Reinventing Medicine with Protein Degradation

May 2024

KYMERA

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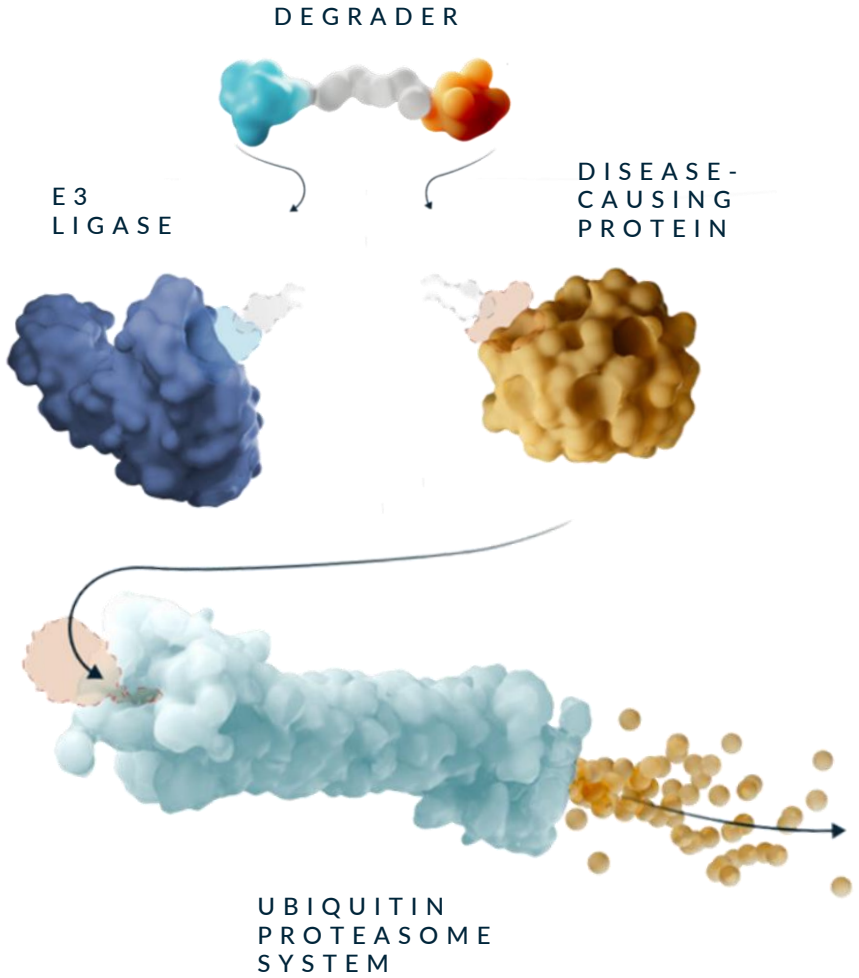
Harnessing a Game-Changing, Novel Modality

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 $745 million in cash and expected runway into the first half of 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



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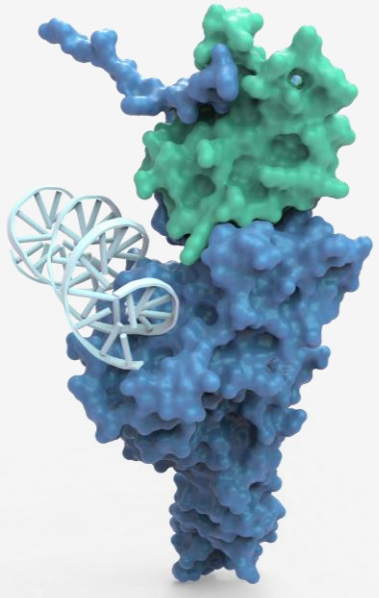
Target Selection Strategy

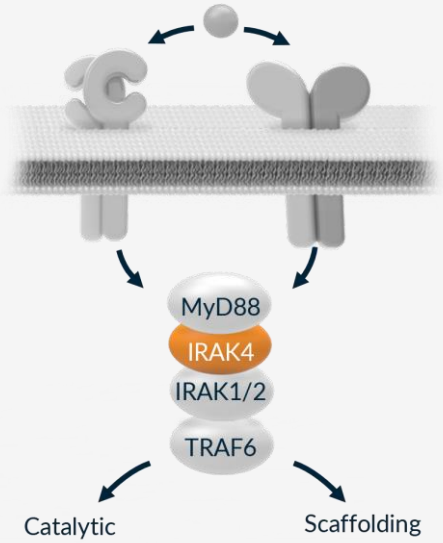
Focus on First- or Best-in-Class Opportunities

Undrugged or Inadequately Drugged targets



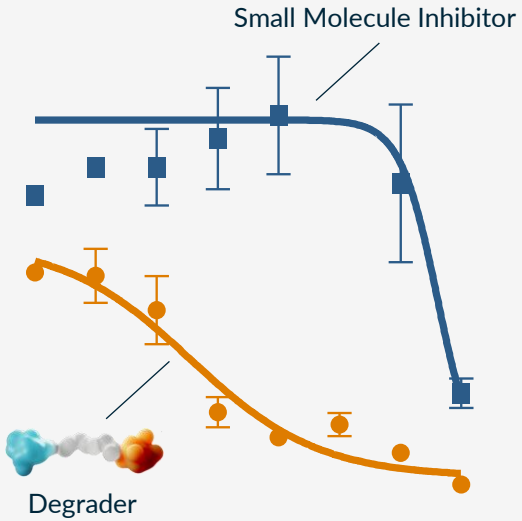
TRANSCRIPTION FACTORS & SCAFFOLDING PROTEINS

Strong Genetic/Pathway Validation



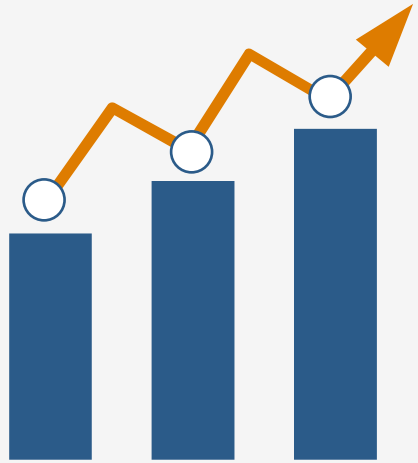
APPROVED DRUGS IN SAME PATHWAY

Clear Path to Early Clinical Differentiation



SUPERIORITY VS PATHWAY DRUGS

Large Clinical/Commercial Opportunities



AREAS OF SIGNIFICANT VALUE CREATION

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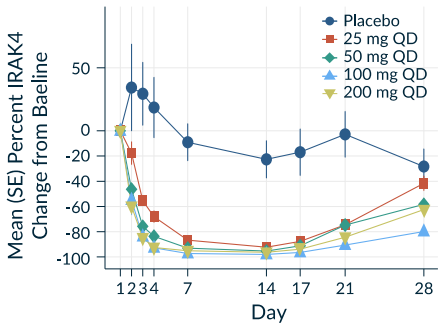
Demonstrating Reproducible and Scalable Clinical Innovation

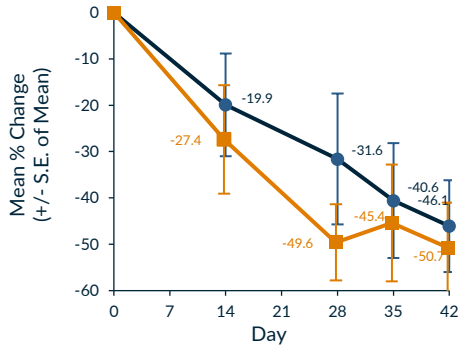
IRAK4 KT-474

IRAK4 Degradation leads to Early POC in HS and AD

IRAK4 Levels



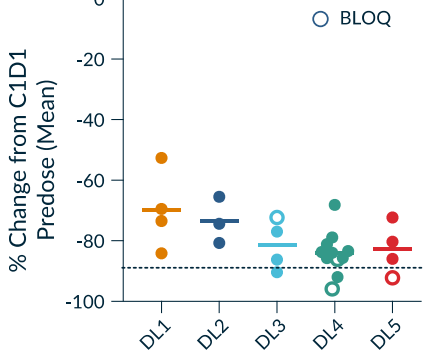
Reduction of AN Counts in HS Patients



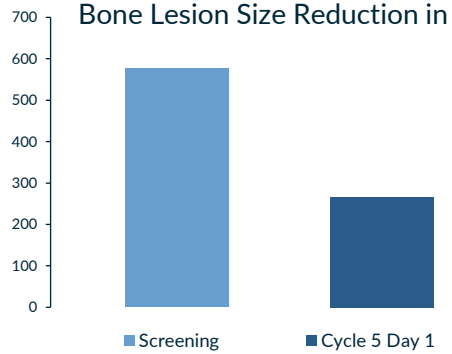
STAT3 KT-333

STAT3 Degradation Leads to Major Response in cHL Patient

STAT3 Levels

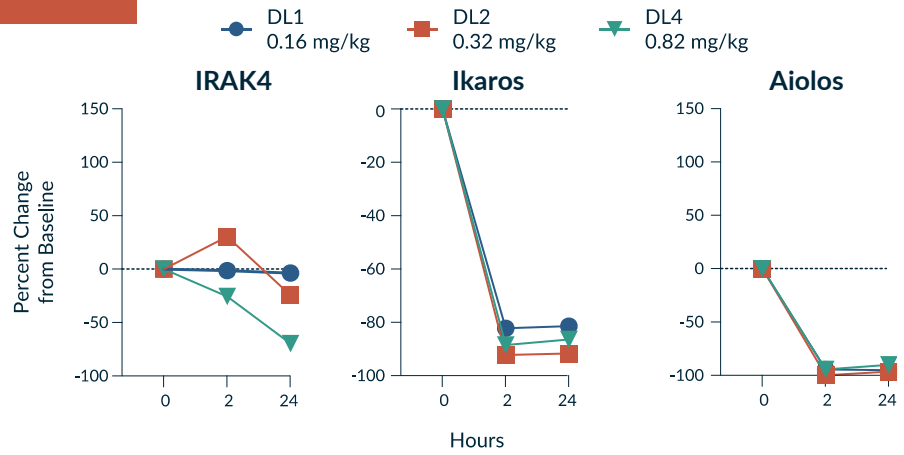


Bone Lesion Size Reduction in cHL Patient



IRAKIMID KT-413

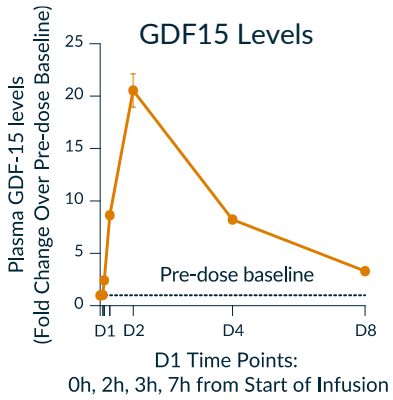
Degradation of IRAK4 and Ikaros/Aiolos



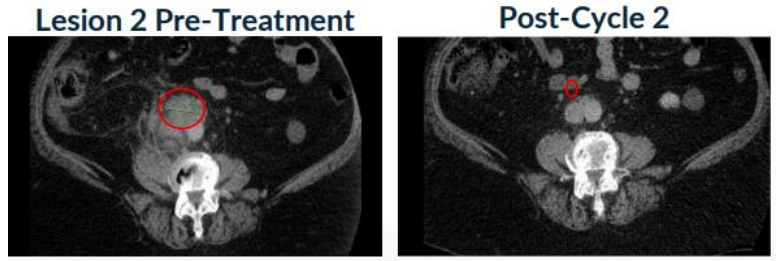
MDM2 KT-253

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

GDF15 Levels



Lesion Size Reduction in MCC Patient



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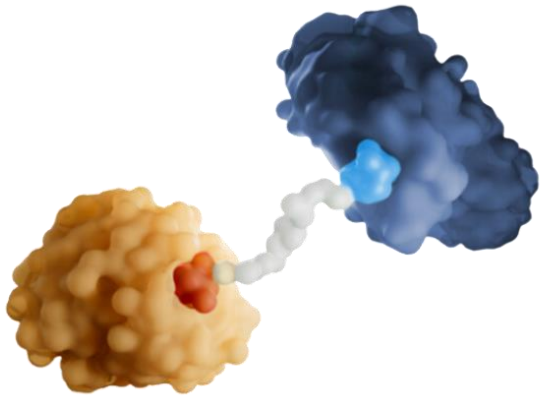
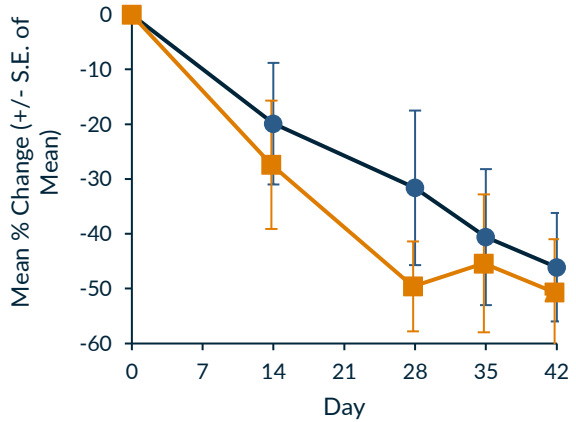
Building a Global Medicines Company

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

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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] **KT-474**	HS, AD, RA, Asthma, IBD, others[2]	HS	AD		Ph2 HS & AD Data: **1H25**	50/50 US sanofi KYMERA
STAT6 **KT-621**	AD, Asthma, COPD, PN, CRSwNP, EoE, others				Phase 1 Start: **2H24**	KYMERA
TYK2 **KT-294**	Psoriasis, IBD, PsA, Lupus, others				Phase 1 Start: **1H25**	KYMERA
Oncology						
STAT3 **KT-333**[3]	PTCL, LGL-L, CTCL, Solid Tumors	Arm A: Lymphomas, Solid Tumors Arm B: T-Cell Leukemias			Ph1 Data: **EHA and 2H24**	KYMERA
MDM2 **KT-253**	Liquid & Solid Tumors	Arm A: Solid Tumors/Lymphomas Arm B: AML, ALL, MF			Ph1 Data: **ASCO and 2H24**	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]Assessment of STAT3 I/I opportunity is ongoing.

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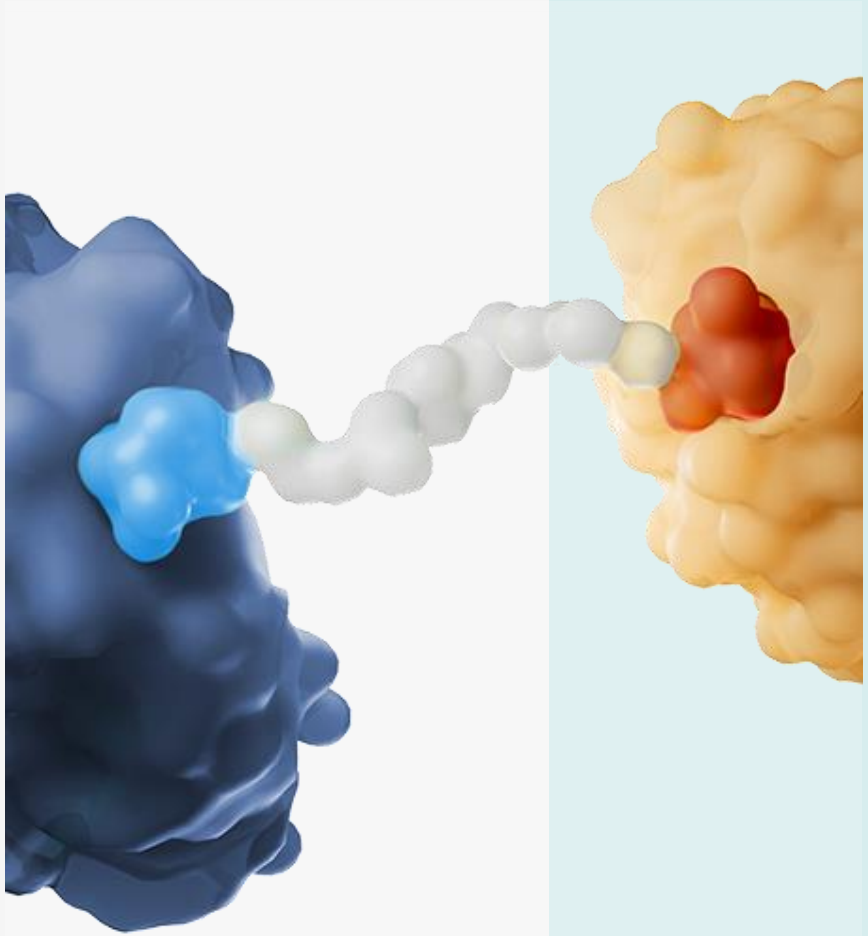

Kymera's Immunology Pipeline

IRAK4, STAT6, TYK2

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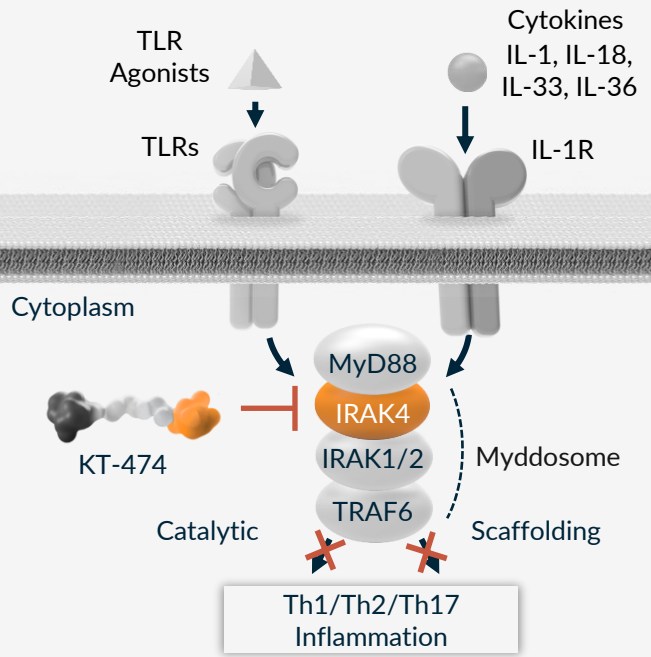
Kymera Immunology Oral Degrader Portfolio

Complementary, First-in-class Mechanisms

IRAK4
SCAFFOLDING KINASE

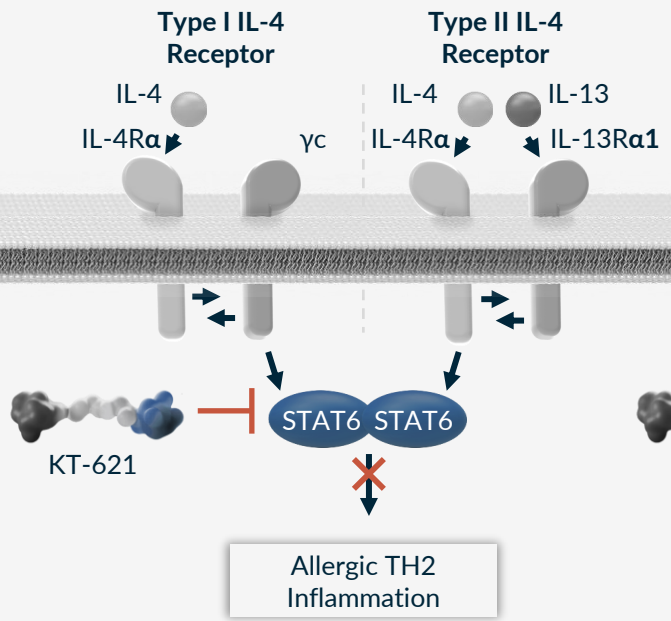
IL-1R/TLR Pathway



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

STAT6
TRANSCRIPTION FACTOR

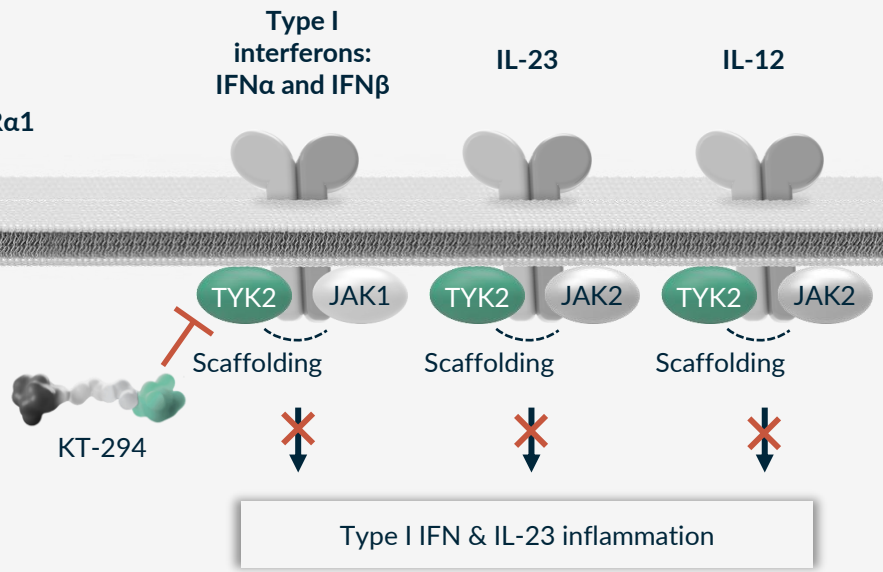
IL-4/13 Pathway



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

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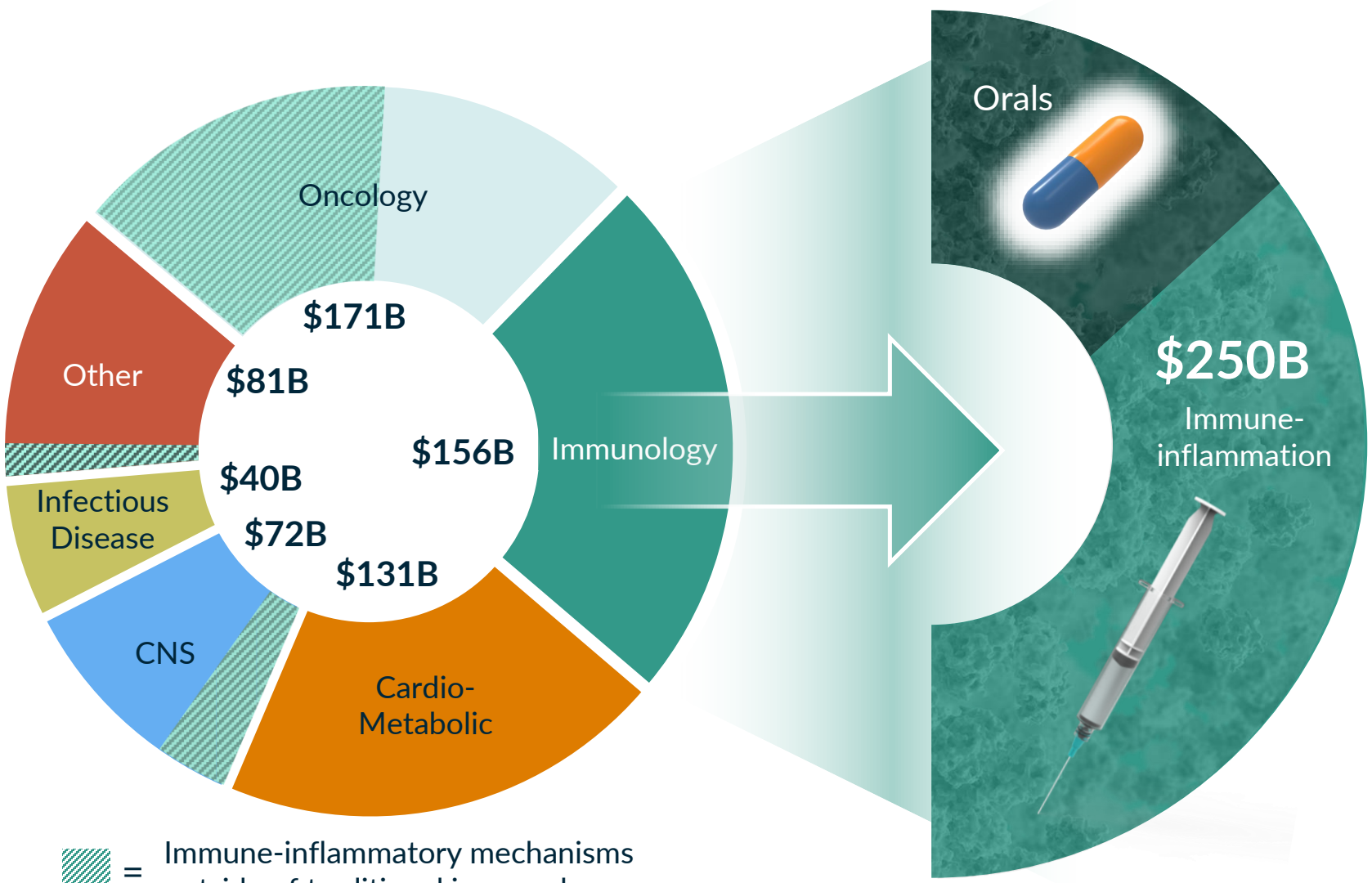
The Opportunity in Immunology



= 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

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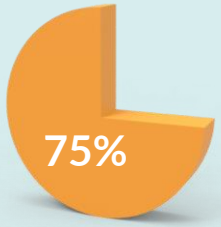
Why Small Molecule Oral Degraders in Immunology

Cosentyx® (secukinumab)

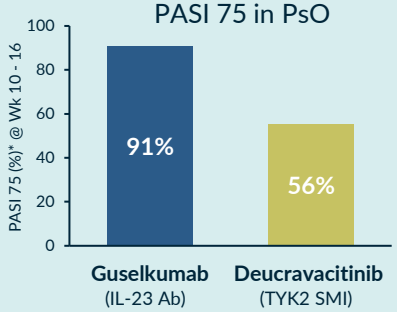
Stelara® (ustekinumab)

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

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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, CRSwNP, EoE, PN, others	• IBD, PsO, PsA, Lupus, others
Next Milestone	• **HS and AD Ph2 data: 1H 2025**	• **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[2]	• 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]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.

