UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): December 14, 2022

KYMERA THERAPEUTICS, INC.
(Exact name of registrant as specified in its charter)

Delaware	**001-39460**	**81-2992166**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(I.R.S. Employer Identification No.)**

Kymera Therapeutics, Inc.
200 Arsenal Yards Blvd., Suite 230
Watertown, Massachusetts 02472
(Address of principal executive offices, including zip code)

(857) 285-5300
(Registrant's telephone number, including area code)

Not Applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trade Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	KYMR	The Nasdaq Global Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On December 14, 2022, the Company held a virtual investor event to provide a clinical update on Part C of the Phase 1 clinical trial evaluating its IRAK4 degrader KT-474 in patients with either hidradenitis suppurativa or atopic dermatitis, as well as an update on its oncology pipeline. A form of the slide presentation is being furnished as Exhibit 99.1 to this Current Report on Form 8-K. The Company undertakes no obligation to update, supplement or amend the materials attached hereto as Exhibit 99.1.

The information in this Item 7.01, including Exhibit 99.1 attached hereto, shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, except as expressly set forth by specific reference in such filing.

Item 9.01. Exhibits

(d) Exhibits

Exhibit No.	Description
99.1	Kymera Therapeutics, Inc. Corporate Presentation, dated December 14, 2022, furnished herewith.
104	Cover Page Interactive Data (embedded within the Inline XBRL document).

SIGNATURE

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Kymera Therapeutics, Inc.

Date: December 14, 2022

By: /s/ Nello Mainolfi
Nello Mainolfi, Ph.D.
Founder, President and Chief Executive Officer

