solid tumor and AML patients*

*As of April 9, 2024, data cut-off date.

MDM2 Degrader: KT-253

First-in-Class Opportunity to Address p53 Wild Type Tumors Across Variety of Tumors

Recent Clinical Data*

Phase 1a data from Arm A and Arm B show evidence of target engagement and p53 pathway activation

Antitumor responses observed in both solid and heme tumors including Merkel Cell Cancer and 2 of 2 post-MPN AML patients

Fidelity of translation of PK, PD, and safety

Phase 1a dose escalation ongoing

Significant Opportunity

Monotherapy opportunity in subsets of solid tumors

Biomarker-based patient selection strategy to be informed by emerging gene signature indicating sensitivity to degrader mechanism

Monotherapy and combination opportunities in hematological malignancies, including AML, ALL, and potentially MF, MDS, and other p53WT tumors

Complete Recruitment: 2H24 Followed by Phase 1 Data

Completion of enrollment in the Phase 1a dose escalation expected in the second half of 2024, and data set shared subsequently

Clinical development strategy includes accelerated registration path in p53 WT tumors with high sensitivity to degrader mechanism such as AML, lymphomas and solid tumors

Additional clinical and preclinical data supporting biomarker-based patient selection strategy to be disclosed in 2024

*As of April 9, 2024, data cut-off date.

Thank You

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