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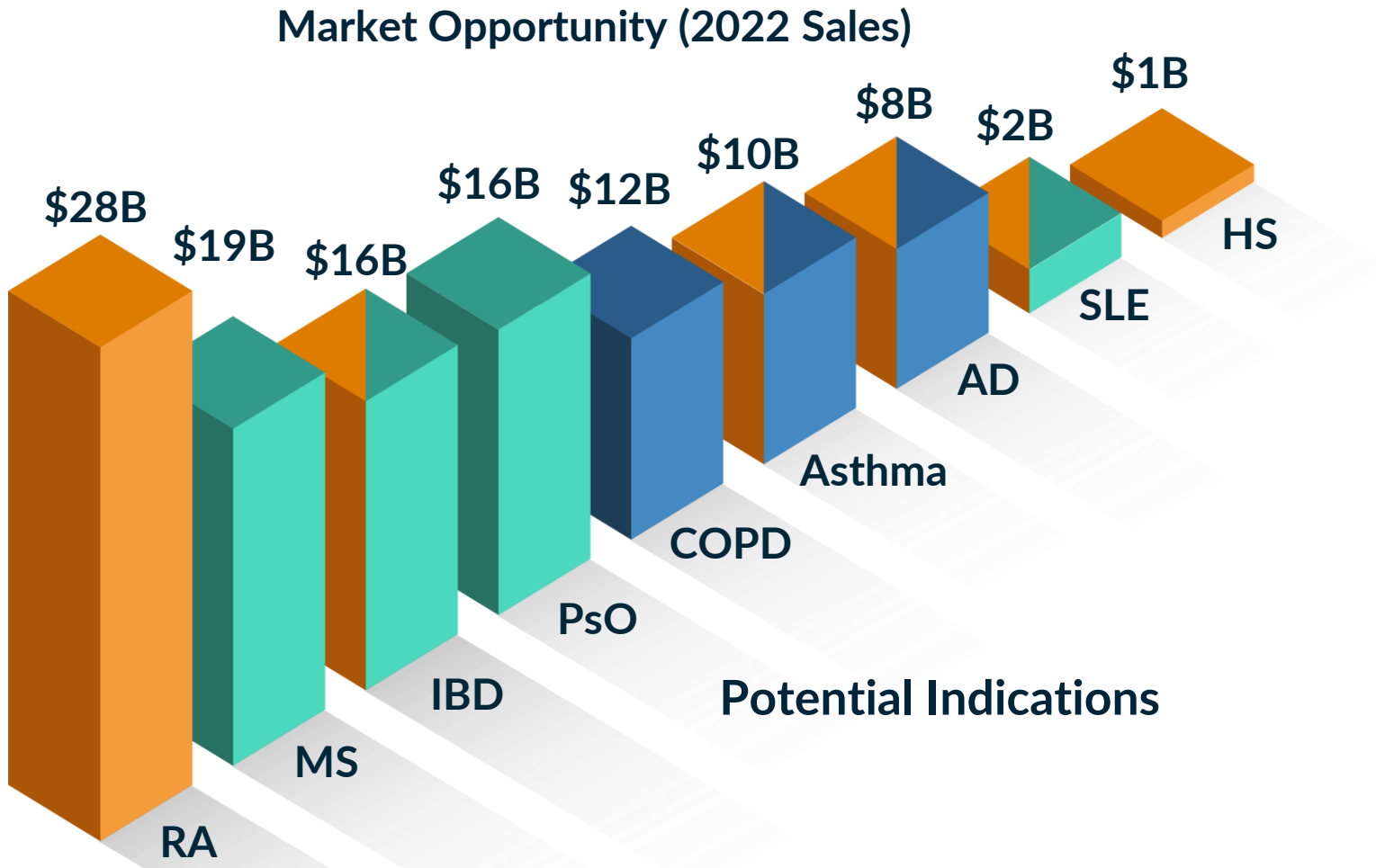
Kymera Immunology Oral Degrader Portfolio

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

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KT-474 (SAR444656)

A First-in-Class Oral IRAK4 Degrader

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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

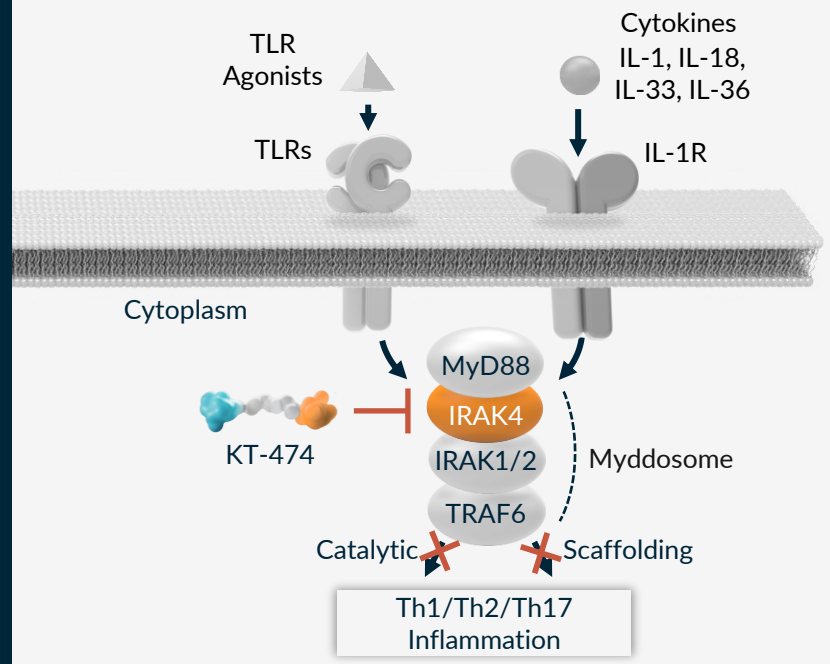
- Adult humans with IRAK4 null mutation are healthy

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

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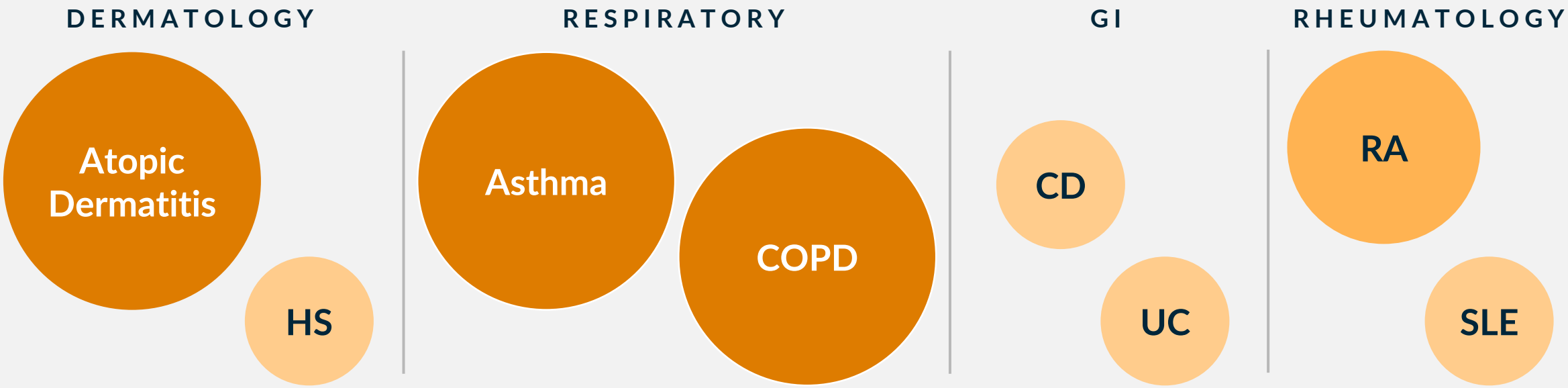
IL-1R/TLR Pathway Potential Impact Across Multiple Immune-Inflammatory Diseases



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)

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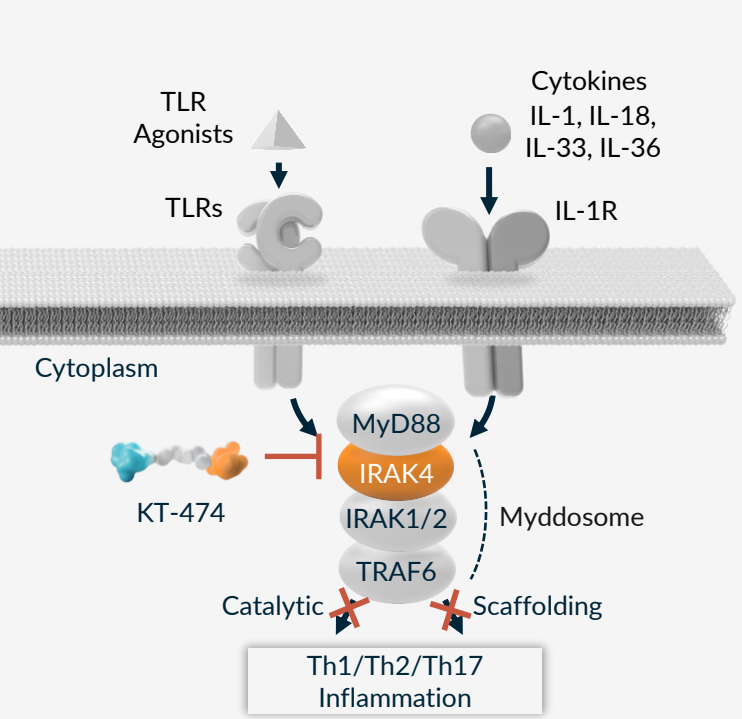
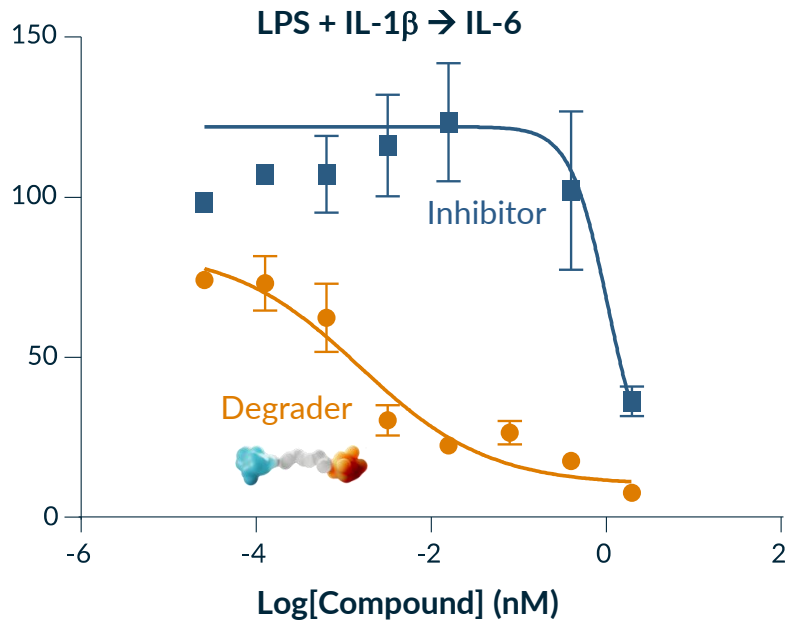
IRAK4 Degrader Advantage



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).

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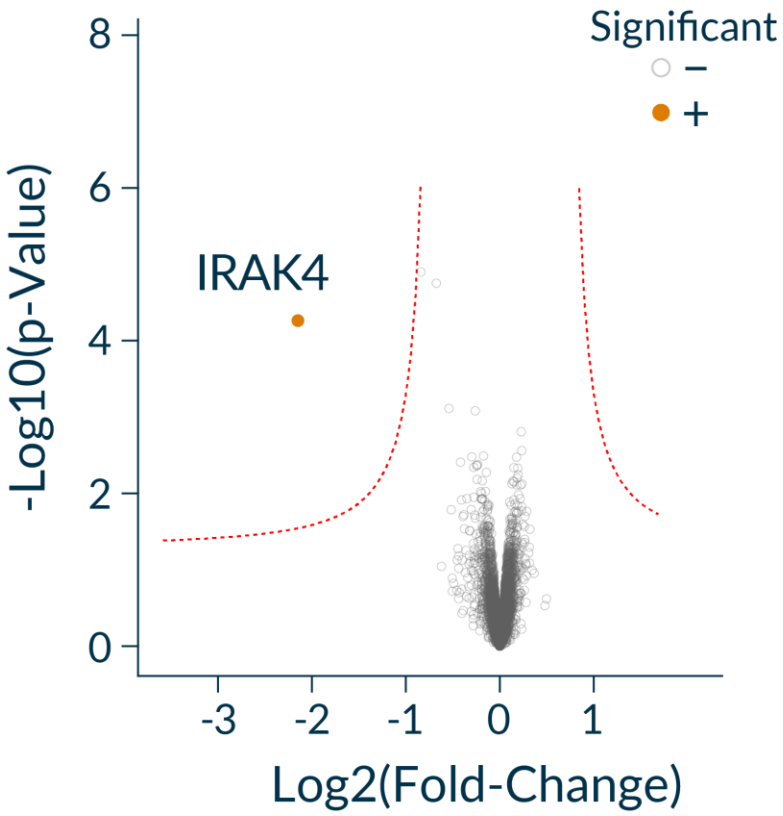
KT-474: Selective and Potent IRAK4 Degrader Active in Multiple Cell Types

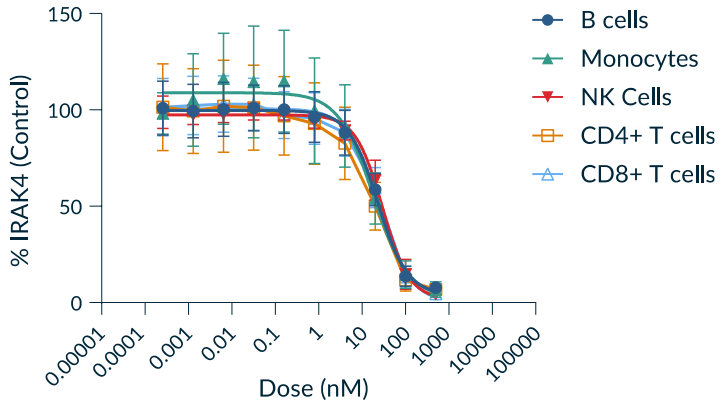
Selectivity in PBMC



- 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

KT-474 Degradation Across Immune Cell Types



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

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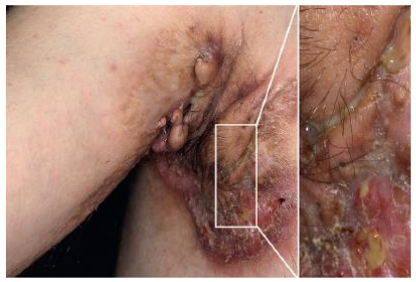
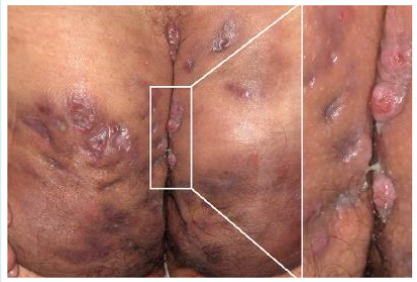
Initial Clinical Focus for KT-474: Moderate to Severe HS and AD

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

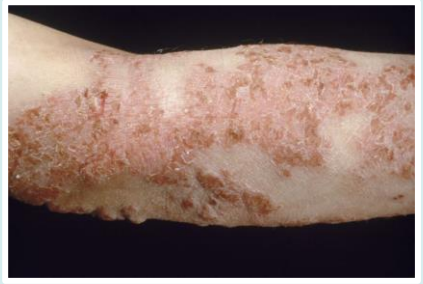
Lesions characterized by pleotropic inflammation with Th1/Th17 skewing; bacterial infection and tissue destruction leading to TLR activation; IL-1 and IL-36 production

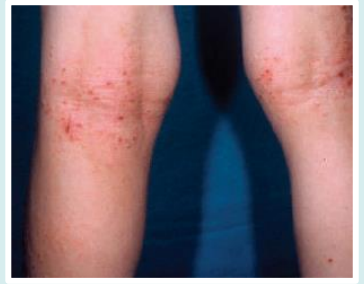
Active agents approved or in development target TNF-α, IL-17 and JAK/STAT pathways

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

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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.

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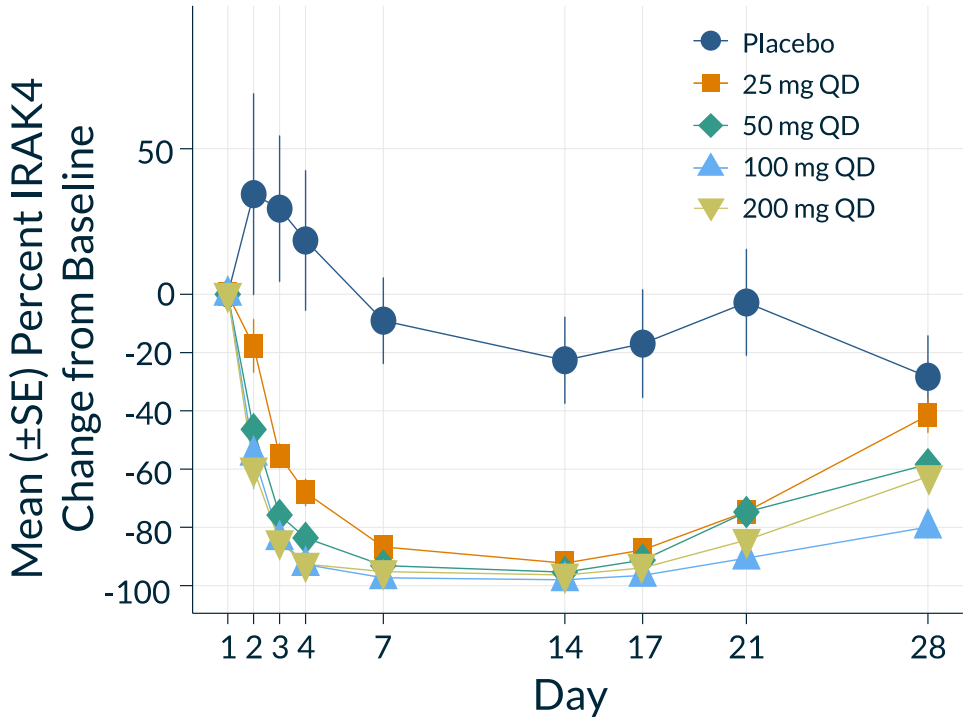
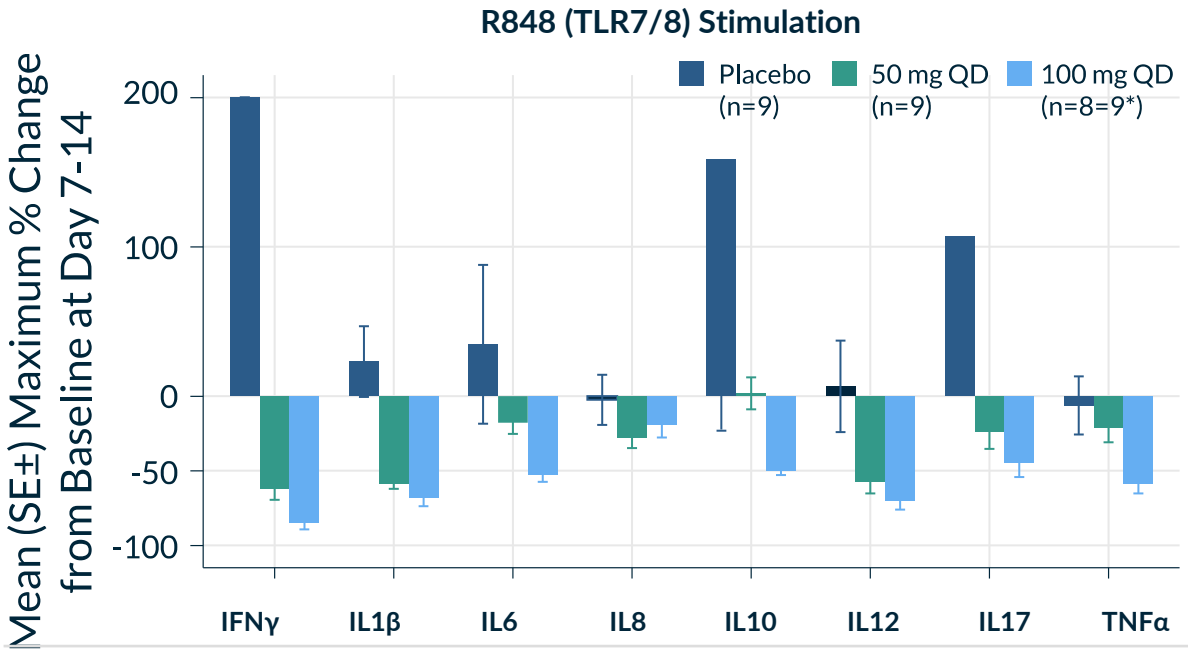
Near-Complete Degradation and Broad Cytokine Impact in Healthy Volunteers

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

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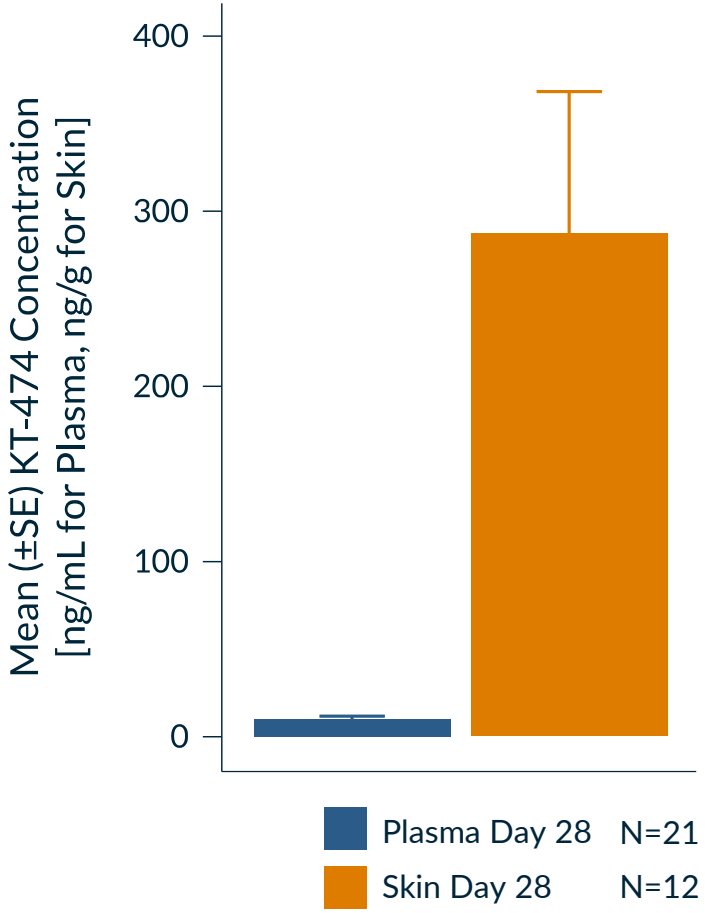
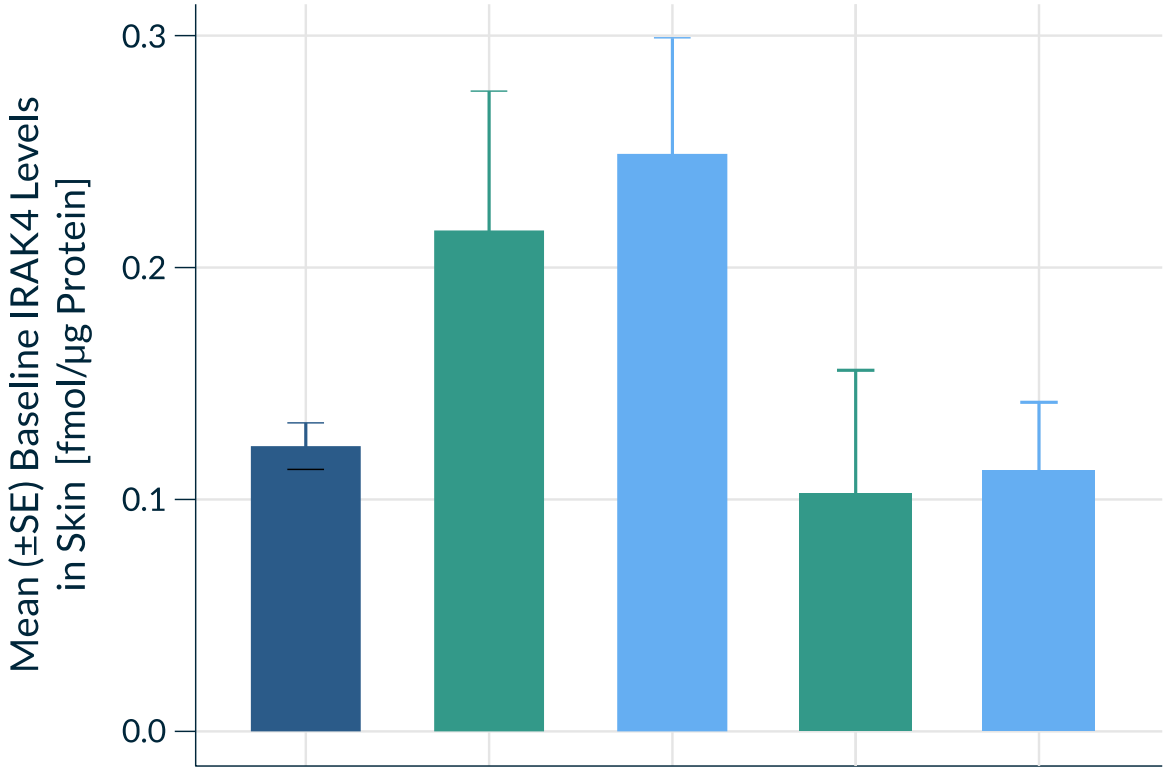
High Skin Exposure and Degradation in Skin of HS and AD Patients