Exhibit 99.1

KT-474 HS and AD Clinical Data and Oncology Pipeline Update

Company Webcast

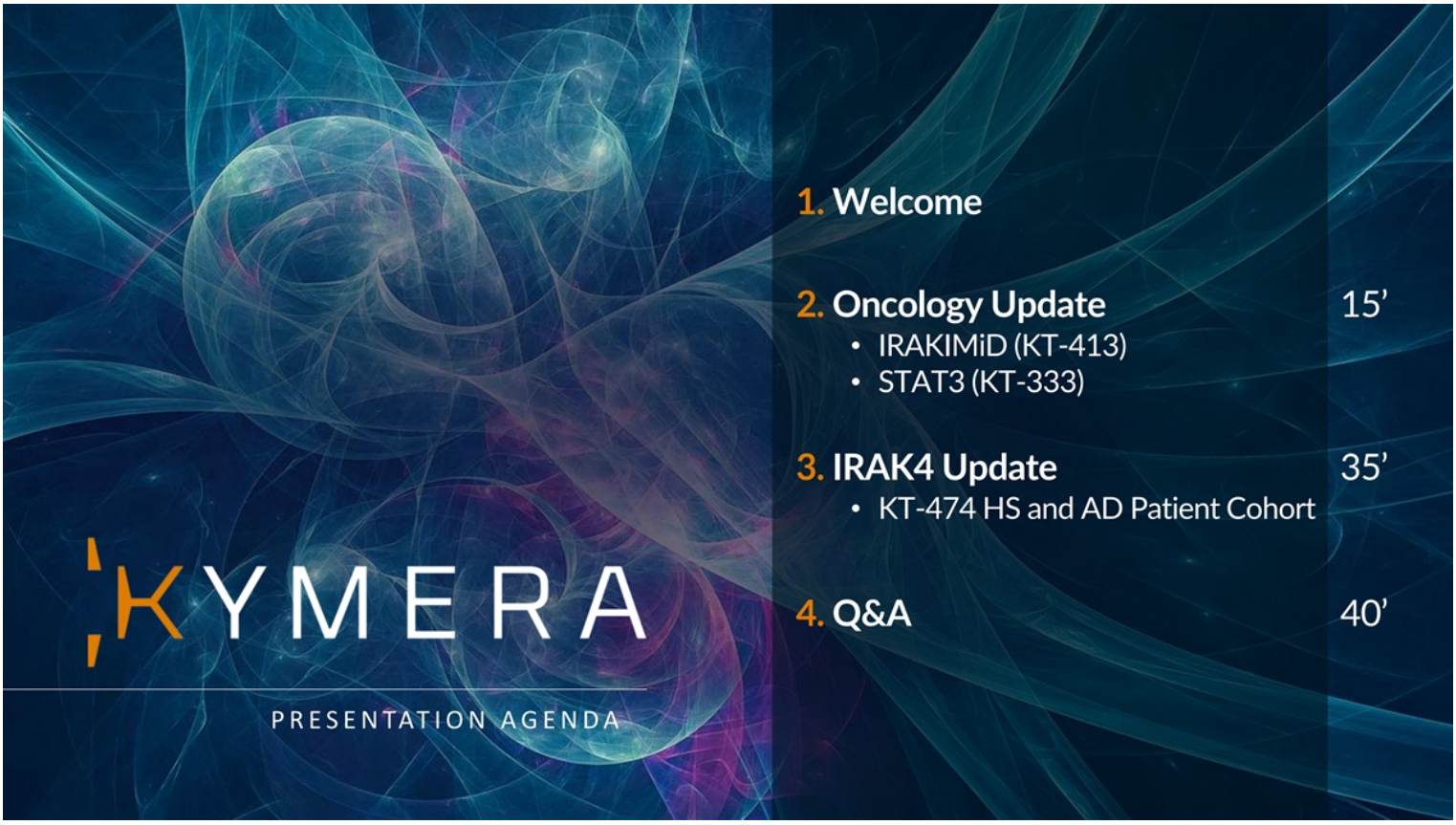
December 14, 2022

Forward-looking Statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 (PSLRA) and other federal securities laws. These statements include information about our current and future prospects and our operations and financial results, which are based on currently available information. All statements other than statements of historical facts contained in this presentation, including express or implied statements regarding our strategy, future financial condition, 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 "aim," "anticipate," "assume," "believe," "contemplate," "continue," "could," "design," "due," "estimate,'' "expect," "goal," "intend," "may," "objective," "plan," "predict," "positioned," "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. These forward-looking statements include statements about our strategy, business plans and objectives for our programs; plans and timelines for the clinical development of our product candidates, including the therapeutic potential, clinical benefits and safety thereof; expectations regarding timing, success and data announcements of current ongoing clinical trials; the ability to initiate new clinical programs; the initiation, timing, progress and results of our current and future clinical trials and current and future preclinical studies and clinical trials of our product candidates and of our research and development programs; our plans to develop and commercialize our current product candidates and any future product candidates and the implementation of our business model and strategic plans for our business, current product candidates and any future product candidates. 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.

Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. Any forward-looking statements are based on management's current expectations and beliefs and are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements including, without limitation, risks associated with: the impact of COVID-19 on countries or regions in which we have operations or do business, as well as on the timing and anticipated results of our current and future preclinical studies and clinical trials, supply chain, strategy and future operations; the delay of any current and future preclinical studies or clinical trials or the development of our drug candidates; the risk that the results of current preclinical studies and clinical trials may not be predictive of future results in connection with current or future clinical trials, including those for KT-474, KT-333 and KT-413; Our ability to successfully demonstrate the safety and efficacy of our drug candidates; the timing and outcome of our planned interactions with regulatory authorities; obtaining, maintaining and protecting our intellectual property; and our relationships with its existing and future collaboration partners. We undertake no obligation to update or revise any forward-looking statements, whether as a result of new information, the occurrence of certain events or otherwise, except as required by law. As a result of these risks and others, including those set forth in our most recent and future filings with the Securities and Exchange Commission, actual results could vary significantly from those anticipated in this presentation, and our financial condition and results of operations could be materially adversely affected. This presentation contains trademarks, trade names and service marks of other companies, which are the property of their respective owners.