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

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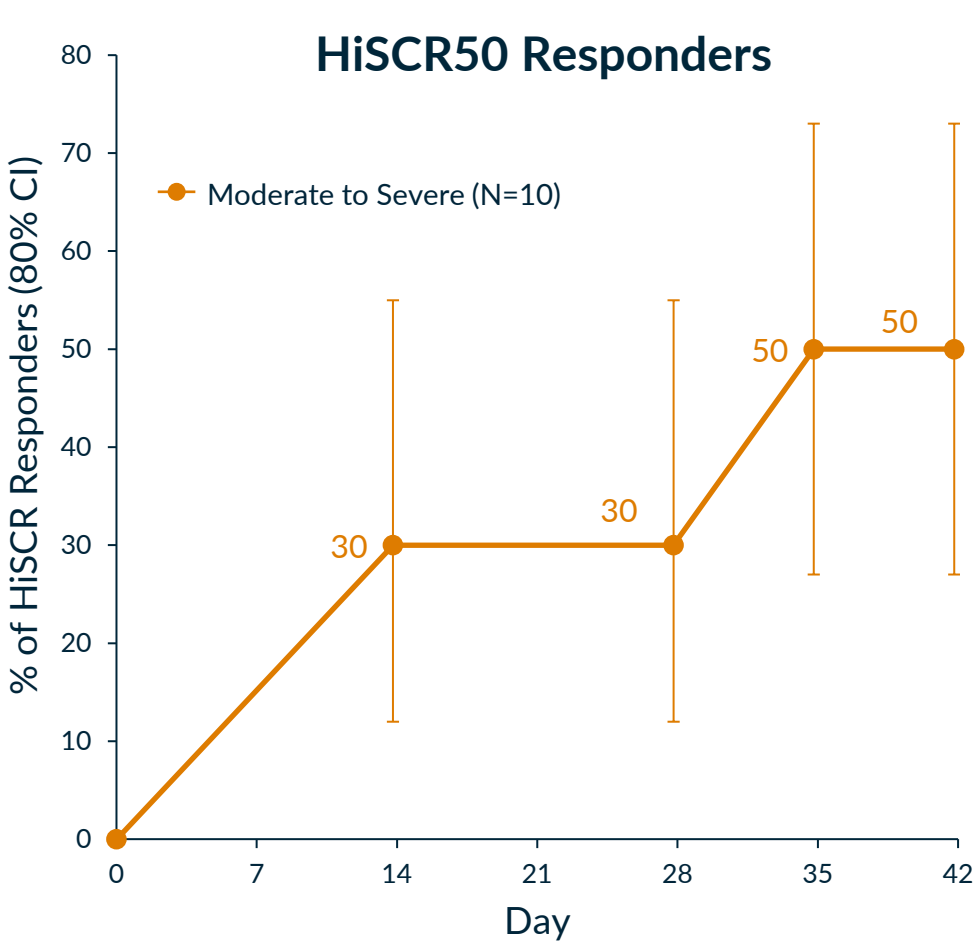
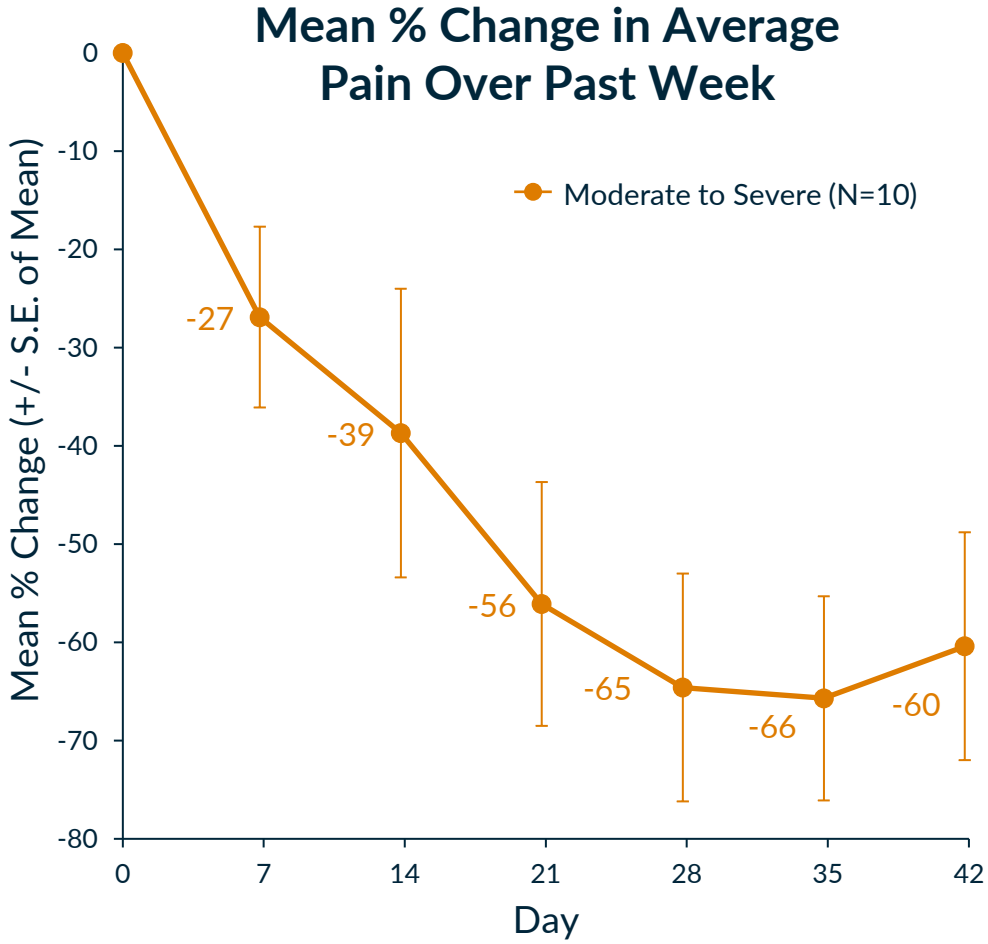
Robust Clinical Impact in HS After Only 28 Days of Dosing





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

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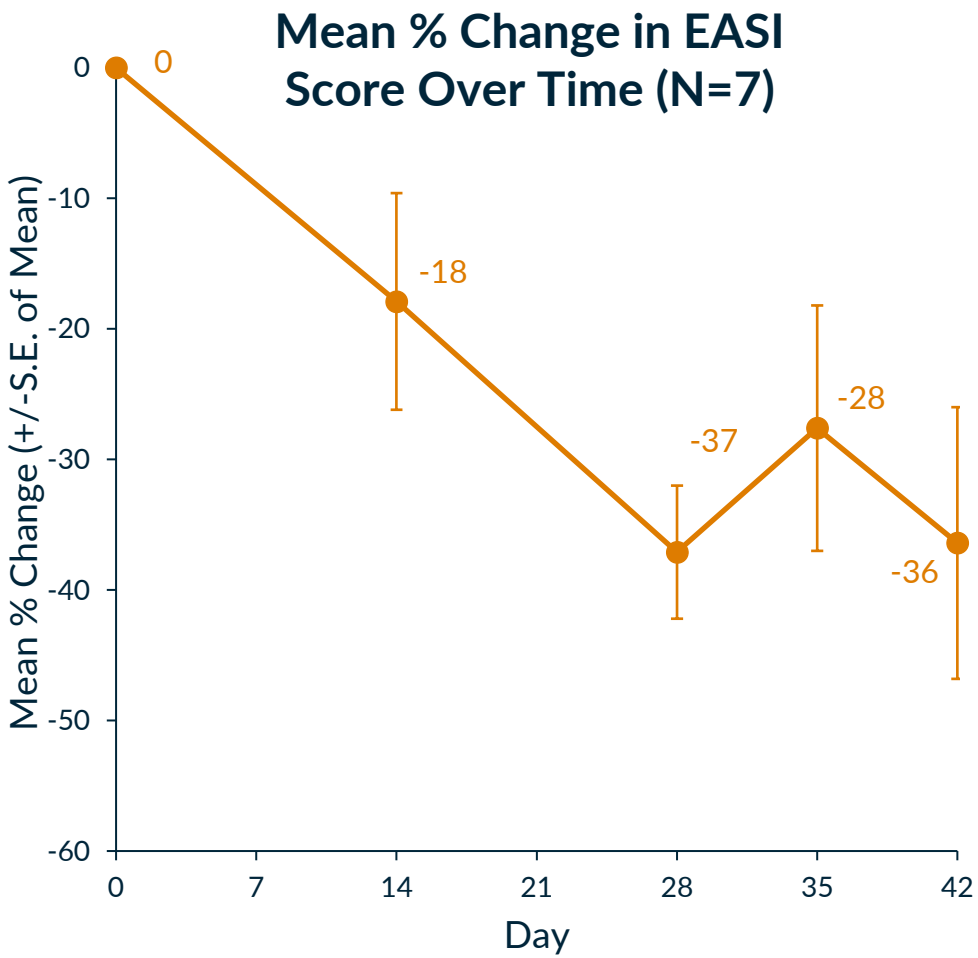
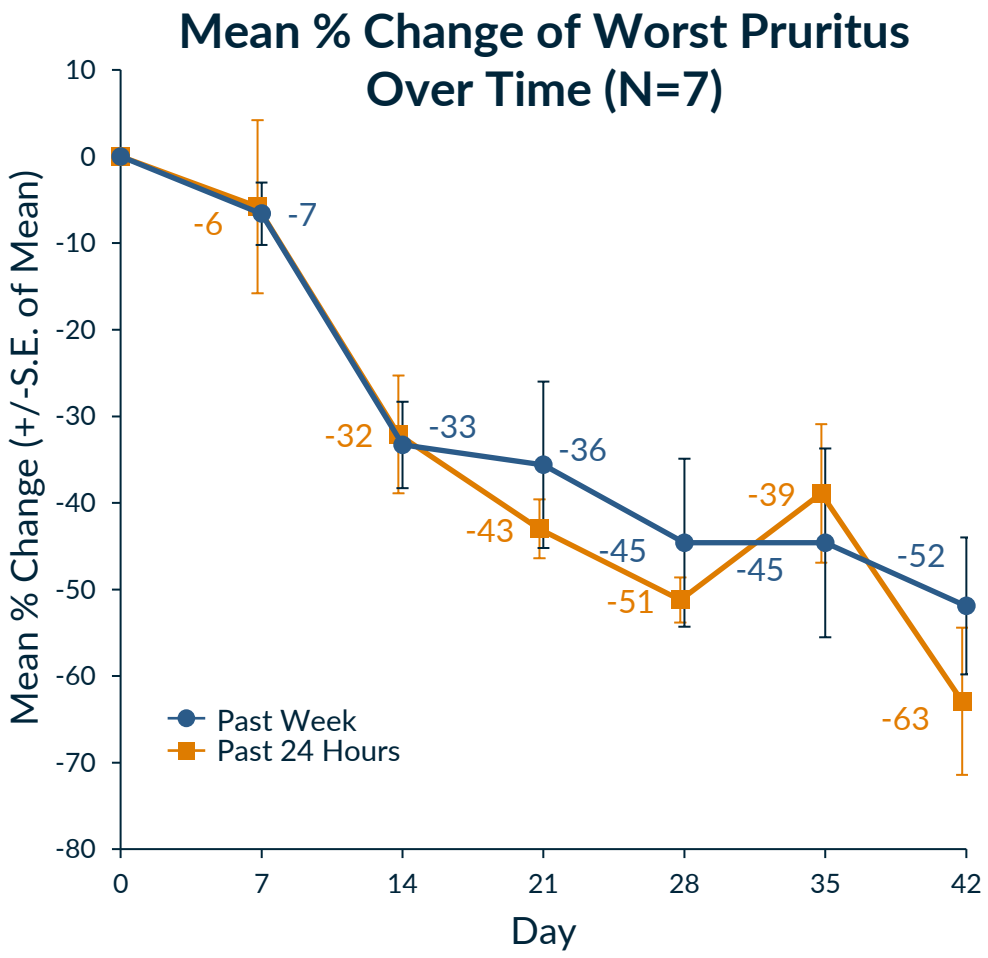
Robust Clinical Impact in AD After Only 28 Days of Dosing





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

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KT-474/SAR444656: Positioned for Clinical Success

Phase 2 HS Trial
(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
- Primary completion (est.): February 2025

Phase 2 AD Trial
(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
- Primary completion (est.): January 2025

Topline data expected 1H 2025

Additional information on the Phase 2 studies can be found at www.clinicaltrials.gov; identifier NCT06028230 (HS) and NCT06058156 (AD); Study Sponsor: Sanofi

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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/Next Steps

Phase 1 complete:

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

Partner Sanofi conducting Phase 2 trials in HS and AD

Phase 2 data expected in 1H 2025

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)

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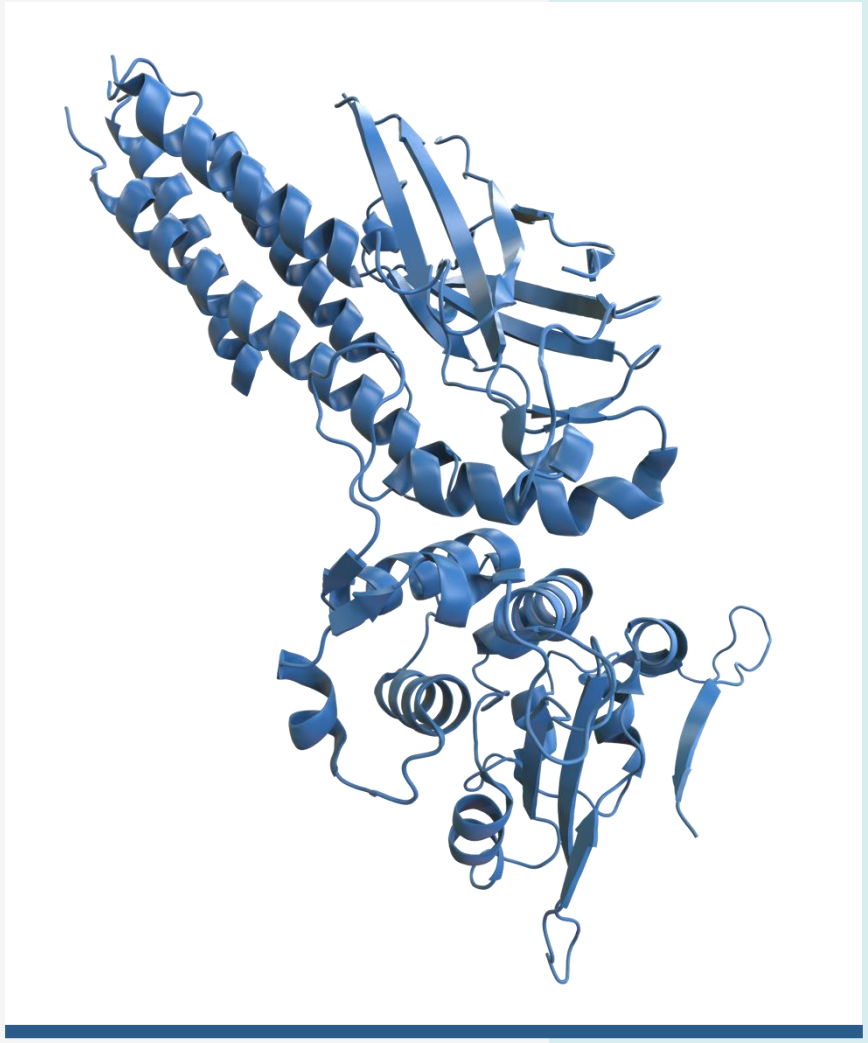

KT-621

A First-in-Class Oral STAT6 Degrader

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STAT6 Biology and Target Rationale

Target Biology and rationale

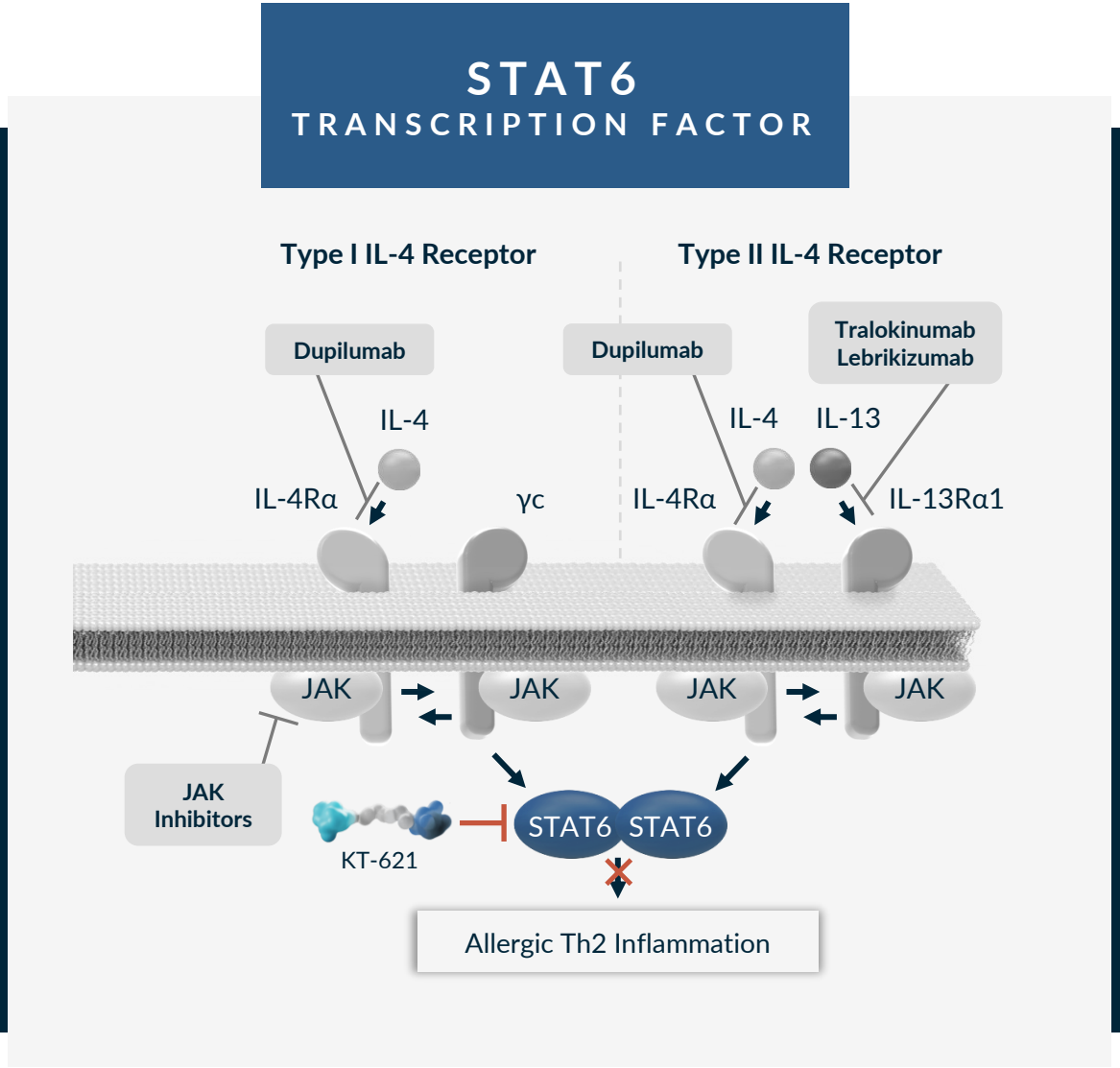
- STAT6 is the specific transcription factor required for IL-4 and IL-13 cytokine signaling
- STAT6 regulated cytokines are clinically validated targets for allergic diseases

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

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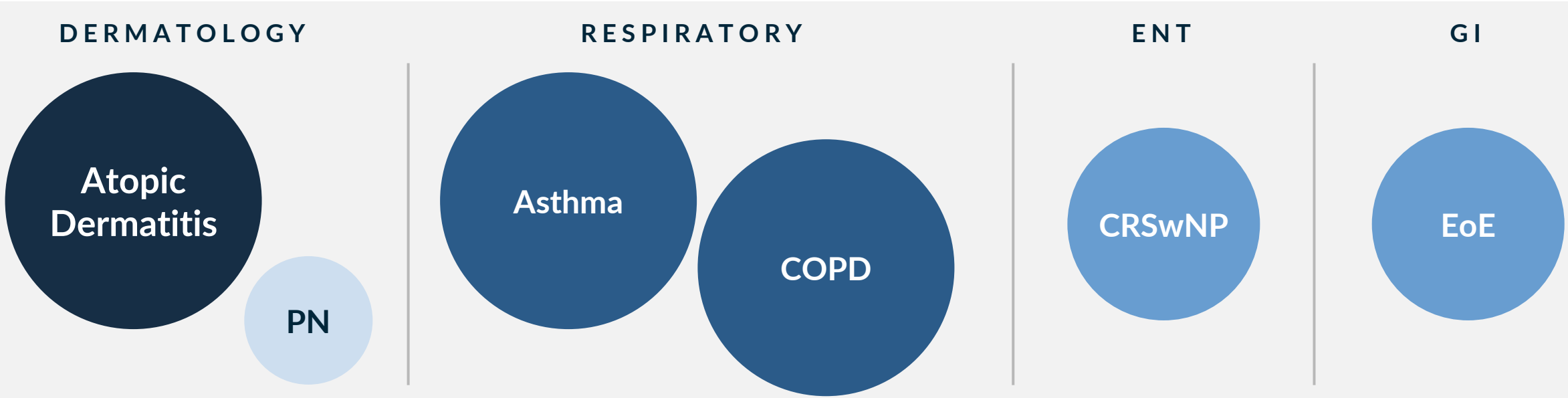
Oral STAT6 Degraders Can Transform Treatment Paradigm in Multiple Indications De-risked by Dupilumab



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)

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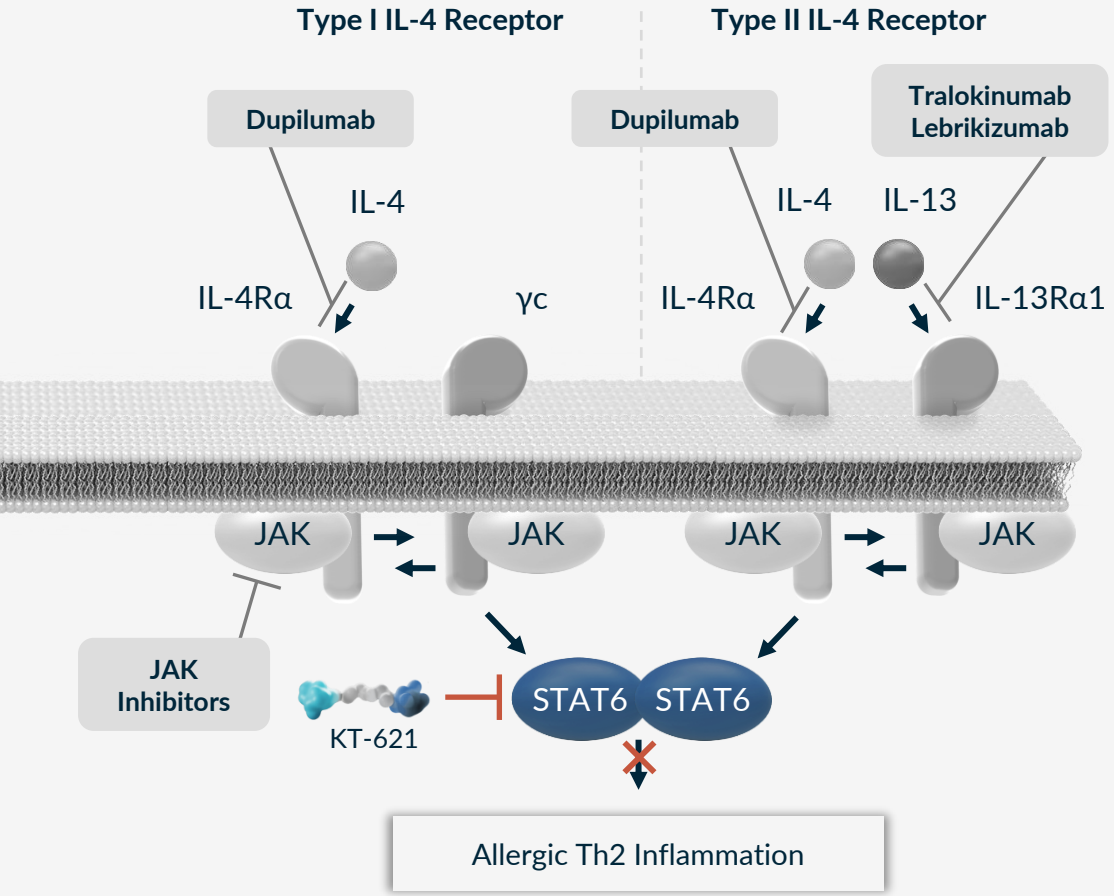
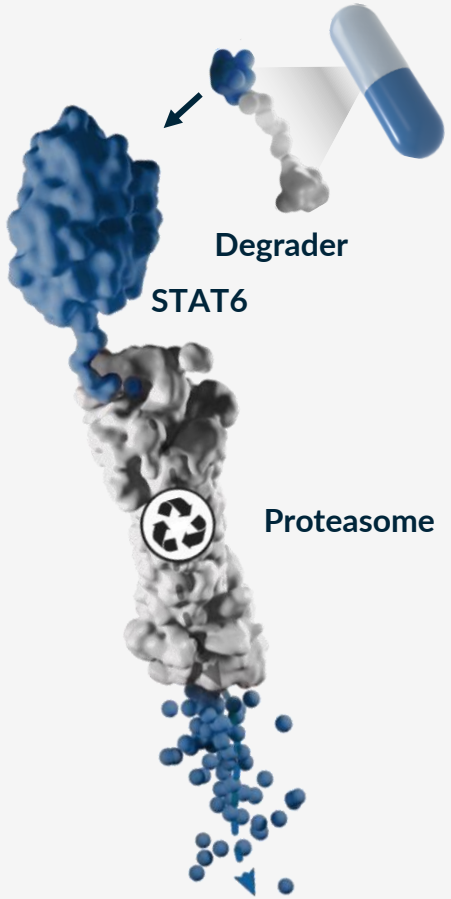
STAT6 Degrader Advantage