Certain information contained in this presentation and statements made orally during this presentation relate to or is based on studies, publications, surveys and other data obtained from third-party sources and the Company's own internal estimates and research. While the Company believes these third-party studies, publications, surveys and other data to be reliable as of the date of the presentation, it has not independently verified, and makes no representation as to the adequacy, fairness, accuracy or completeness of, any information obtained from third-party sources. In addition, no independent sources has evaluated the reasonableness or accuracy of the Company's internal estimates or research and no reliance should be made on any information or statements made in this presentation relating to or based on such internal estimates and research.


KYMERA
PRESENTATION AGENDA
1. Welcome
2. Oncology Update 15'
• IRAKIMiD (KT-413)
• STAT3 (KT-333)
3. IRAK4 Update 35'
• KT-474 HS and AD Patient Cohort
4. Q&A 40'

Introduction to Kymera

Kymera is a **leader in Targeted Protein Degradation** (TPD)

Building a **fully-integrated**, global biotech company

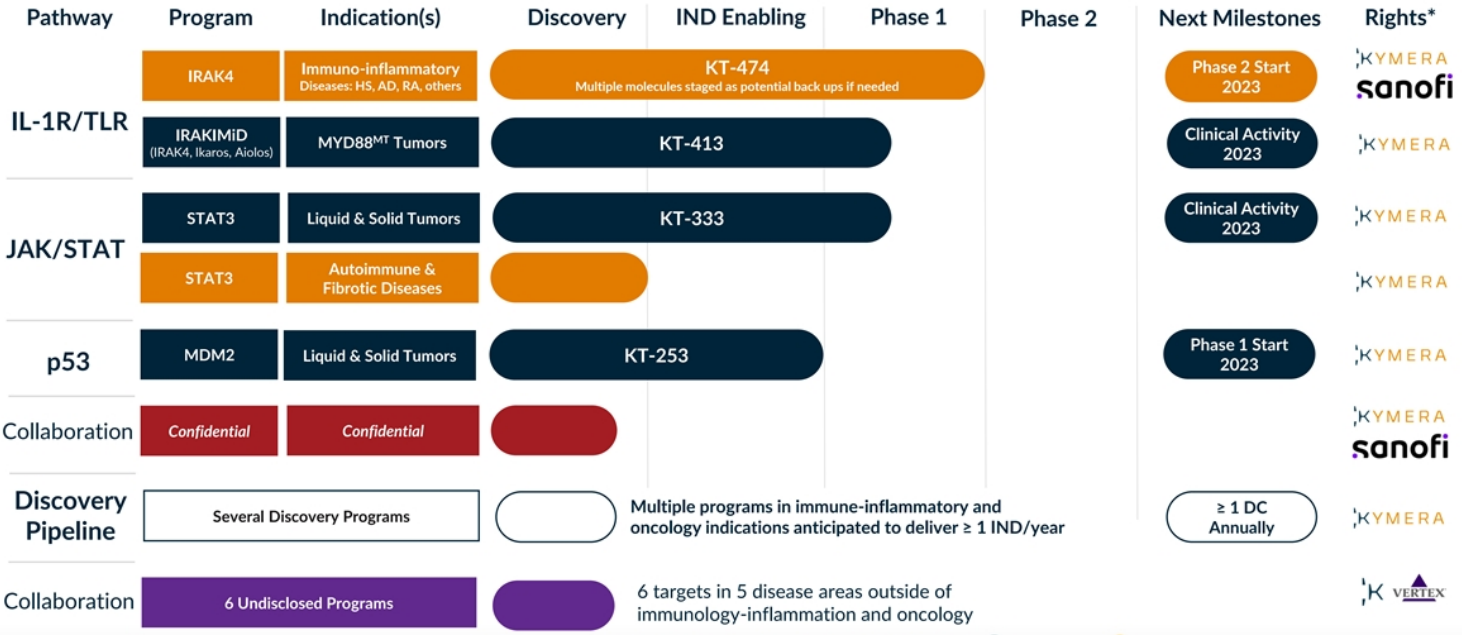
Initial focus in Immunology/ Inflammation and Oncology, but already a **disease-agnostic platform**

Accelerating **forward integration** through key strategic **partnerships**

Key accomplishments to date:

- Since 2016 founding, advanced **4 clinical stage programs** and developed a deep pipeline **positioned to deliver ≥1 IND/year**
- Unique **target selection strategy** based on using TPD to unlock high value, undrugged targets
- First to advance degraders (**KT-474**) in **healthy volunteers and patients with HS and AD**, demonstrating **degrader vs. small molecule inhibitors (SMI) biological differentiation**, and potential **best in class profile in I/I**
- Demonstrated **fidelity of translation of PK, PD and safety** across three clinical programs in I/I and oncology patients
- Well capitalized with **$596 million of cash** as of 9/30/22 positioning Kymera to accelerate and **expand clinical impact in areas with large clinical and commercial opportunities**

Kymera's Pipeline of Novel Protein Degraders



*Option to participate equally in the development and commercialization of Sanofi-partnered programs in the US.
RA: Rheumatoid arthritis, AD: Atopic Dermatitis, HS: Hidradenitis suppurativa

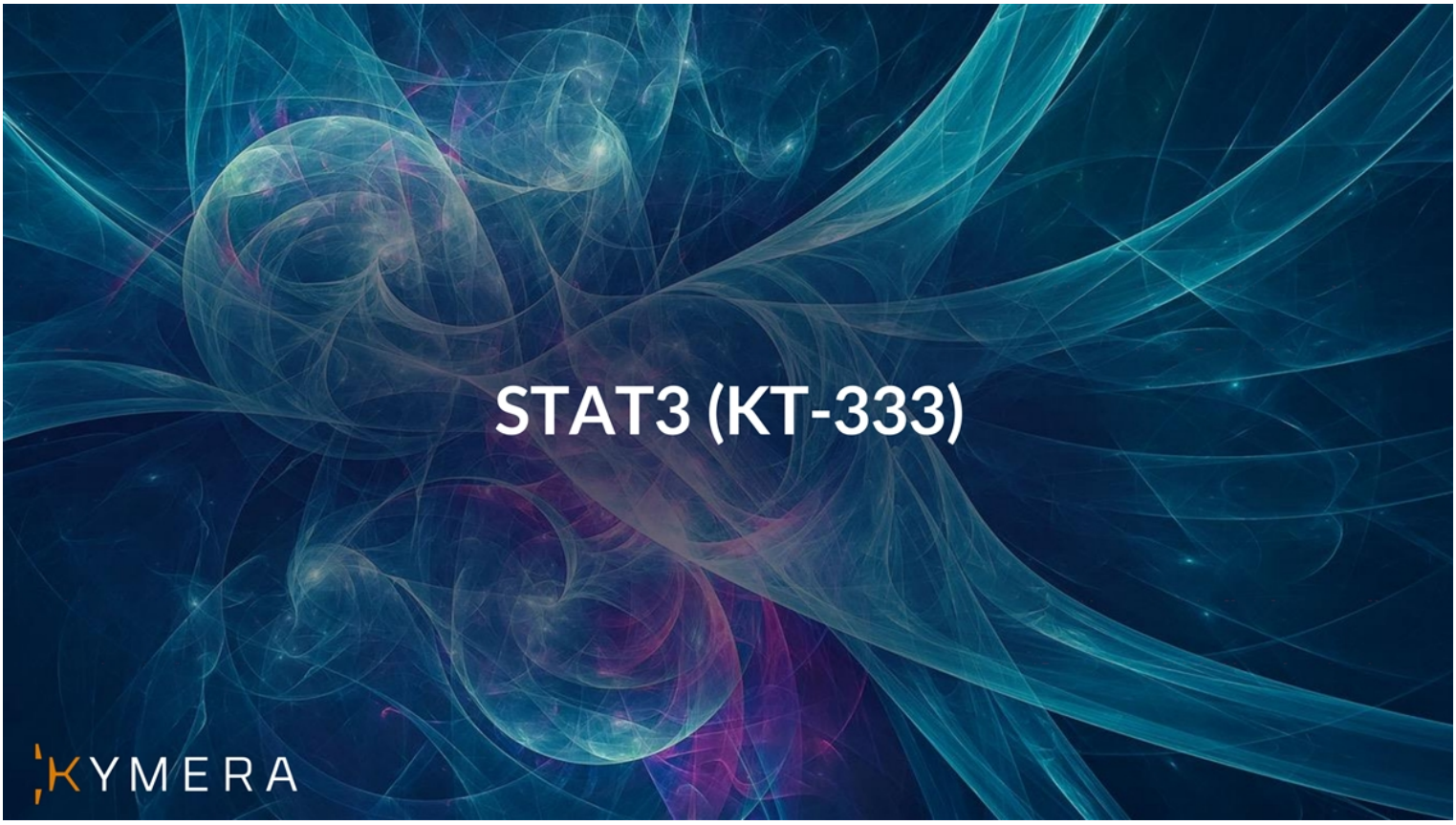
Presentation Summary

Oncology

- KT-333 and KT-413 Phase 1 trials in dose escalation phase
- Both molecules demonstrating PK/PD consistent with pre-clinical models
- No dose-limiting toxicities observed to date
- KT-253 IND cleared; Phase 1 trial expected to commence in early 2023

KT-474

- Part C cohort complete: data supportive of promising clinical and market opportunities in HS and AD