- 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*

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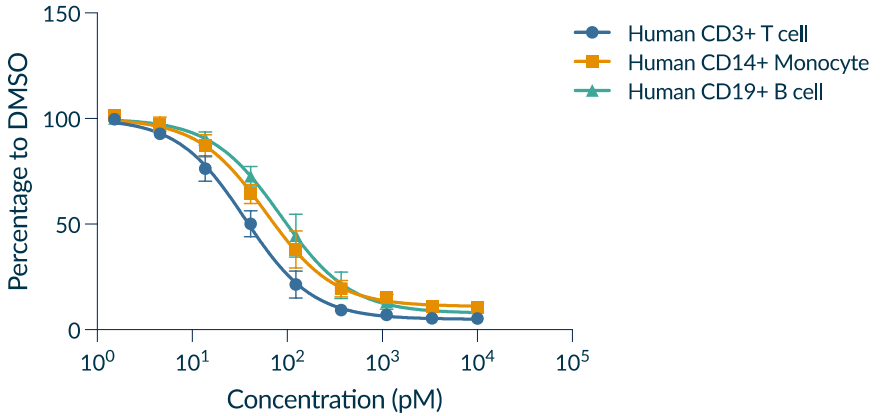
KT-621: A Picomolar Degrader of STAT6

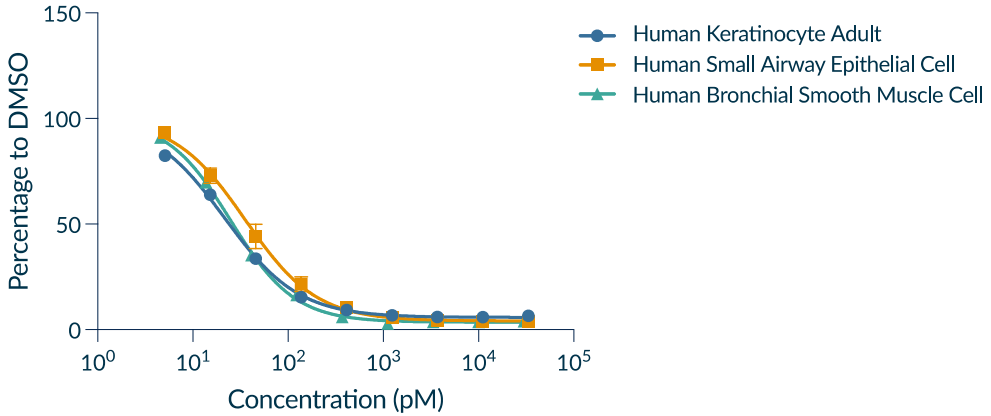
Consistent Degradation Across All Disease Relevant Cell Types Evaluated

	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



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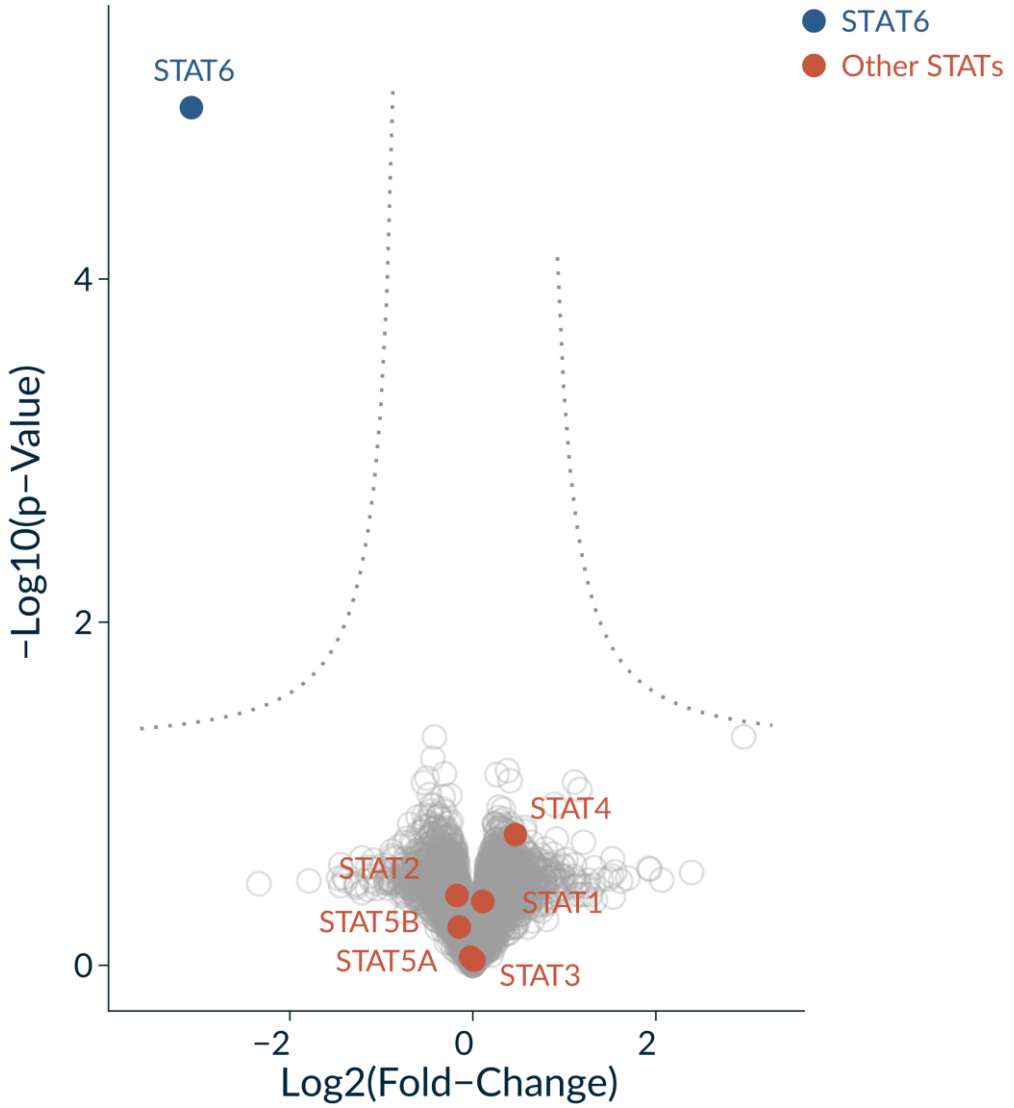
KT-621: Exquisite Degradation Selectivity for STAT6

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

No other STATs are degraded to any extent



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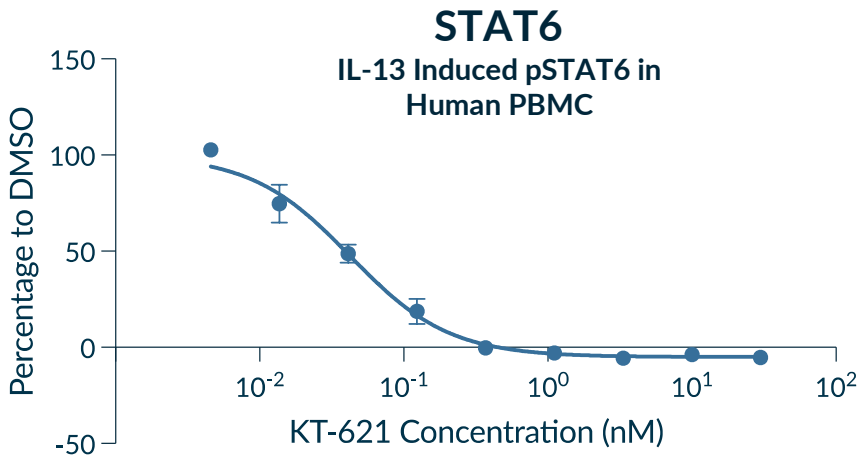
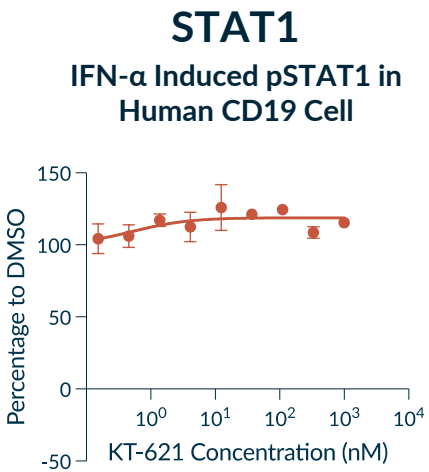
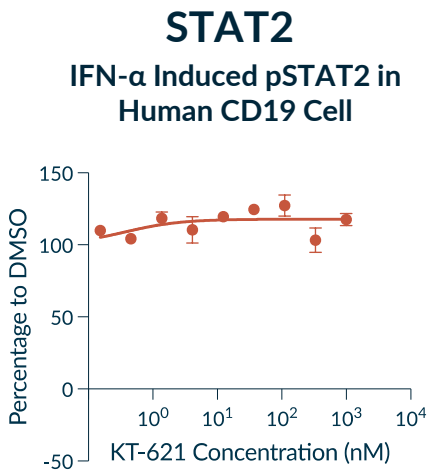
KT-621: Exquisite Pathway Selectivity for STAT6

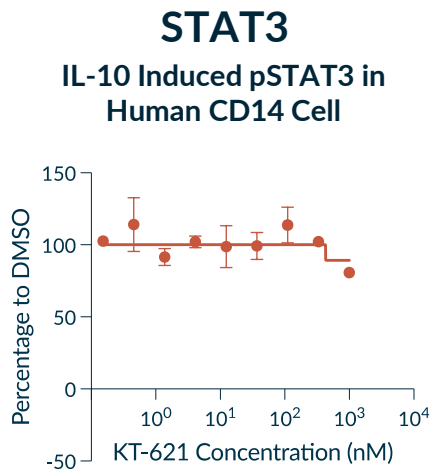
No Impact on Any Other STAT Pathway Observed

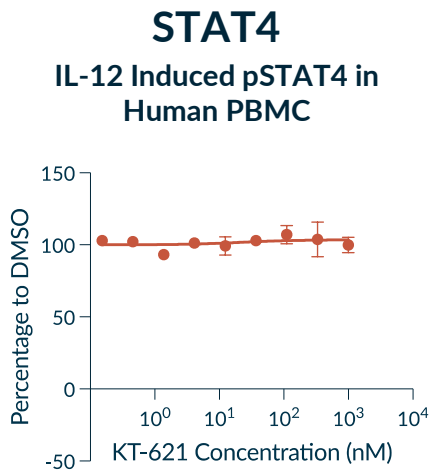
STAT assays	KT-621, IC_{50} (nM)
IFN-α induced pSTAT1	> 1000
IFN-α induced pSTAT2	> 1000
IL-10 induced pSTAT3	> 1000
IL-12 induced pSTAT4	> 1000
IL-2 induced pSTAT5	> 1000
IL-13 induced pSTAT6	0.042

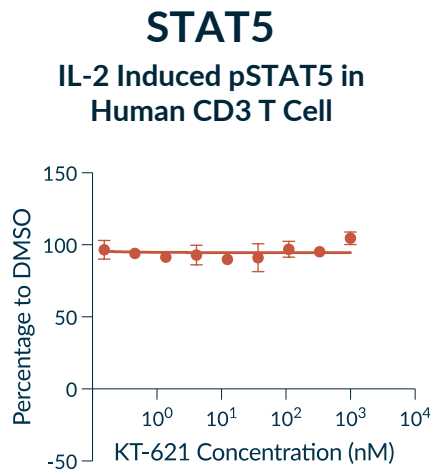












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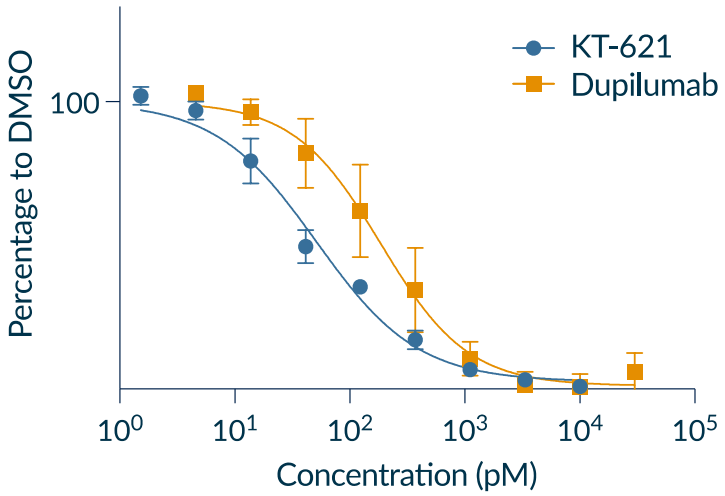
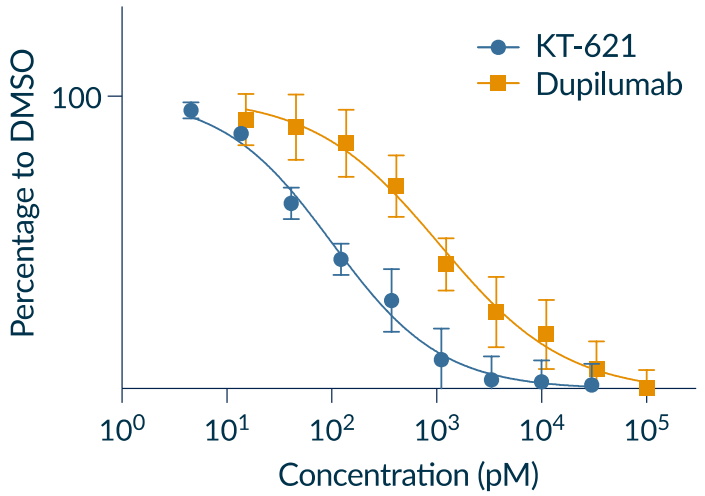
KT-621 Fully Blocks IL-4/13 Pathway in Human TH2 Functional Assays with IC_{50}'s Lower than Dupilumab

		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

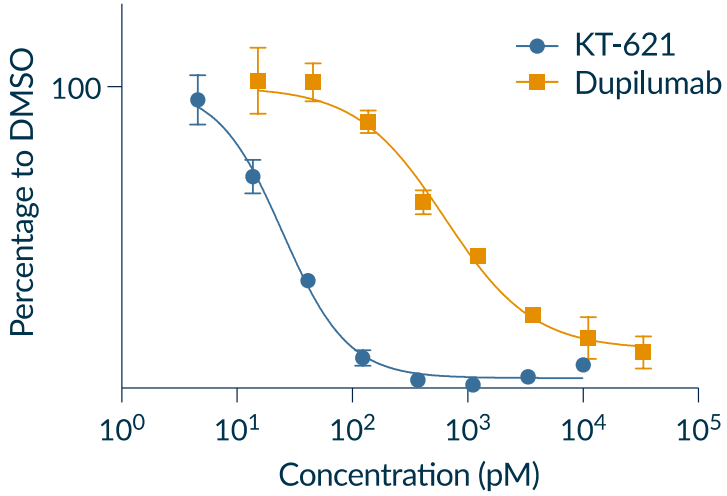
IL-4 Induced TARC Release in Human PBMC



IL-13 Induced CD23 Expression in Human CD19 B Cell



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



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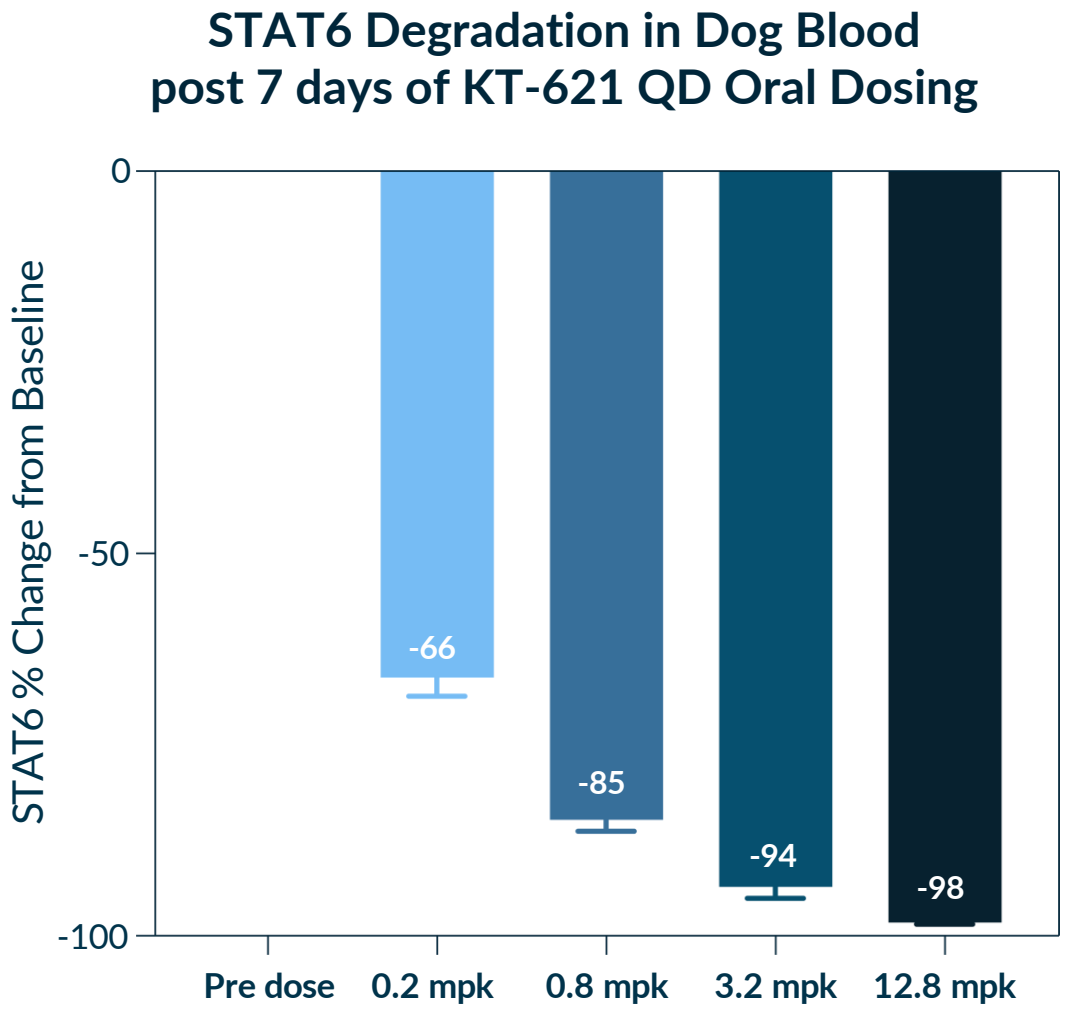
KT-621 Achieves Dose Dependent Deep Degradation of STAT6 *in vivo* with Low Oral Doses

KT-621 potently degrades STAT6 across multiple preclinical species

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



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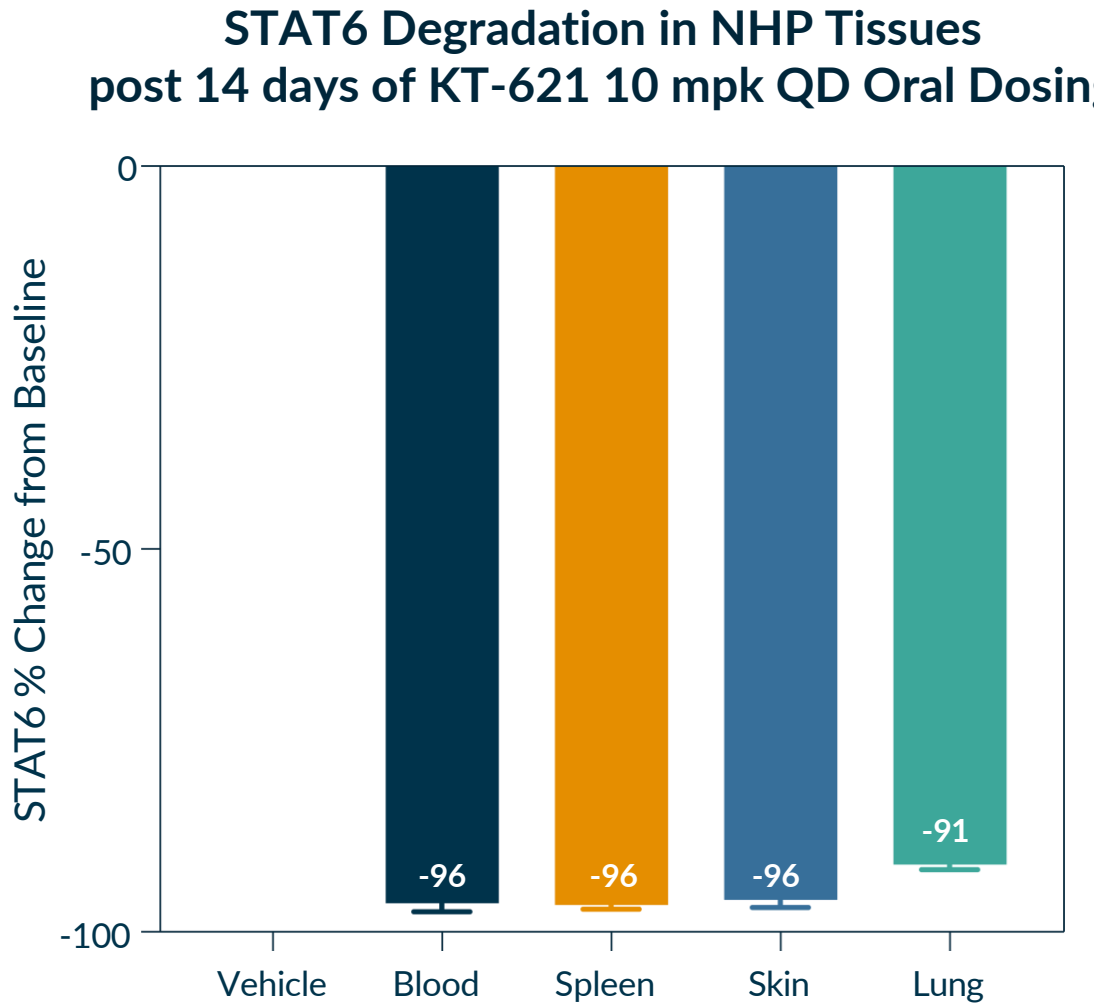
KT-621 Degrades STAT6 in Disease Relevant Tissues in NHP

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



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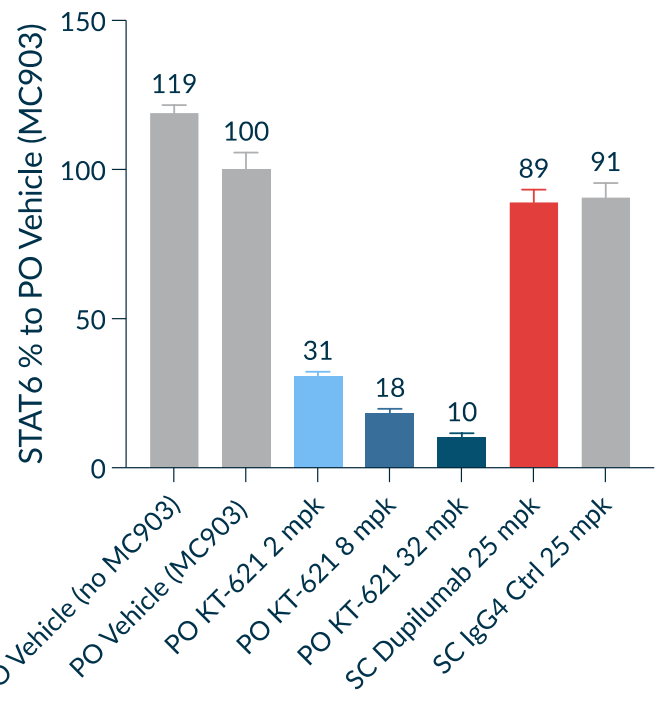
KT-621 Has Comparable *in vivo* Activity to IL-4Rα Saturating Dose of Dupilumab in the MC903 Atopic Dermatitis Model

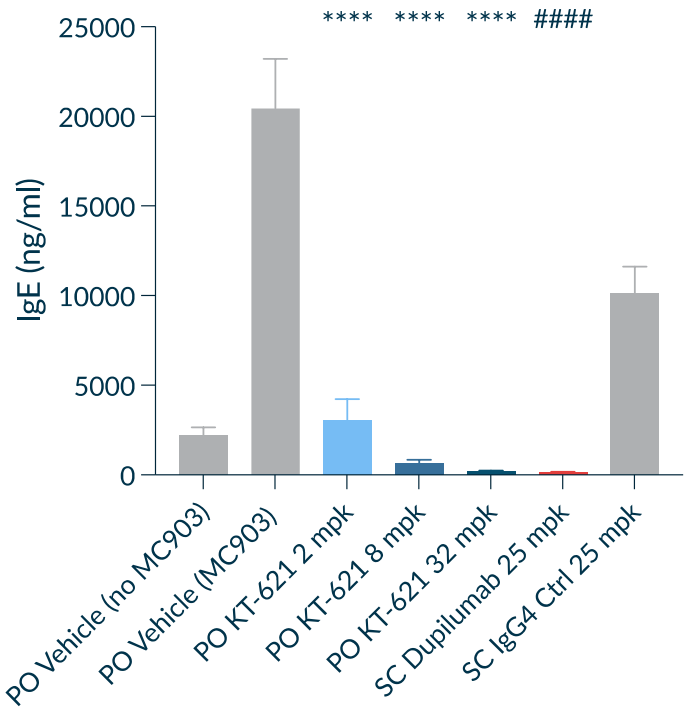
An atopic dermatitis model induced by topical application of low-calcemic vitamin D3 analog MC903 with prominent Th2 inflammation in the IL4/IL4RA humanized mice:

- **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

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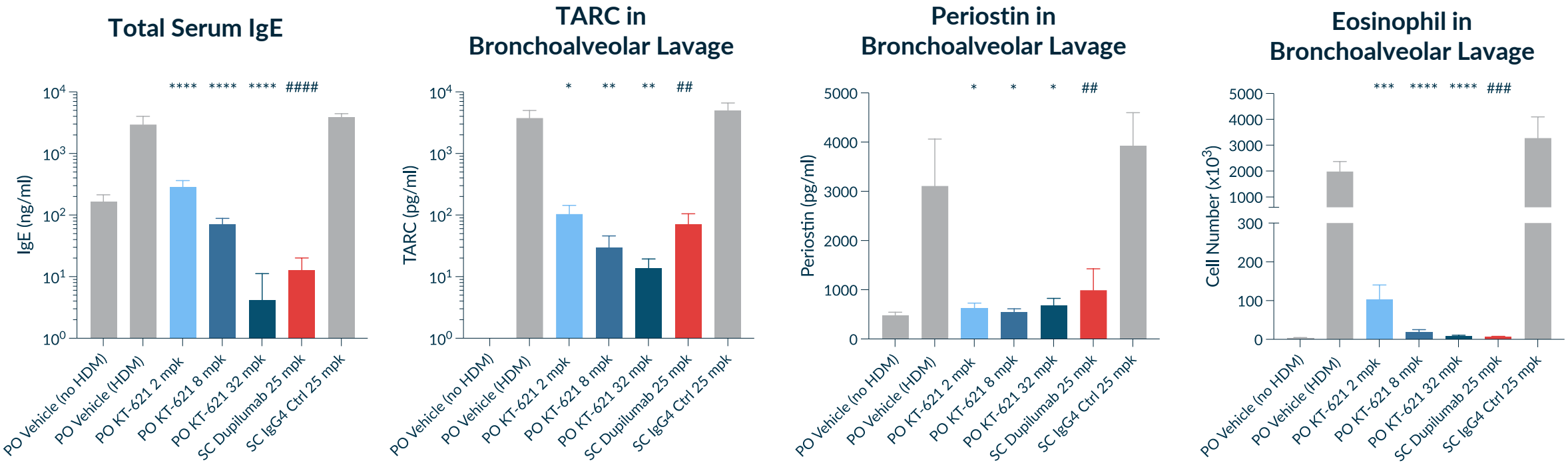
KT-621 Blocks TH2 Inflammation in vivo Equally or Better than an IL-4Rα Saturating Dose of Dupilumab in the Intranasal HDM Asthma Model

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)

- **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**



*Significance to PO vehicle (HDM); # Significance to SC IgG4 Ctrl 25 mpk

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Oral STAT6 Degrader: KT-621

Potential for dupilumab-like activity with oral small molecule profile

Upcoming Presentations: DDW & ATS 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

KT-621, 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 at >40x efficacious concentration

Currently in IND enabling studies

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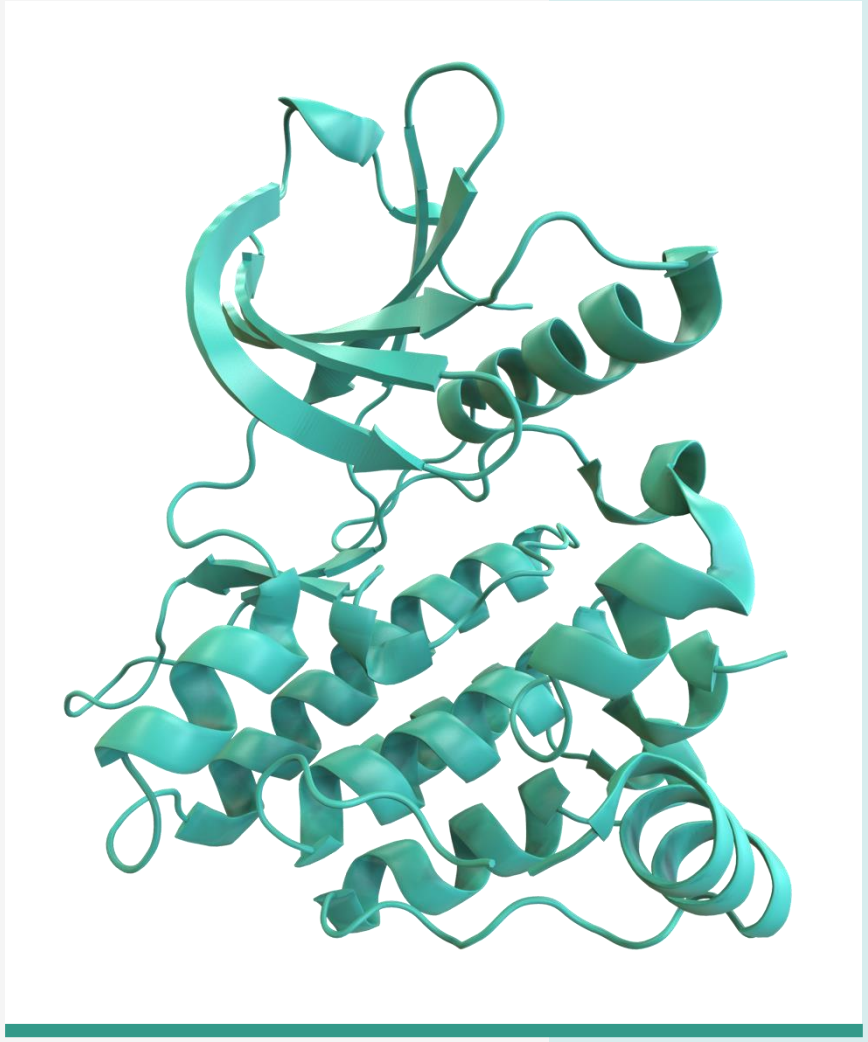

KT-294

A First-in-Class Oral TYK2 Degrader

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TYK2 Biology and Target Rationale

Target Biology and Rationale

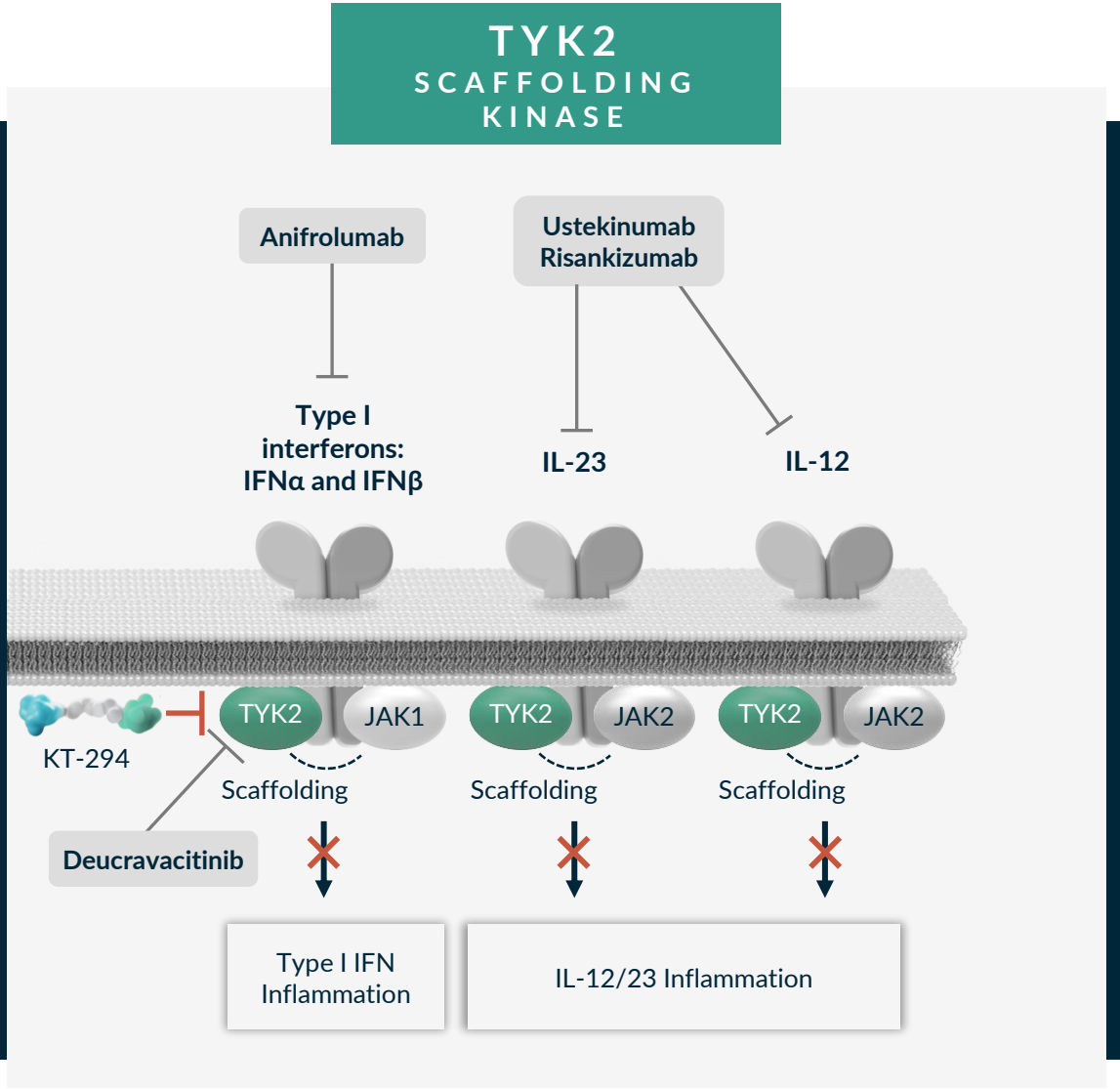
- TYK2 is a member of the JAK family required for Type I IFN, IL-12 and IL-23 cytokine signaling
- TYK2 regulated cytokines are clinically validated targets for autoimmune and inflammatory diseases

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



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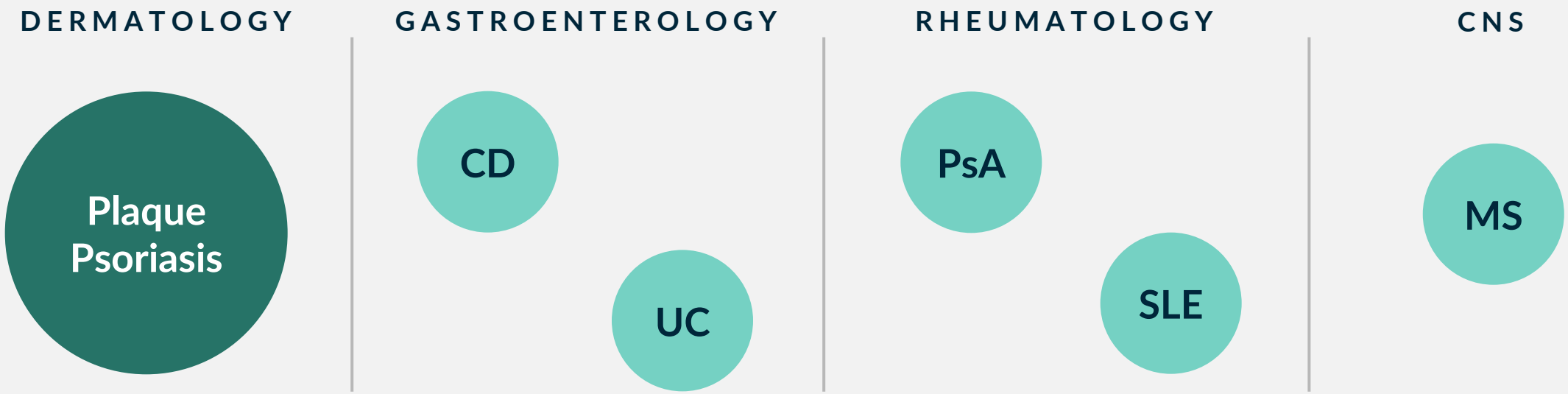
Patient Impact of TYK2: Potential Best-In-Class Opportunity in I&I



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

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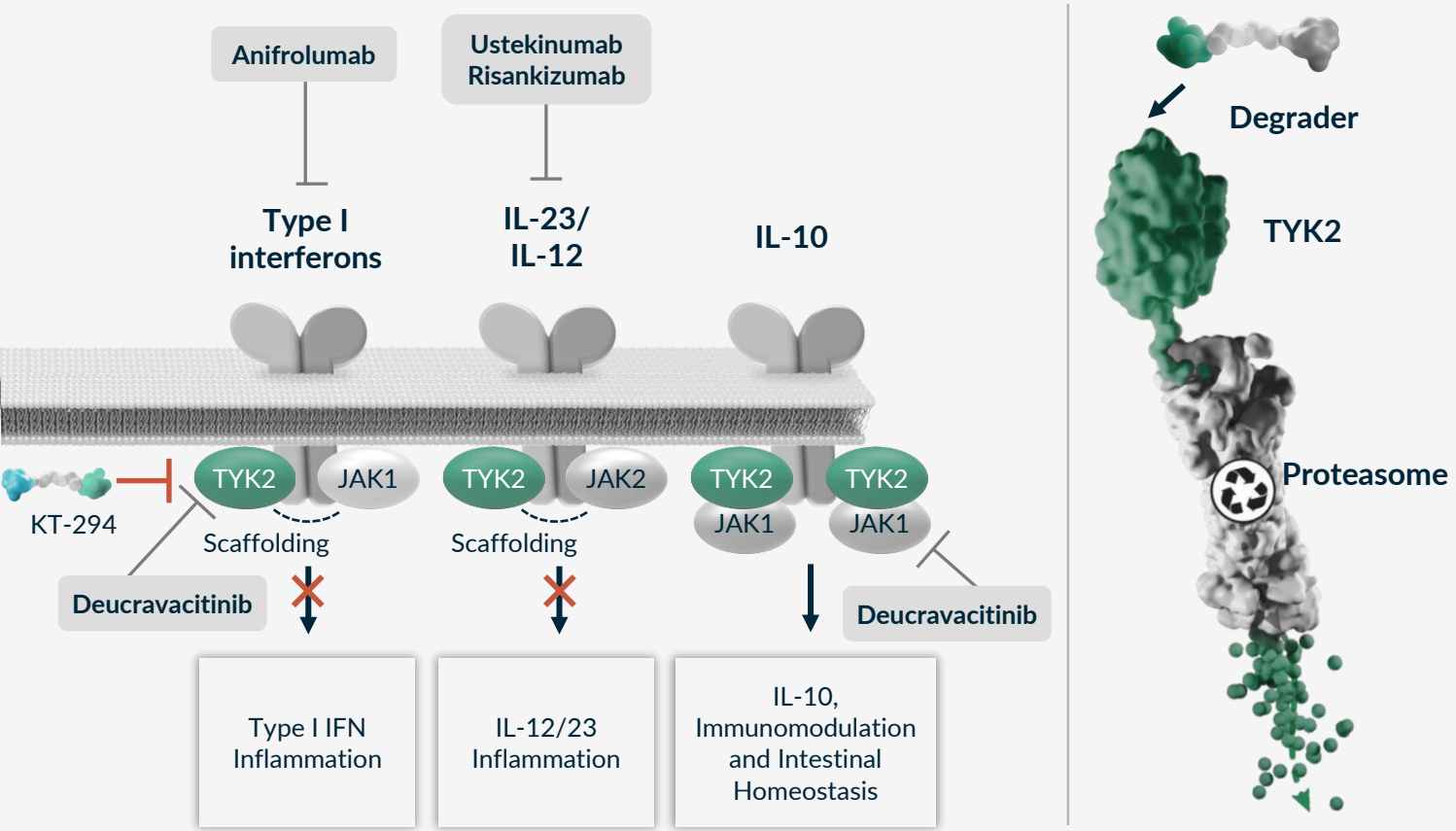
TYK2 Degrader Advantage

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

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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

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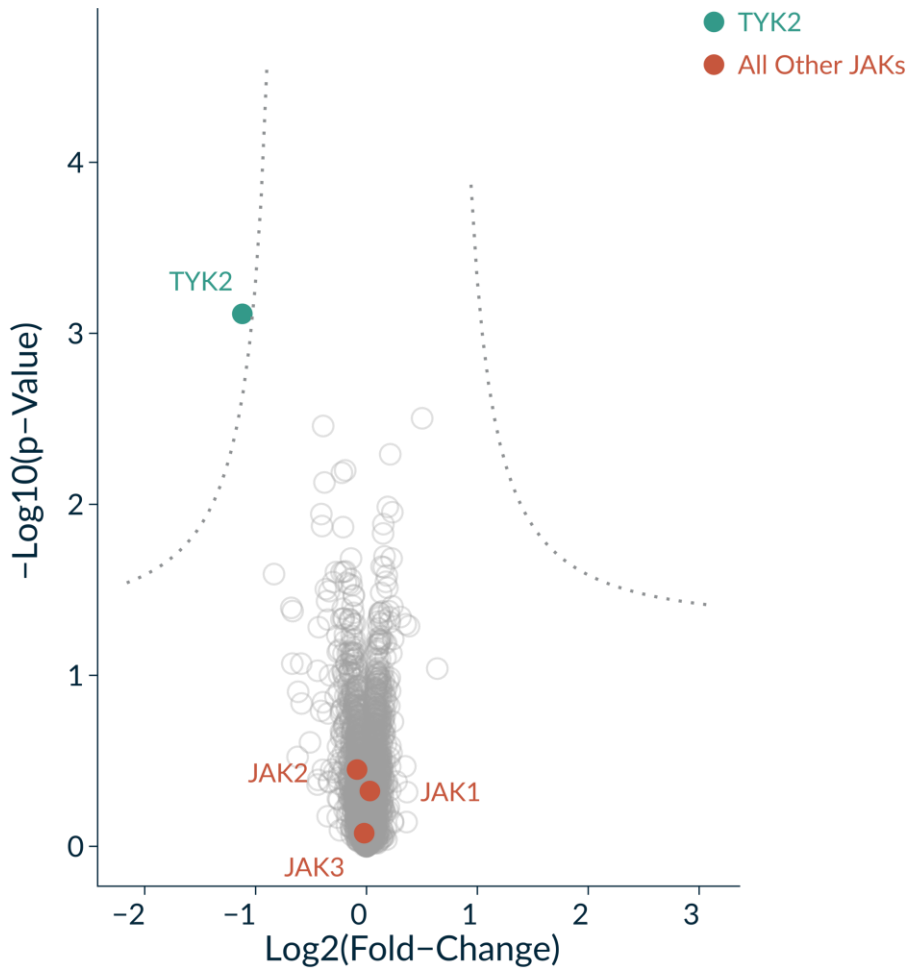
KT-294, a Highly Selective Picomolar TYK2 Degrader, Recapitulates TYK2 Human Deficiency Biology

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**

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

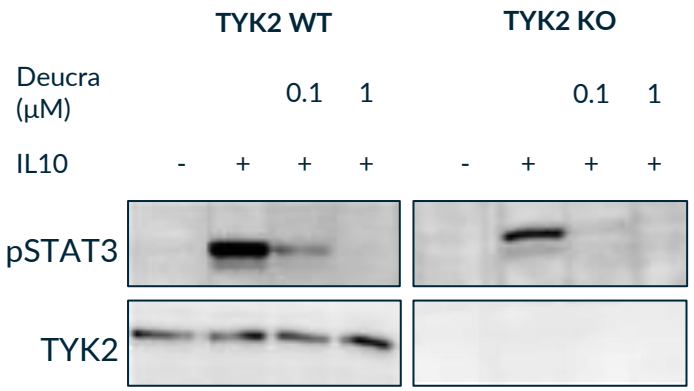
IL-10 has essential roles in intestinal homeostasis

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

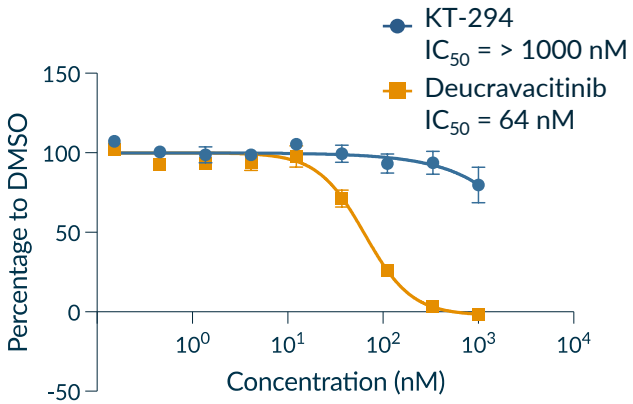
Deucravacitinib inhibits IL-10 because of its anti-JAK1 activity; KT-294 spares JAK1 and as a result IL-10

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

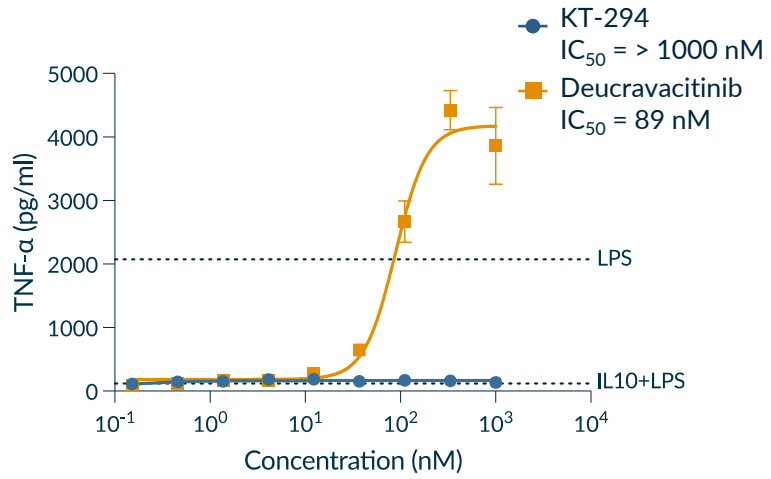
Deucravacitinib Inhibited IL-10 induced pSTAT3 in TYK2 KO EBV B Cell



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



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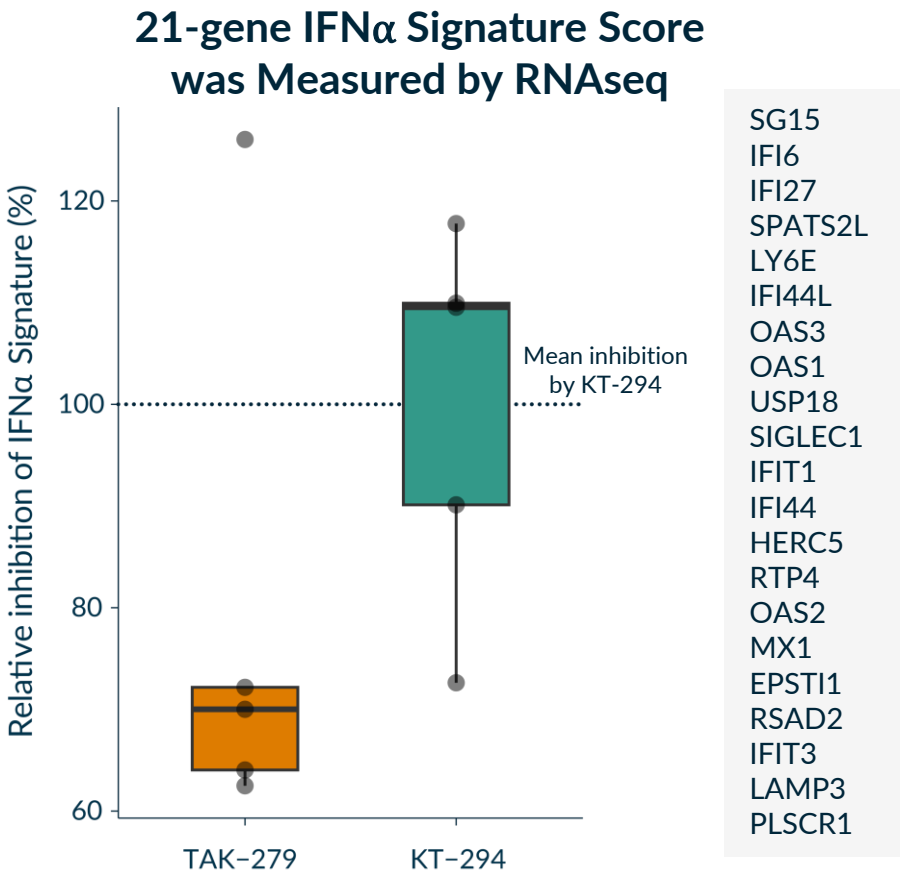
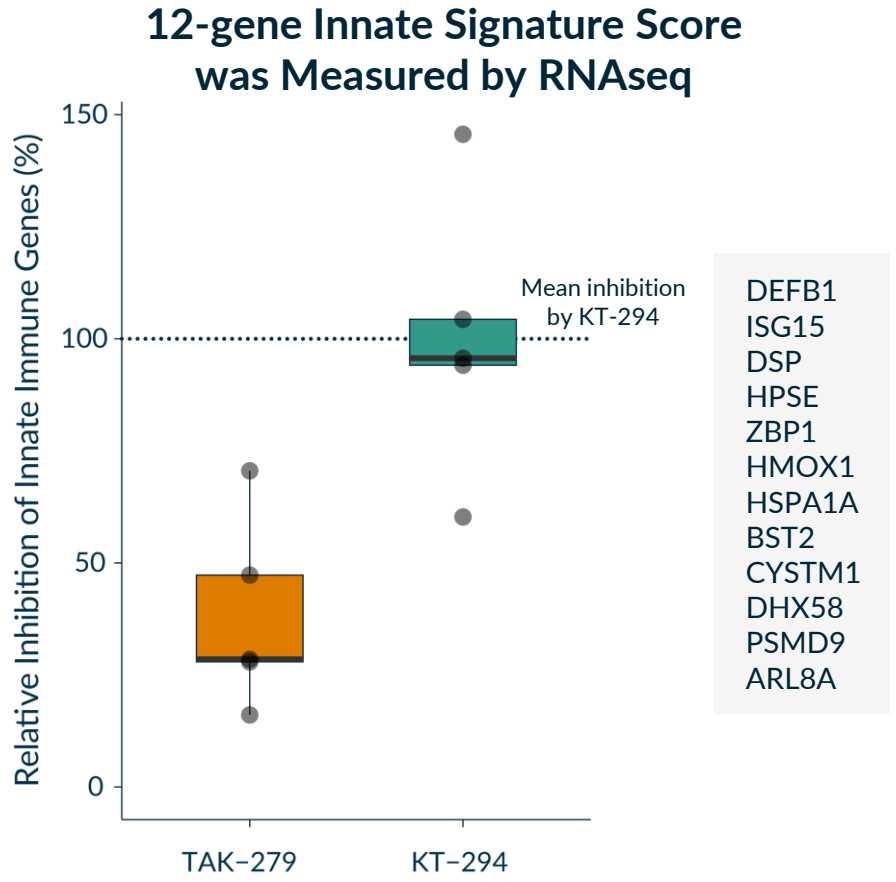
Superior Inhibition of Type I IFN Pathway and Innate Immunity by KT-294 vs TAK-279