  - PK/PD in patients in line with healthy volunteers with broad impact on disease relevant cytokines in blood and skin of HS and AD patients
  - KT-474 generally well-tolerated; QTc spontaneously returned to normal baseline during the dosing period
  - Clinical endpoints suggest promising potential in both HS and AD, supporting targeting IRAK4 and clear differentiation of degrader versus small molecule inhibitors
  - Sanofi officially committed to advance KT-474 into Phase 2 clinical trials, initially in HS and AD


STAT3 (KT-333)
KYMERA

STAT3 Degraders In Oncology: KT-333

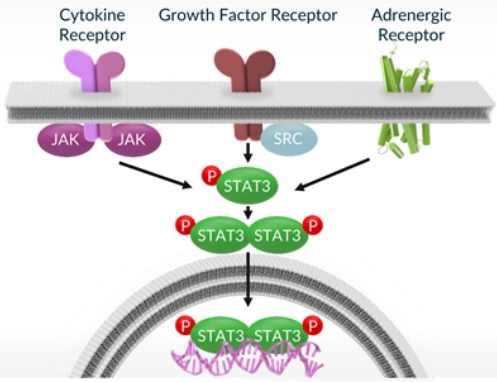
- High degree of validation of JAK-STAT pathway in oncology and immuno-oncology supported by >25k publications
- Traditionally undrugged target
- First-in-class opportunity to address STAT3 driven pathology across large and diverse indications

	U.S.		R.O.W.	
	Prevalence	Incidence	Prevalence	Incidence
Peripheral T-cell lymphoma (PTCL)	~13k	~6.5k	~27k	~15k
Cutaneous T-cell lymphoma (CTCL)	~30k	~2.6k	~67k	~6k
Large granular lymphocyte leukemia (LGL-L)	~4.5k	<1k	~24k	~3k
Solid Tumors, PD-1 Combo (e.g. Stage IV MSI-H CRC)	~30k	~5k	~78k	~20k

Source: Bionest, SEER. GlobalData; ROW includes EU, UK, Japan and China.

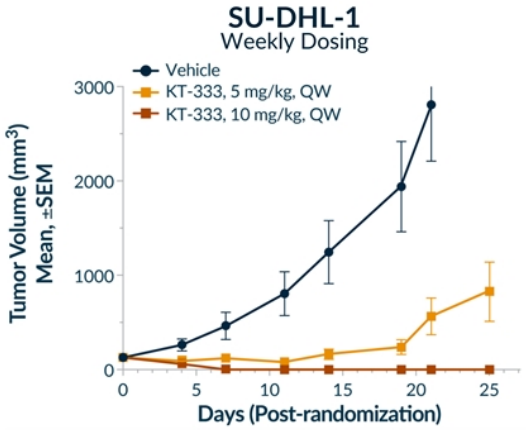
STAT3 Has Unique Tumor Cell Intrinsic and Extrinsic Mechanisms