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

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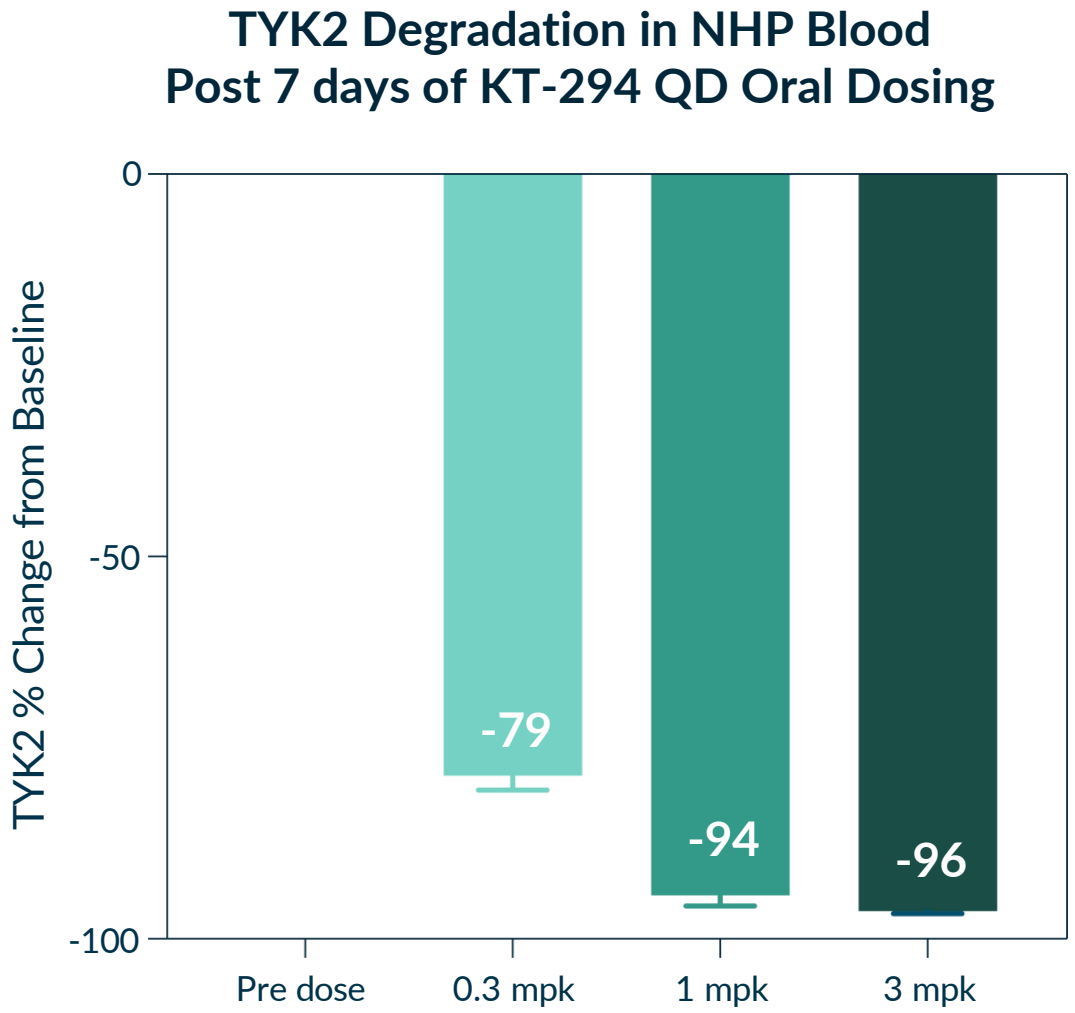
KT-294 Achieved Dose Dependent Deep Degradation of TYK2 *in vivo* with Low Oral Doses

KT-294 potently degrades TYK2 across multiple preclinical species

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



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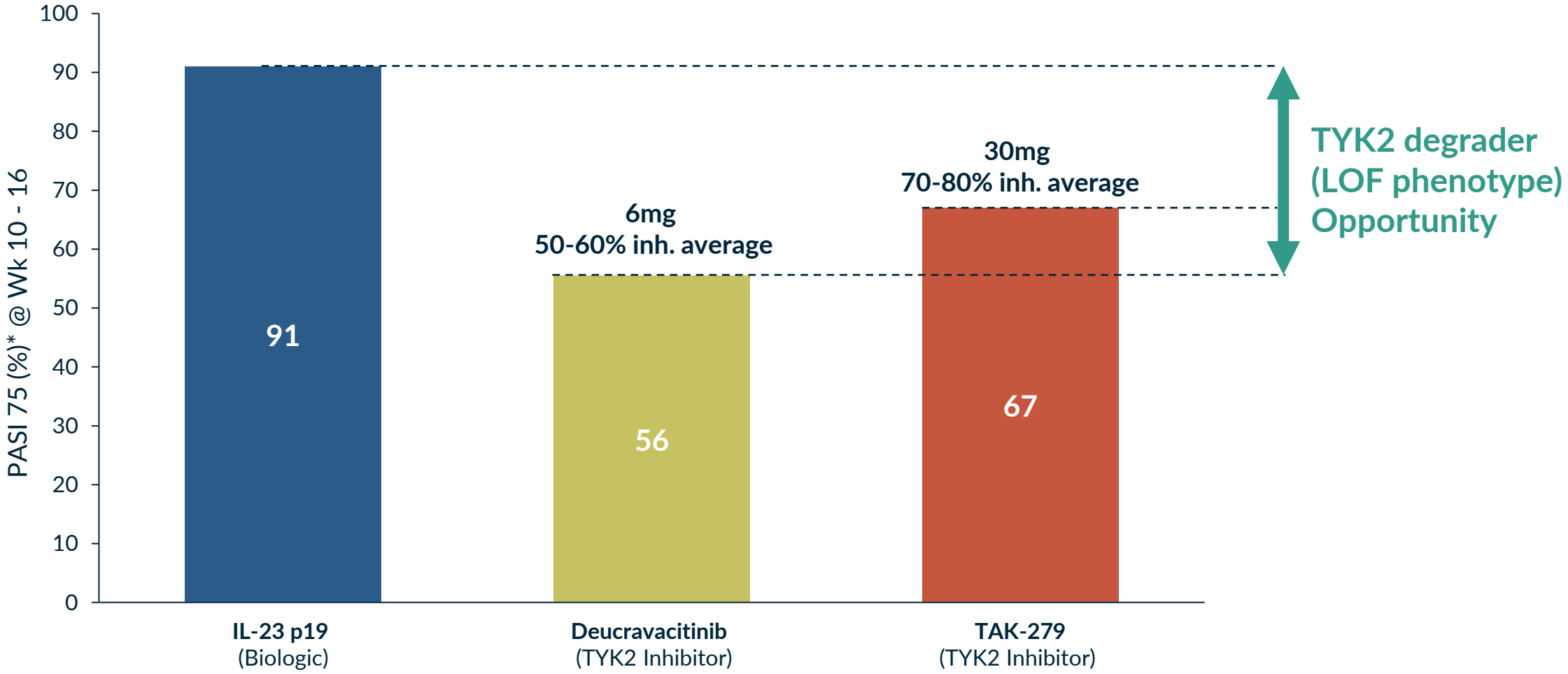
TYK2 SMI's Do Not Reach Maximal Target Engagement

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.

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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**

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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

KT-294, 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

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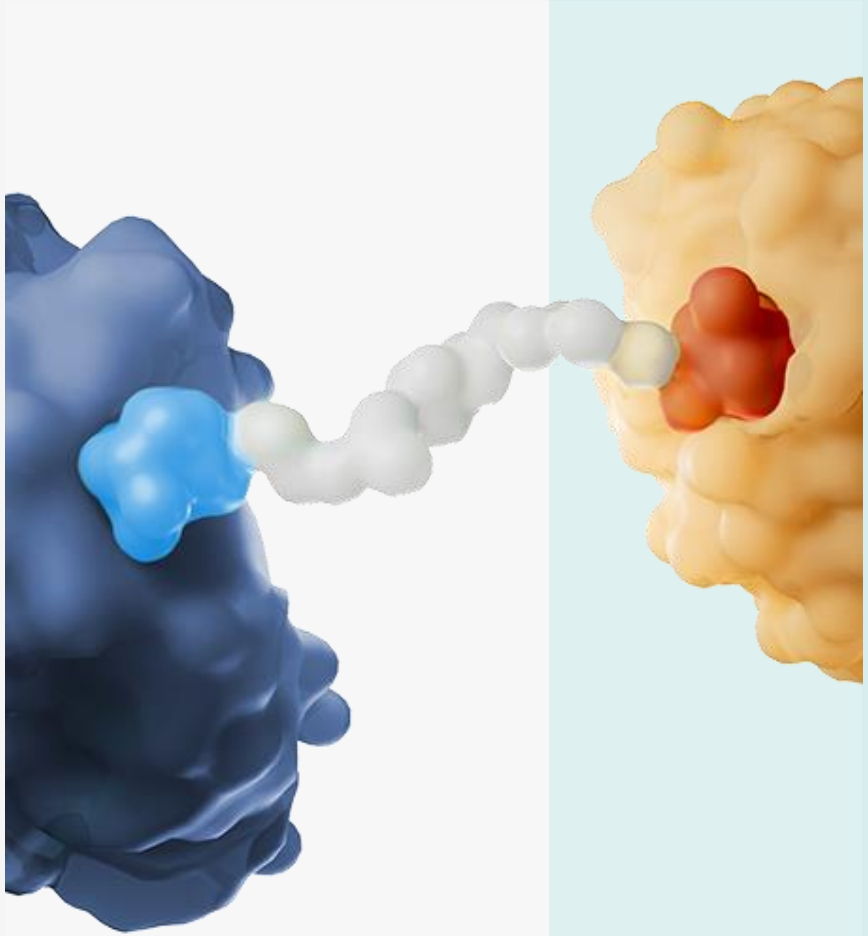

Kymera's Oncology Pipeline

MDM2, STAT3

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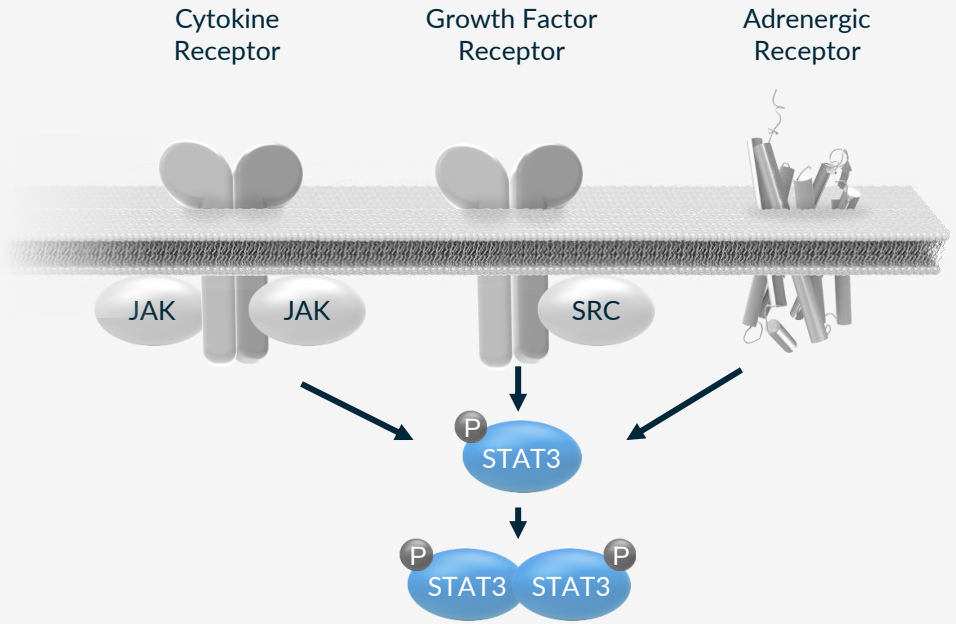
Kymera Oncology Degrader Portfolio

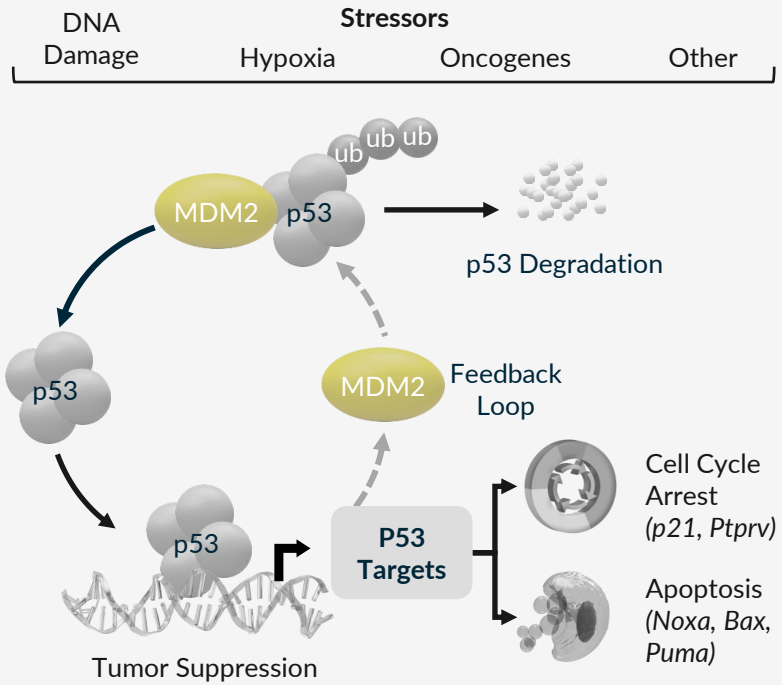
Targeting undrugged or poorly drugged targets in areas with large clinical and commercial impact, with focus on mechanisms that can address both liquid and solid tumors

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**

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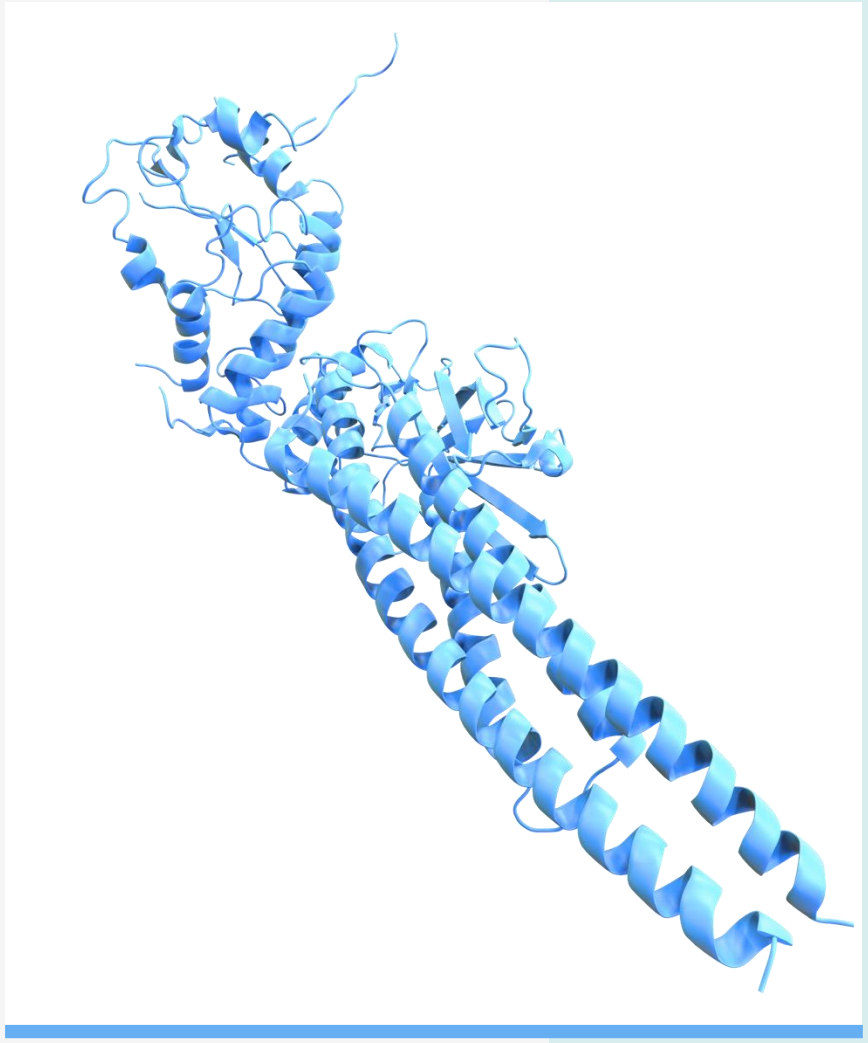

KT-333

A First-in-Class STAT3 Degrader

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STAT3 Biology and Target Rationale

Target Biology and Rationale

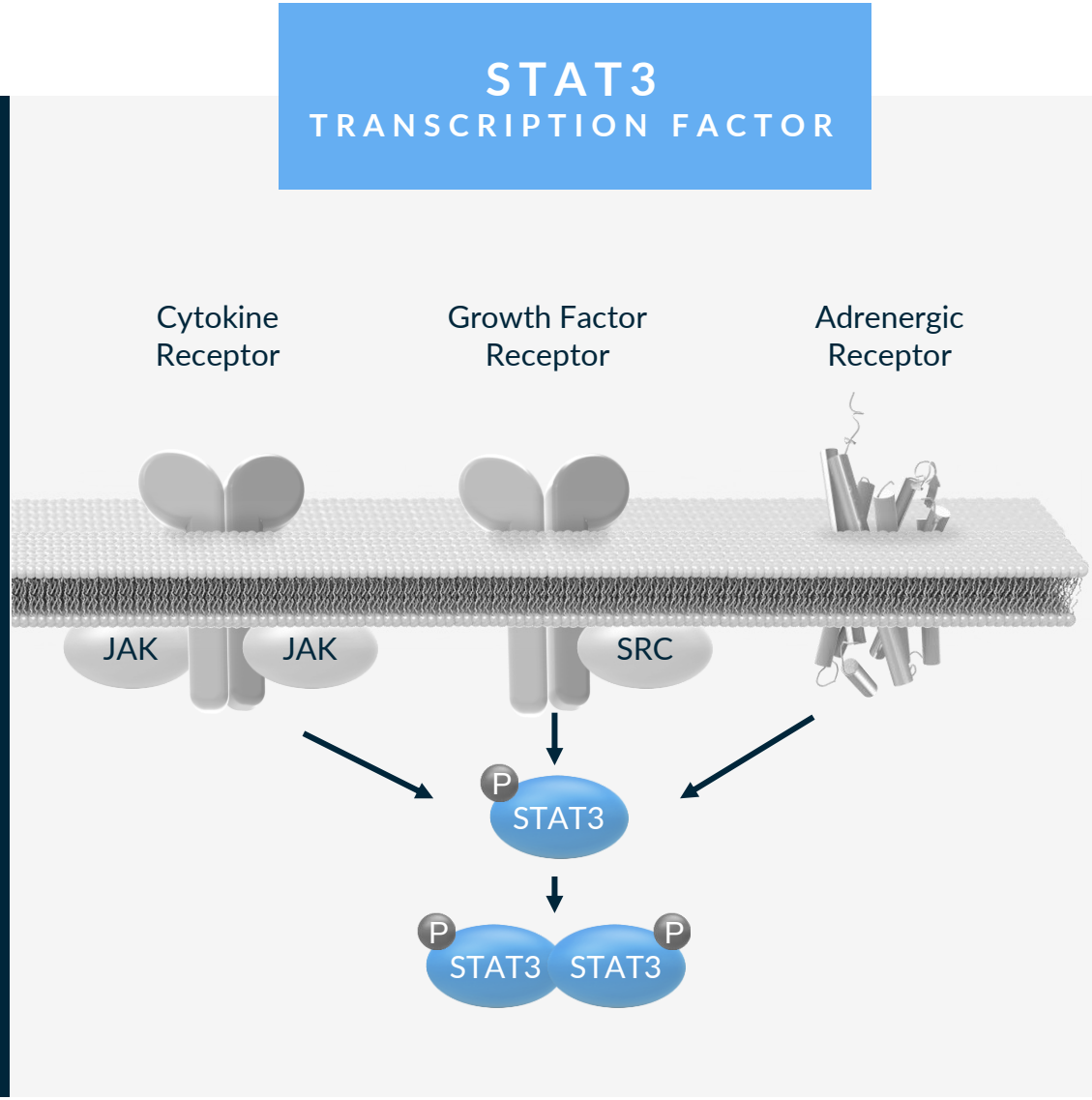
- STAT3 is a largely undrugged transcription factor activated through cytokine and growth factor receptors via JAKs and non-JAK mediated mechanisms
- STAT3 plays a role in tumor biology, evasion of immune surveillance and inflammation/fibrosis
- No known drugs selectively block STAT3 broadly across all 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



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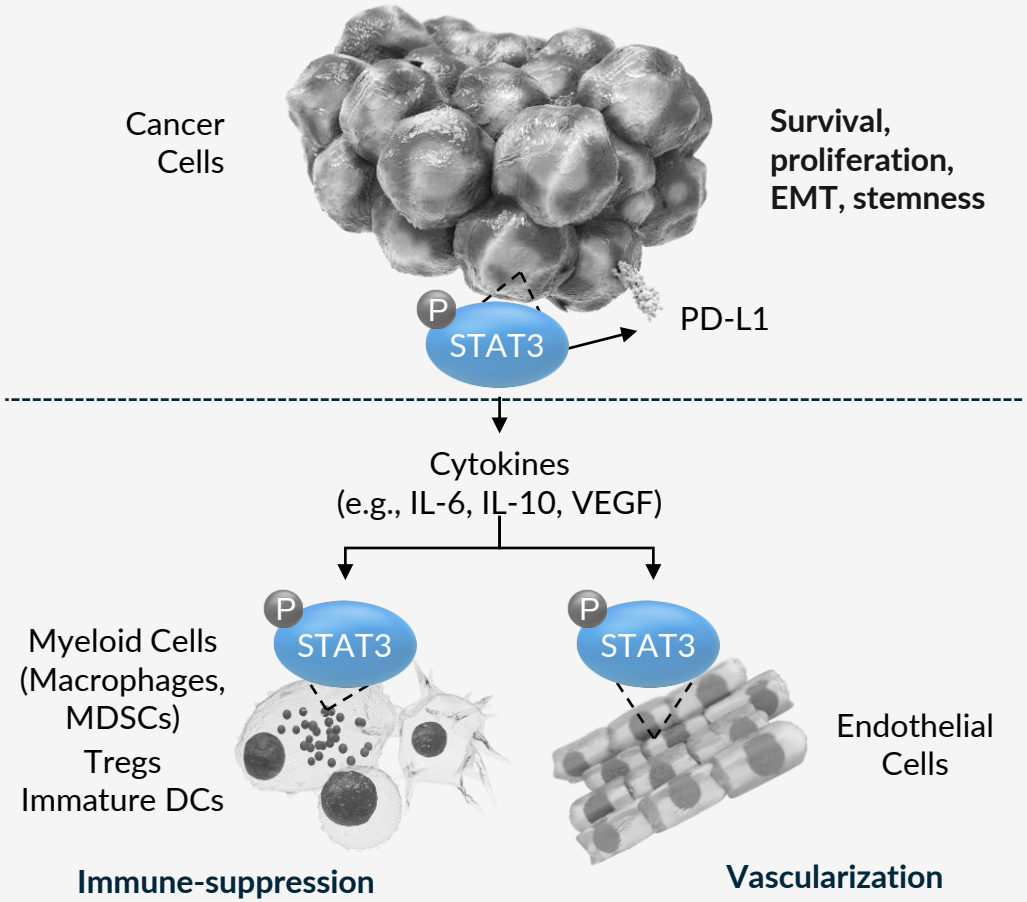
STAT3 Has Unique Tumor Cell Intrinsic and Extrinsic Mechanisms

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) & 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 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, cHL, others)



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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 anti-tumor activity** across multiple T-cell lymphoma models (ALCL and CTCL)	• **TME remodeling with induction of IFN-γ signature** in solid tumor models leading to **sensitization to anti-PD-1** • **Single agent growth inhibition in solid tumor** models (undisclosed)
Clinical	• Anti-tumor activity in ongoing Phase 1a study in CTCL and Hodgkin's lymphoma with **multiple PRs**	• **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 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, Ricciuti B 2022 JTO. Note: R.O.W = France, Germany, Italy, Spain, UK, and Japan.