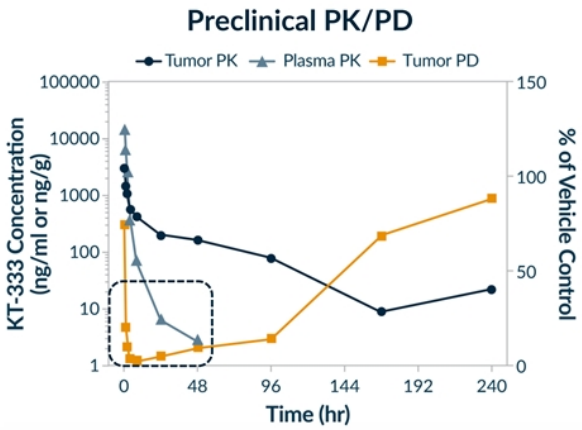
- **Intrinsic**: Hyperactivation of STAT3 via either receptor signaling, or hotspot mutations promotes gene expression programs involved with survival, proliferation, stemness and metastasis of tumor cells
- Opportunities in STAT3-dep. malignancies (e.g., T cell maligs., DLBCL, AML) and drug resistant tumors (e.g., TKI res. oncogene-driven solids)
- **Extrinsic**: STAT3 promotes the differentiation and activity of immunosuppressive and endothelial cells, resulting in an immunosuppressive tumor microenvironment
- Opportunities in multiple heme and solid tumor indications that are not responsive to immune checkpoint inhibitors



KT-333 Highly Active on Intermittent Dosing Regimens

Complete Tumor Regressions Associated with Robust STAT3 KD for ~48h in Preclinical Models

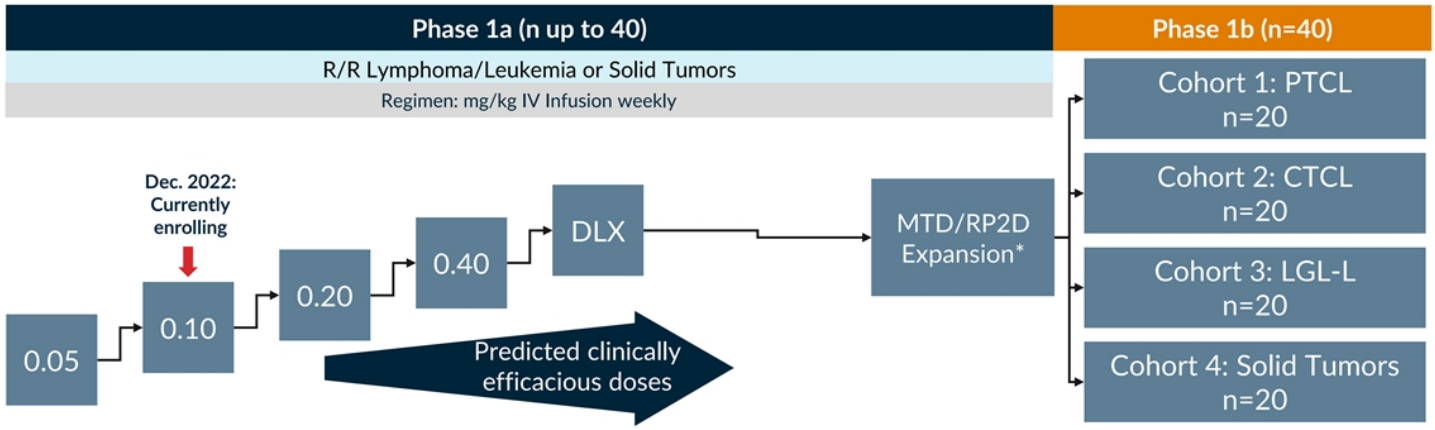




- Dose- and degradation-dependent tumor growth inhibition observed with once-weekly dosing in ALK+ ALCL
- 10 mg/kg sufficient to drive full tumor regression in SU-DHL- 1 that was durable for multiple weeks after the last dose (on day 14)