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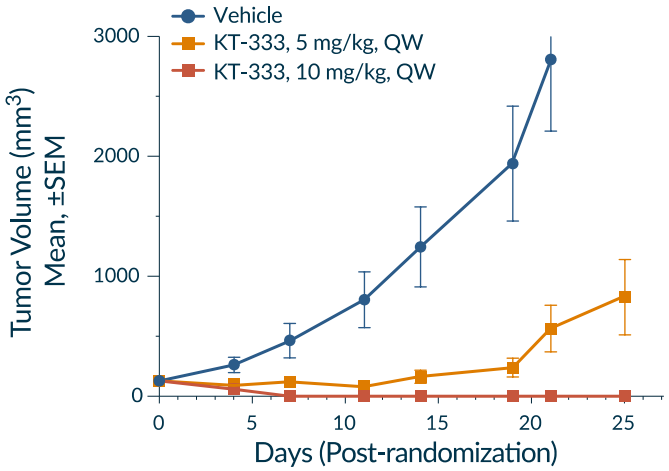
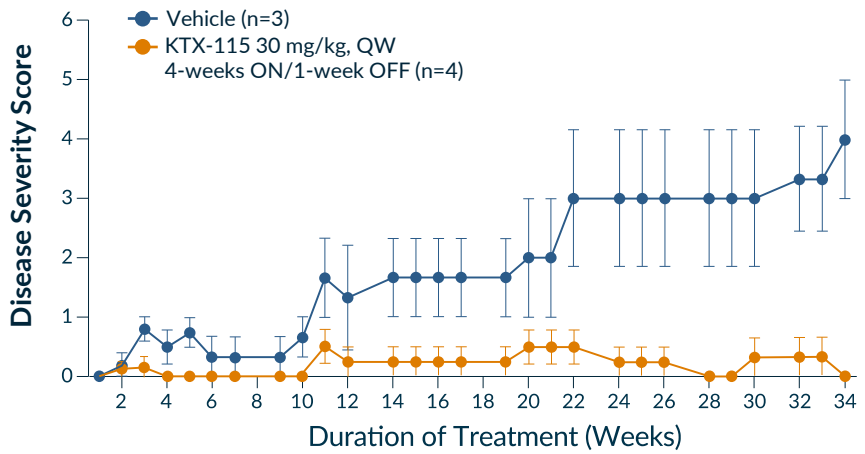
Durable Anti-Tumor Activity of STAT3 Degradation as a Single Agent in Preclinical Models of T cell Lymphoma



ALK+ ALCL
SU-DHL-1

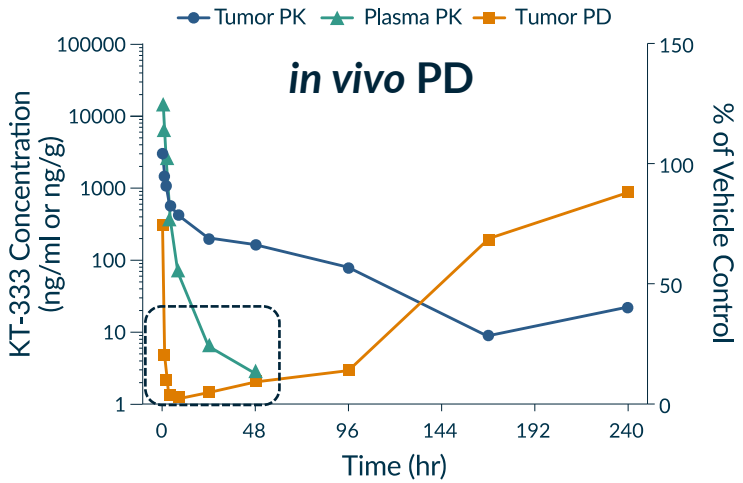
64th ASH® Annual Meeting and Exposition



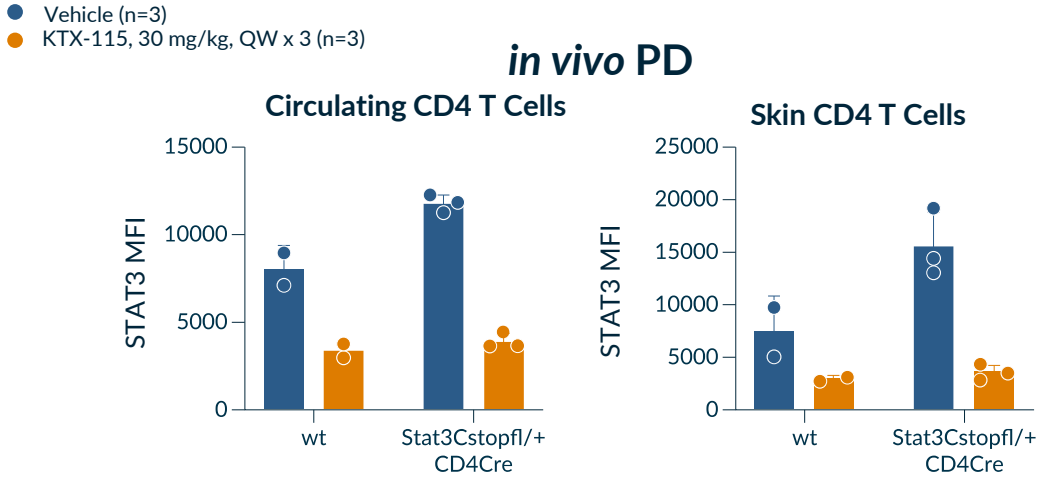
CTCL
GEMM *Fanok et al. (2018)*
Collaboration with NYU

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



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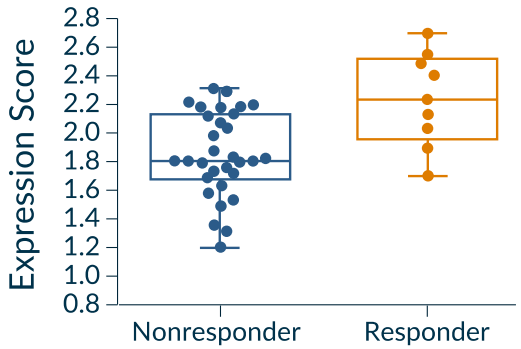
STAT3 Degradation Elicits an IFNγ Gene Signature in TME and Sensitizes Solid Tumor Mouse Models to PD-1 Inhibition

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

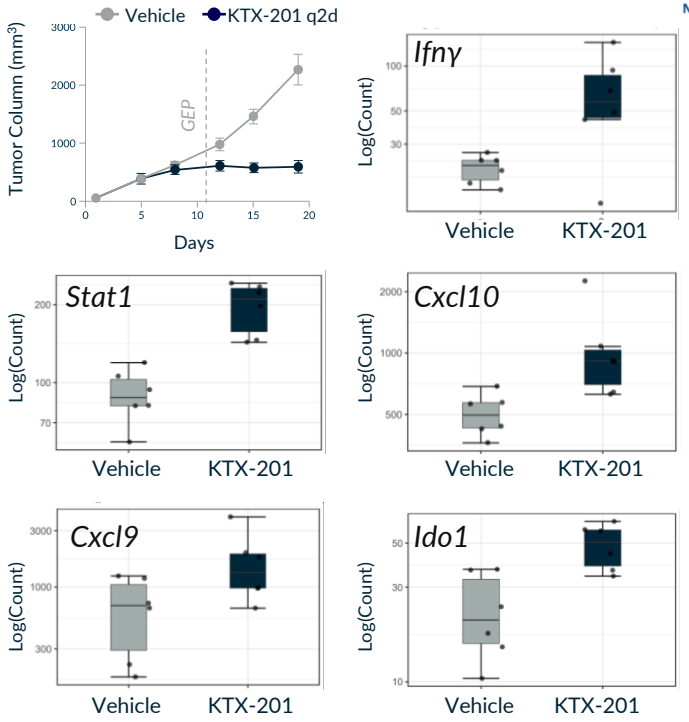
IFNγ, and Expanded Immune Gene Signature

IFN-γ
IDO1
CXCL10
CXCL9
HLA-DRA
STAT1
IFNG

IFNγ Signature



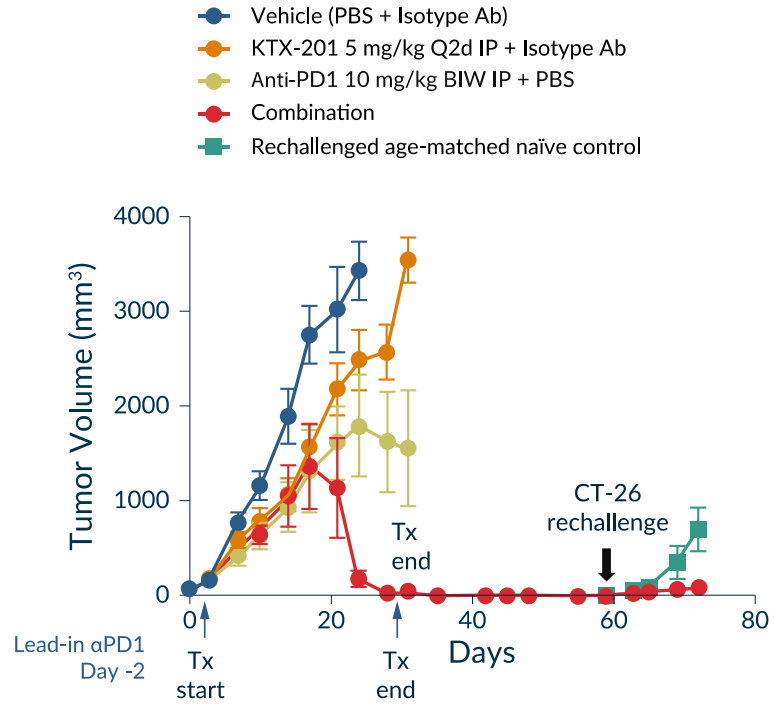
IFNγ mRNA Signature in TME Elicited by STAT3 Degradation in CT-26 Preclinical Model



On treatment - Day 11; n=6/grp

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

CT-26



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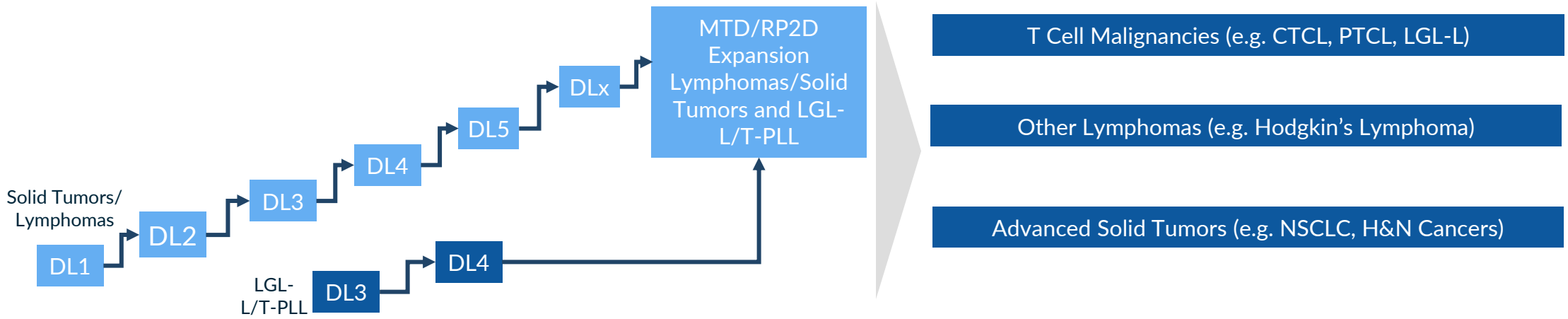
KT-333: Phase 1, Multicenter, Dose-Escalation and Expansion Trial to Evaluate KT-333

Adult Patients with Lymphomas, Leukemias and Solid Tumors

Phase 1a
Dose Escalation & MTD/RP2D Expansion (n=~45)

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

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KT-333 Safety Summary: DL1-5

Data cut-off date of October 18, 2023

- Overall, KT-333 well-tolerated with primarily Gr. 1-2 AEs
- 2 DLTs observed (Gr. 3 stomatitis, Gr. 3 arthralgia) both in LGL-L patients at DL5; No DLTs in solid tumor/lymphoma patients at any dose level
- Led to protocol amendment to assess safety/MTD in solid tumor and lymphoma patients separately from leukemic patients (LGL-L, T-PLL)
  - Solid tumor/lymphoma- currently at DL5 with plan to continue dose escalation as planned
  - LGL-L/T-PLL- currently at DL3 with max escalation to DL4
- Most common related AEs across all patients (n=29), n (%):
  - Stomatitis, 6 (21%)
  - ALT increase, 3 (10%)*
  - AST increase, 2 (7%)*
- Related Grade 3 AEs**: 1 pt each: Stomatitis, arthralgia, weight decreased

*all Gr 1; **no Gr 4 or Gr 5 related AEs

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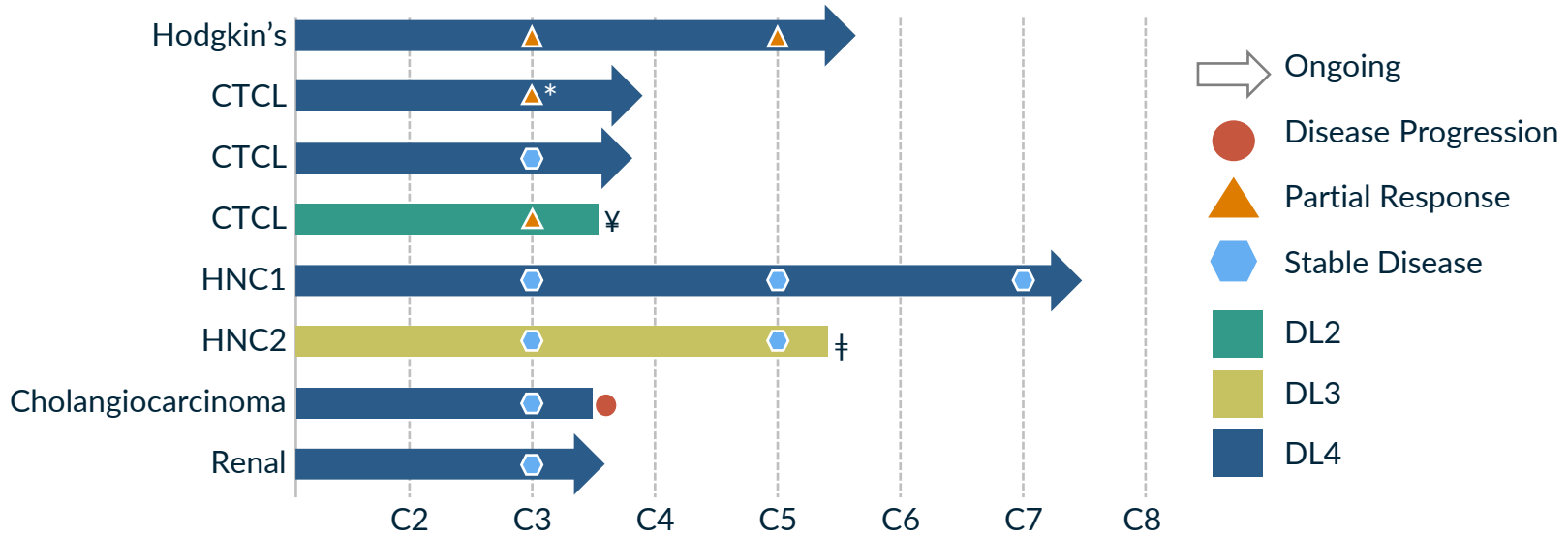
Responses Observed Across Multiple Tumor Types During Dose Escalation of KT-333

Data cut-off date of October 18, 2023

Tumor Type	Best Response
CTCL (n=5)	**2 PR** **1 SD** 2 PD
cHL (n=1)	**1 PR**
PTCL (n=1)	1 PD
LGL-L (n=2)	Not Evaluable
Solid Tumors (n=12)	**4 SD*** 8 PD

*Mucoepidermoid carcinoma of parotid gland (C7+), sinonasal adenocarcinoma (C5), cholangiocarcinoma (C3), renal cell cancer (C3+)

Duration on Treatment for Patients with Response of SD or Better



* Received steroids during 1st week of C1 to treat symptoms arising from Sezary Syndrome; ¥ Discontinued d/t AE (Gr. 2 squamous cell carcinoma of skin); ‡Discontinued d/t PI discretion (stable disease at discontinuation); HNC1 = Mucoepidermoid carcinoma of parotid gland; HNC2 = Sinonasal adenocarcinom

- **Disease control in 3 of 5 CTCL patients including 2 PR's and 1 SD; 1 PR in cHL, demonstrating single agent activity in liquid tumors supported by preclinical data**
- **In solid tumors, where preclinically no strong single agent activity was observed, a pattern of more prolonged SD in H&N tumors was seen with overall 4 patients with SD**

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Robust STAT3 Degradation in PBMCs and Tumor

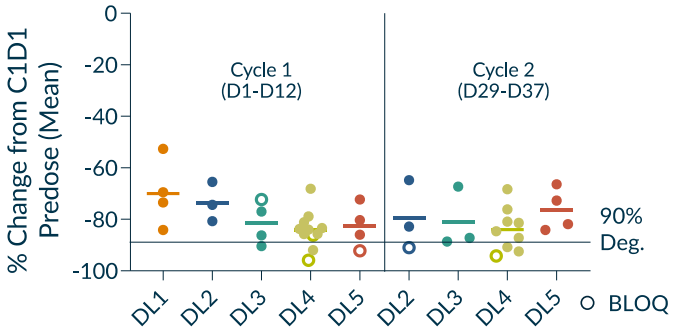
Maximum Degradation of STAT3 in PBMCs

Per Cohort (min, max; N)

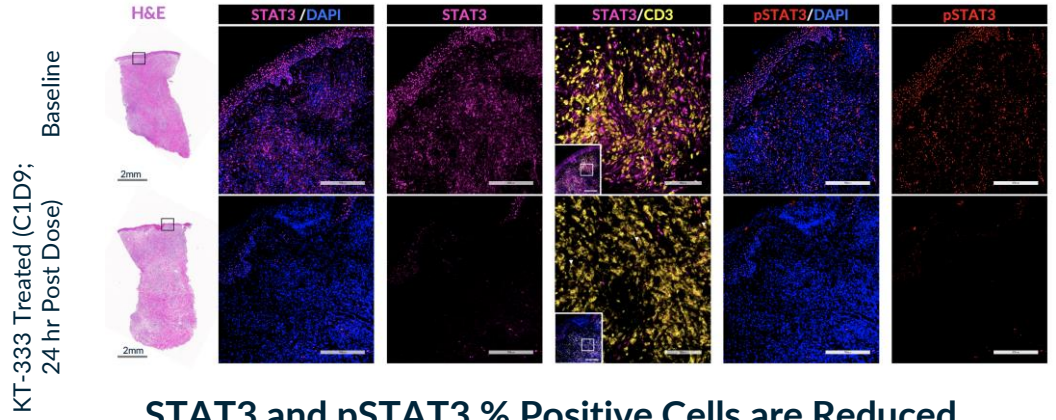
Dose Level	Cycle 1 D1-D12	Cycle 2 D29-D37
0.05 mg/kg	**-69.9%** (-52.6%, -84.1%; 4)	N/A
0.1 mg/kg	**-73.5%** (-65.5%, -80.7%; 3)	**-79.5%** (-64.8%, -91.0%*; 3)
0.2 mg/kg	**-81.5%** (-72.3%*, -90.4%; 4)	**-81.0%** (-67.3%, -88.6%; 3)
0.4 mg/kg	**-84.0%** (-68.1%, -95.9%*; 11)	**-84.0%** (-68.3%, -94.2%*; 9)
0.7 mg/kg	**-82.7%** **(-72.3%, -92.2%*; 4)**	**-76.3%** (-66.4%, -84.1%; 4)

*BLOQ

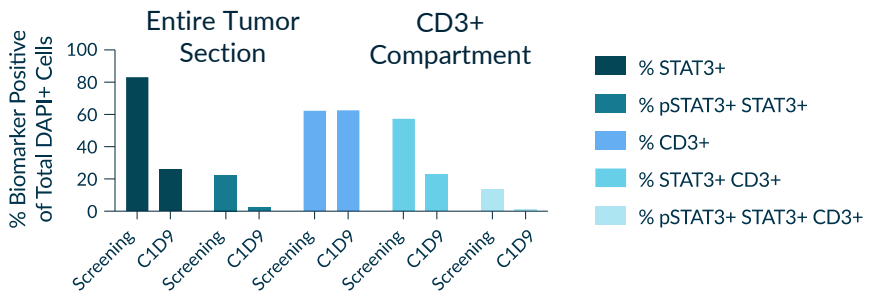
Per Patient (min, max; N)



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

- **Strong proof-of-mechanism for KT-333 with up to 96% maximum degradation of STAT3 in PBMCs**
- **STAT3 and pSTAT3 positive cells reduced by 69% and 87% in tumor**

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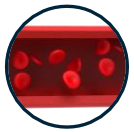
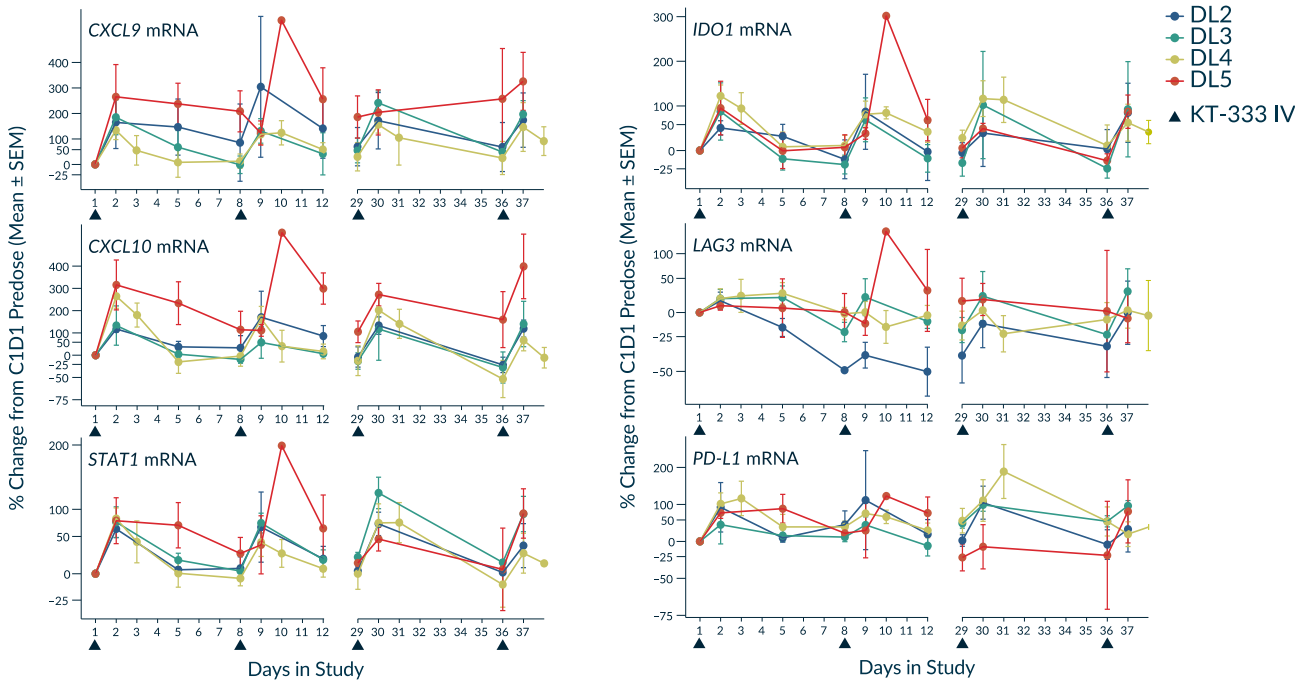
STAT3 Degradation Elicits IFN-γ Response Gene Signature in Blood and Tumor

Blood

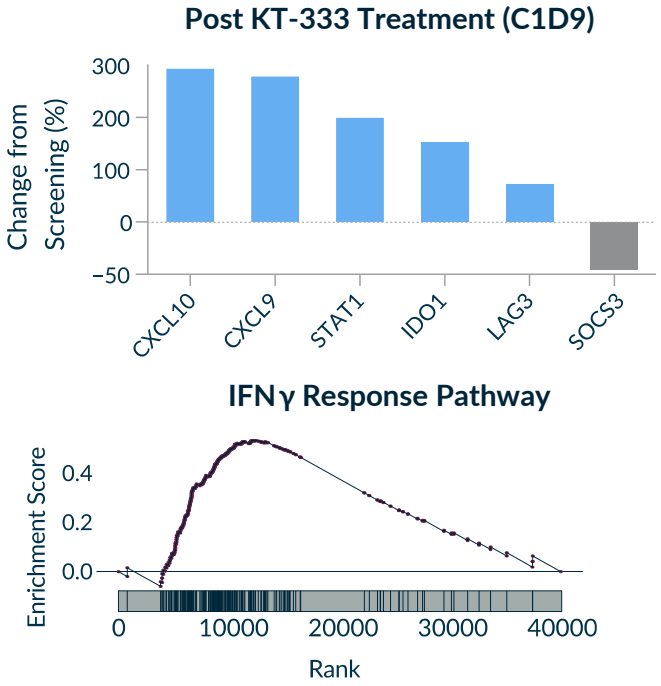


Time Course of Transcriptional Induction of Select IFNγ Stimulated Genes Post KT-333 Infusion



Tumor

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



Induction of IFN-g 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

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STAT3 Degrader: KT-333

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

Upcoming Presentation: EHA 2024

Interim Clinical Data

Strong proof-of-mechanism with up to 96% maximum degradation of STAT3 in PBMCs

STAT3 and pSTAT3 positive cells reduced by 69% and 87% in tumor

Disease control in 3 of 5 CTCL patients (2 PR's and 1 SD) and 1 PR in cHL, demonstrating single agent activity

Robust STAT3 knockdown and induction of antitumor IFN-γ response in tumor biopsies

In solid tumors, a pattern of more prolonged SD in H&N tumors was seen with overall 4 patients with SD

Significant Opportunity

First heterobifunctional degrader against an undrugged target in the clinic

Clinical development strategy includes monotherapy direct registrational path in STAT3 dependent T cell malignancies

Opportunity for expansion into solid tumors in combination with immune checkpoint inhibitors and targeted therapy

P1a Completion: 2024

Completion of Phase 1a dose escalation expected 2024

Evaluate next steps including potential expansion into Phase 1b at RP2 dose in liquid and solid tumors

Solid tumor opportunity in combination with immune checkpoint inhibitors and target therapy to be informed by preclinical data and planned analysis of TME remolding in solid tumor biopsies from ongoing trial

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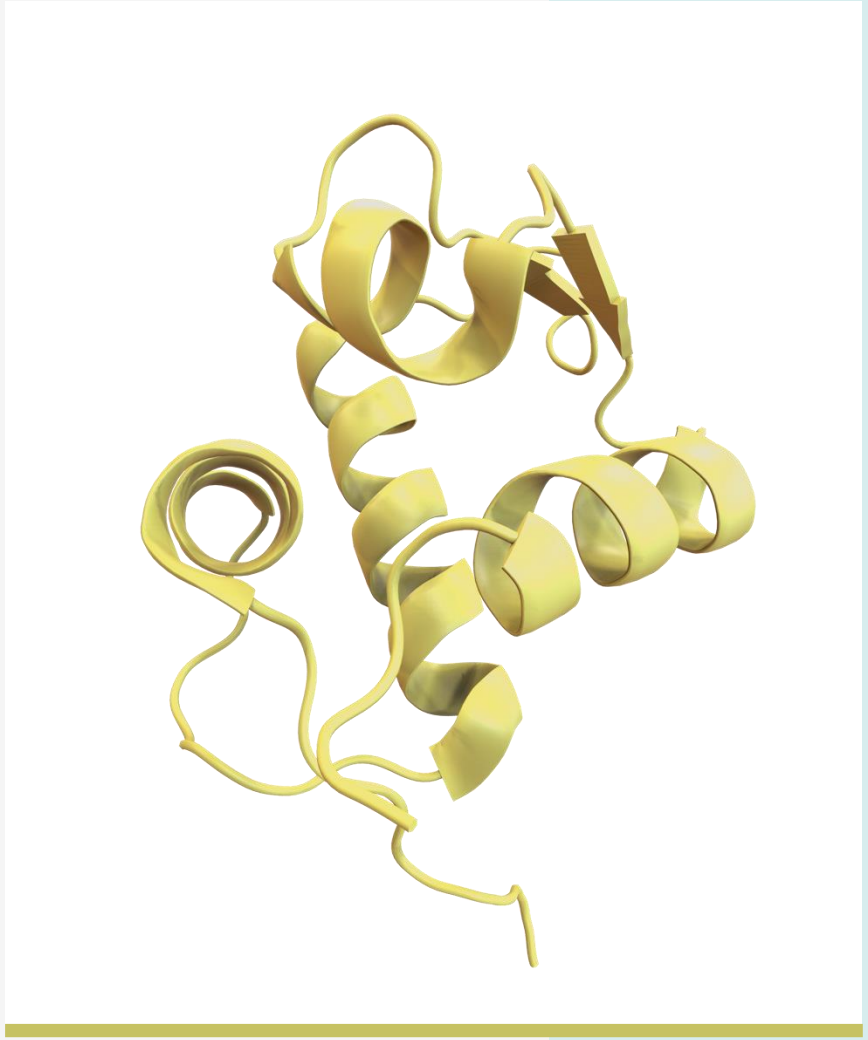

KT-253

A First-in-Class MDM2 Degrader

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MDM2 Biology and Target Rationale

Target Biology and Rationale

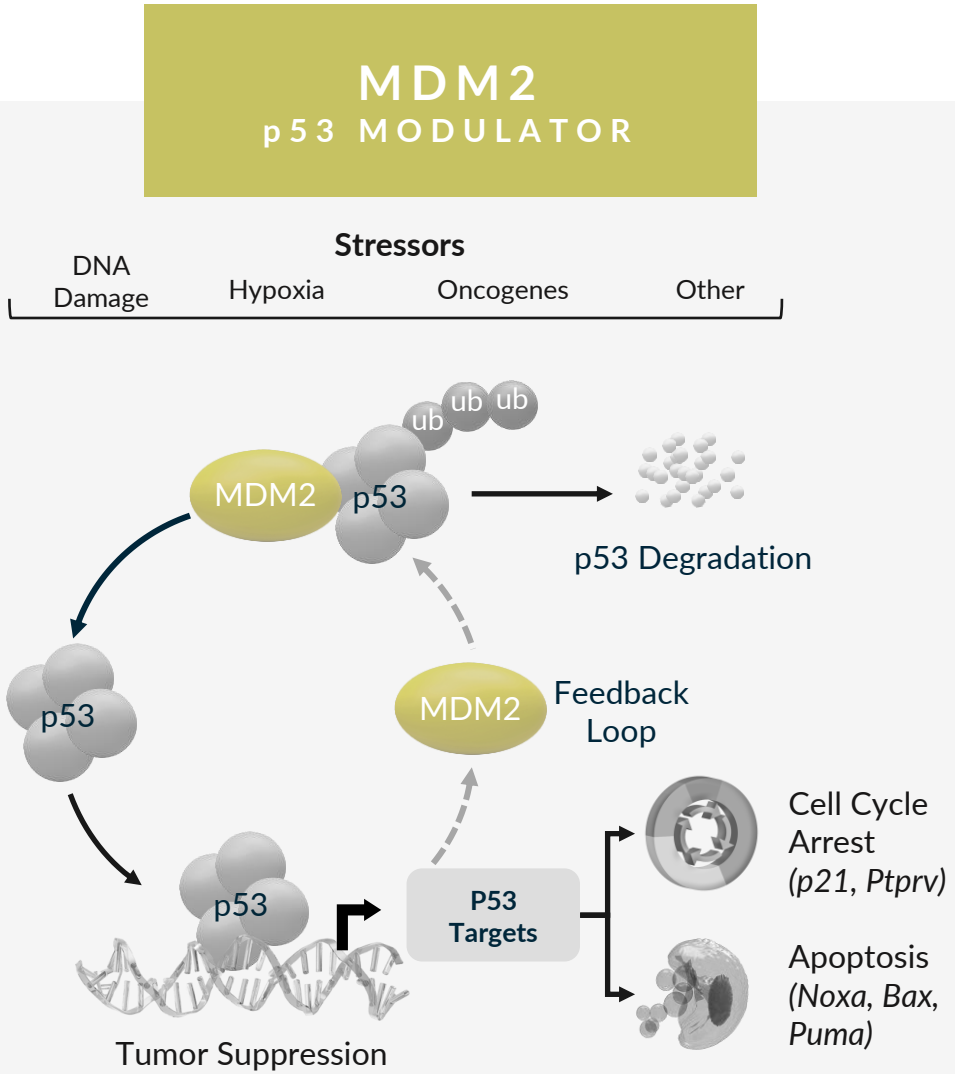
- MDM2 is the E3 ligase that modulates p53, the largest tumor suppressor
- MDM2 overexpression and amplification can inactivate p53 in the 50% of tumors that are p53 WT
- Activity of small molecule inhibitors of MDM2 limited by p53-MDM2 feedback loop that interferes with pharmacologic effect of SMIs

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
- Only MDM2 degradation has potential to phenocopy impact of genetic deletion in p53 WT tumors



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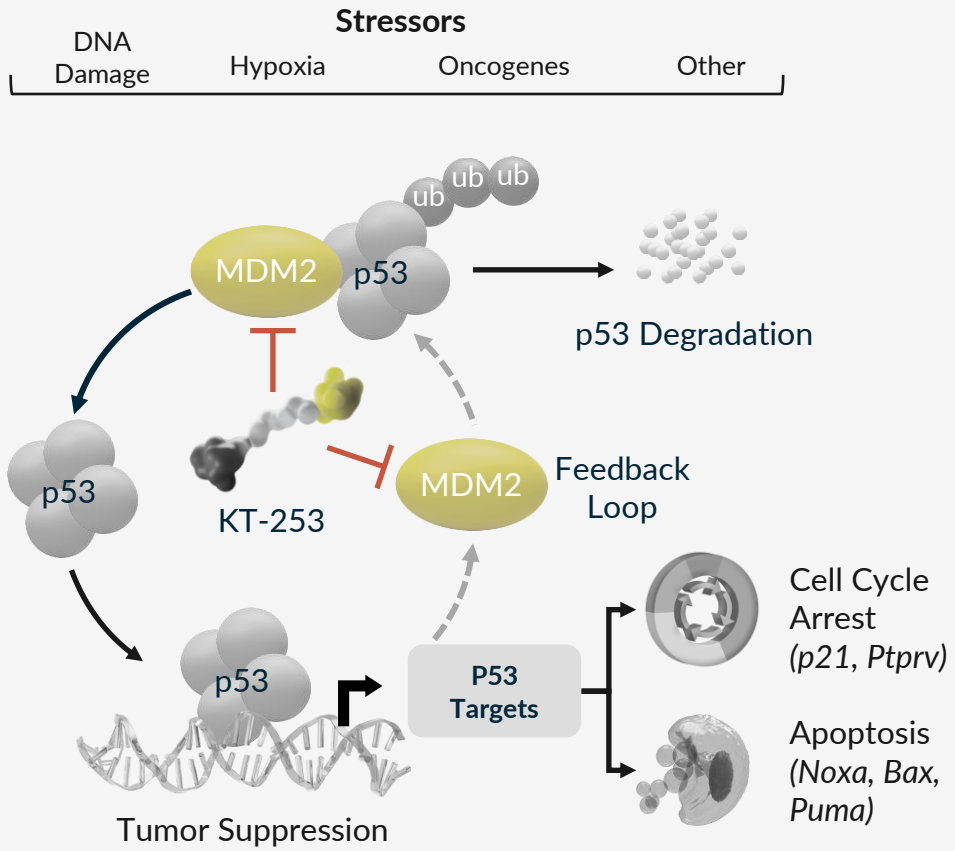
MDM2 Degrader Advantage



- 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

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KT-253: 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

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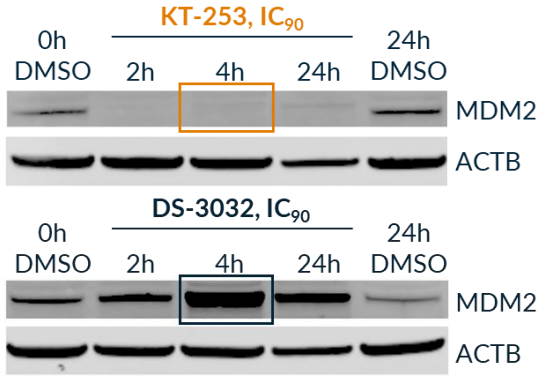
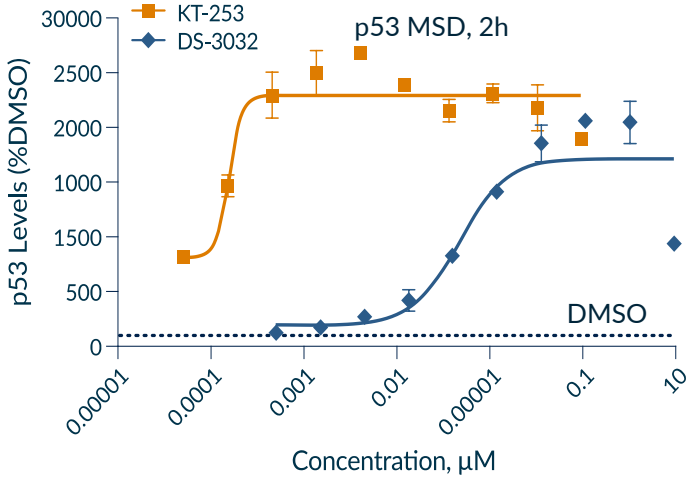
KT-253's Potent p53 Stabilization with Brief Exposures Drives Apoptosis in Cancer Cells

KT-253 Keeps MDM2 Levels Undetectable, Stabilizing p53

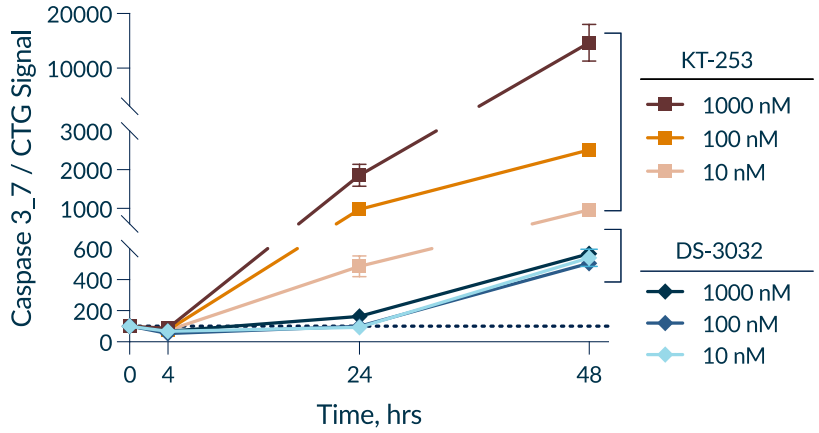


MDM2 levels are increased by the small molecule inhibitor (feedback loop), impairing p53 stabilization

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

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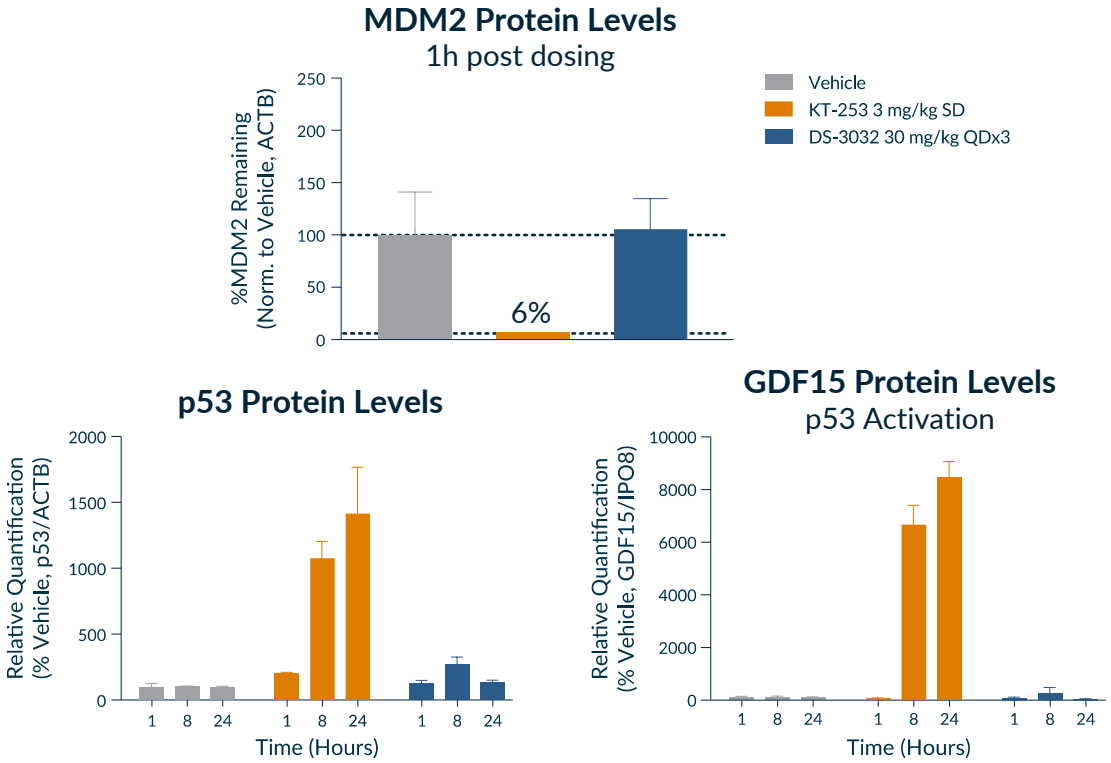
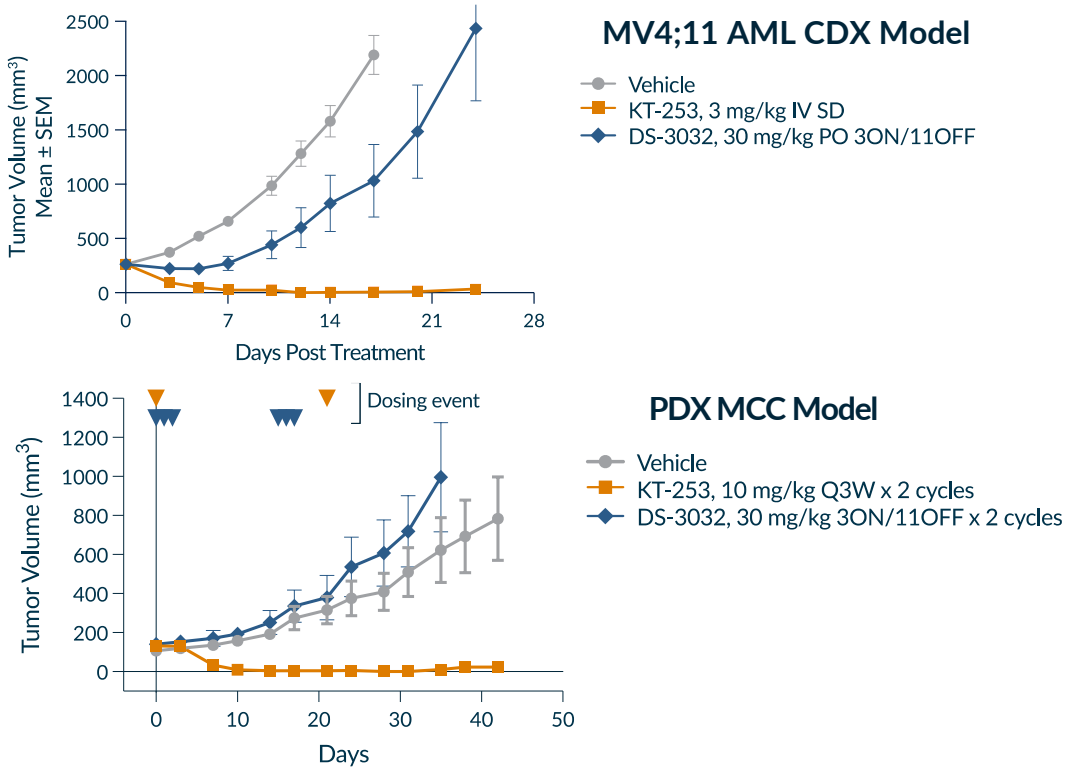
KT-253 Potently Degrades MDM2 leading to Pathway Impact and Antitumor Activity Superior to SMI in AML and MCC Models

MDM2 Degradation Leads to Superior P53 Upregulation vs SMI



- 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

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



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

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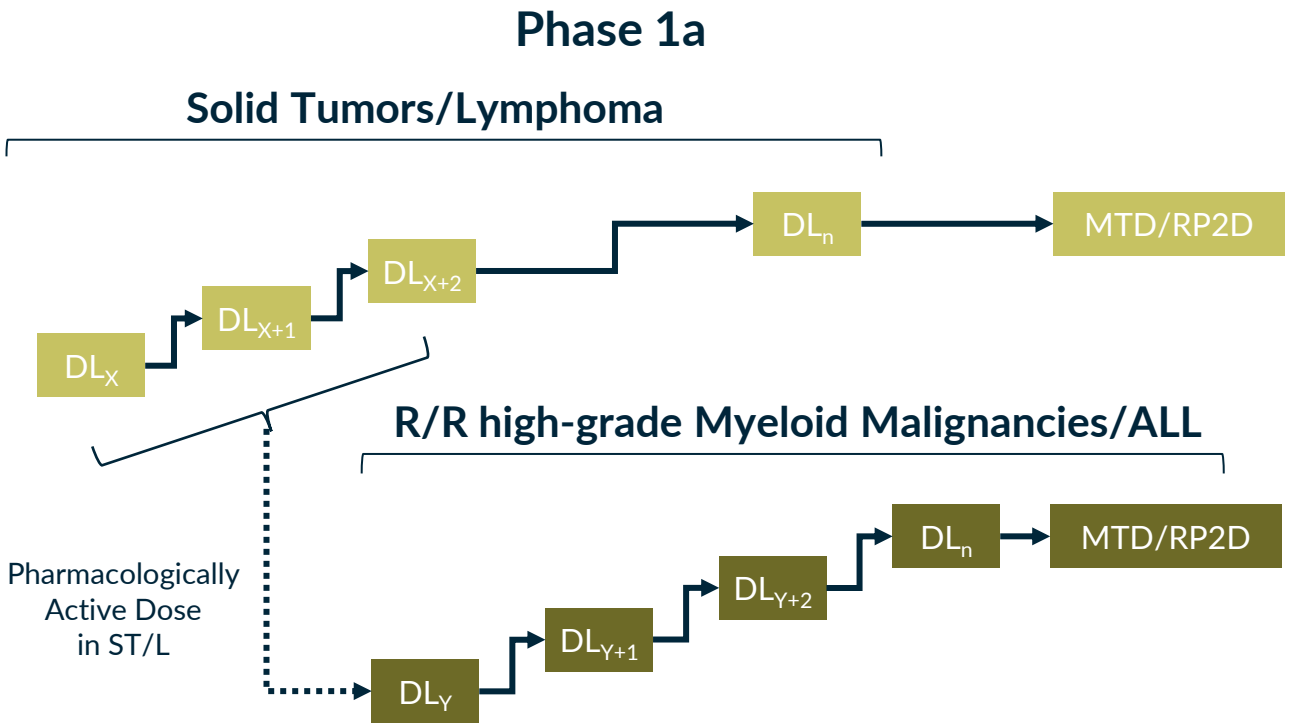
KT-253 Phase 1a: Study Design



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

Clinical Trial Design

- Arm A: R/R Solid Tumors and Lymphomas
  - 9 patients enrolled across first three dose levels
- Arm B: R/R high-grade Myeloid Malignancies/ALL
  - Enrollment initiated
- Regimen: IV infusion once every 3 weeks

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KT-253 Clinical Summary

As of October 20, 2023, Cut-off

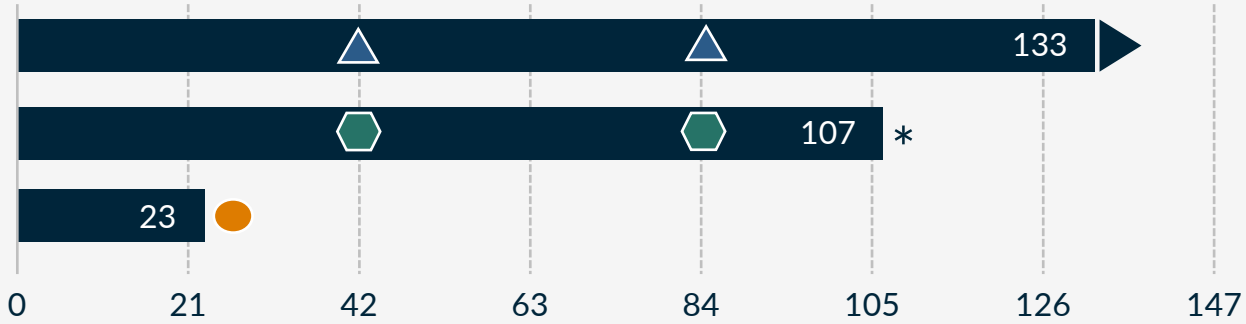
Initial Results: Arm A

- Robust PD in blood in first two dose cohorts (POM)
- Antitumor activity in dose level 1

Safety

- No dose-limiting toxicities across dose levels 1-3; no thrombocytopenia or neutropenia even after 6 cycles
- Related AEs (observed in at least 2 patients): Nausea (n=3): Grade 1 (n=2) and Grade 2 (n=1); Diarrhea (n=2): Grade 1
- One SAE deemed related to KT-253: Hypotension: Grade 3, occurred during cycle 4
  - Due to decreased oral intake; resolved with treatment including IV fluids; Patient remains on study without dose reduction or recurrence of hypotension

Days on Study – Dose Level 1 (0.05 mg/kg)



Merkel Cell Carcinoma

Fibromyxoid Sarcoma

Uveal Melanoma

Ongoing

Discontinued (Progressive Disease)

Partial Response

Stable Disease

*Patient discontinued from study

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MDM2 Degrader: KT-253

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

Upcoming Presentation: ASCO 2024

Interim Clinical Data

Interim Phase 1a data from Arms A show evidence of target engagement and p53 pathway activation

Fidelity of translation of PK, PD, and safety

Initial evidence of antitumor activity and without hematological toxicities

Arms A and B recruiting 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

P1a Completion: 2024

Completion of Phase 1a dose escalation expected 2024

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

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Pipeline with Clear Line of Sight to Large Value Creation

	Potential Indications	2024	2025	2026+	Upcoming Milestones	Rights
Immunology – Oral QD Small Molecule Degraders						
IRAK4[1] **KT-474**	HS, AD, RA, Asthma, IBD, other[3]	HS Ph2 ▲ HS Late Development AD Ph2 ▲ AD Late Development			Ph2 HS & AD Data: **1H25**	sanofi KYMERA **50/50 US**
STAT6 **KT-621**	AD, Asthma, COPD, PN CRSwNP, EoE	IND	Ph1 ▲ Mid-Late Development		Ph1 Start: **2H24**	KYMERA
TYK2 **KT-294**	Psoriasis, IBD, PsA, Lupus, other	IND	Ph1 ▲ Mid-Late Development		Ph1 Start: **1H25**	KYMERA
Oncology						
STAT3[2] **KT-333**	PTCL, LGL-L, CTCL, Solid Tumors	Ph1 ▲ Mid-Late Development			Ph1 Data: **EHA and 2H24**	KYMERA
MDM2 **KT-253**	Liquid & Solid Tumors	Ph1 ▲ Mid-Late Development			Ph1 Data: **ASCO and 2H24**	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]Assessment of STAT3 I/I opportunity is ongoing ▲ = key data readout

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

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2024 PRIORITIES

- Completion of enrollment in oral IRAK4 degrader KT-474 Phase 2 trials in HS and AD by partner Sanofi (topline data 1H 2025)
- Initiation of oral STAT6 degrader KT-621 Phase 1
- IND ready for oral TYK2 degrader KT-294
- Additional oncology proof-of-concept data for the STAT3 degrader KT-333 and MDM2 degrader KT-253

Thank You

NASDAQ: KYMR

www.kymeratx.com
@KymeraTX

For additional information contact:
investors@kymeratx.com
media@kymeratx.com
inquiries@kymeratx.com

KYMERA THERAPEUTICS
500 North Beacon Street, 4th Floor
Watertown, MA 02472

KYMERA