- Based on preclinical model (STAT3 dependent ALK+ ALCL), target PD >90% STAT3 KD for ~48 hours to achieve robust anti-tumor activity

KT-333: Phase 1, Multicenter, Dose-Escalation and Expansion Trial to Evaluate KT-333 in Adult Patients with PTCL, CTCL, LGL-L, and Solid Tumors



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

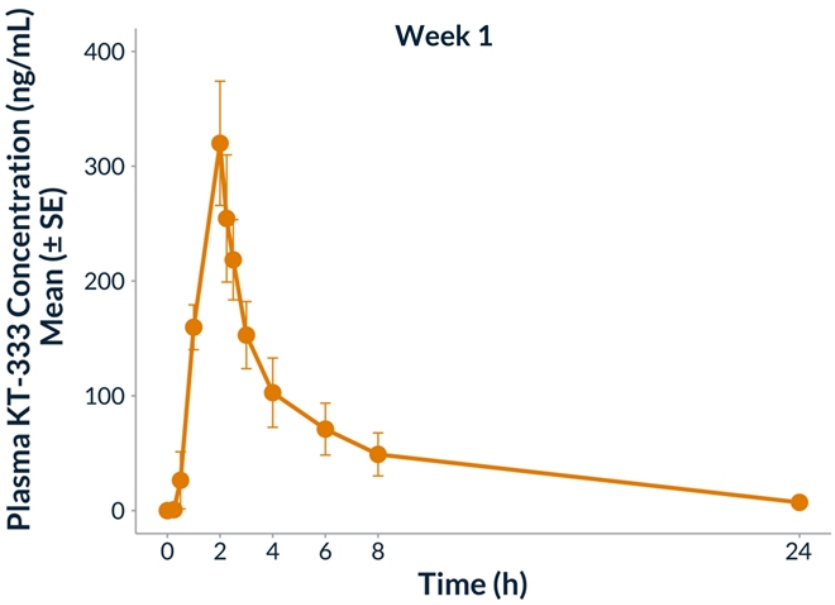
MTD: Maximum Tolerated Dose. RP2D: Recommended Phase 2 Dose. ORR: Overall Response Rate

Interim Safety Data Summary

Dose Level 1

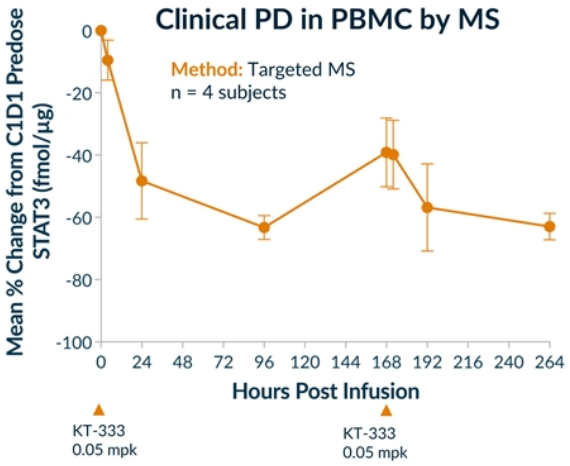
- 4 patients at Dose Level 1 (DL1, 0.05 mg/kg)
- All 4 patients heavily pretreated (≥3 prior lines)
  - 3 solid tumor
  - 1 CTCL
- No DLTs, no treatment-related SAEs, no AEs leading to discontinuation

Summary of PK Data From 4 Patients Enrolled in DL1



PK Parameter	DL1 → 0.05 mg/kg Week 1 (n = 4)
C_{max} (ng/mL)	306 (30.9%)
AUC (ng.h/mL)	1550 (66.4%)
Vd (L/kg)	0.278 (17.5%)
CL (L/h/kg)	0.0450 (62.5%)
$t_{1/2}$ (h)	6.25 (78.8%)

STAT3 Degradation in Blood at Dose Level 1 (DL1: 0.05 mpk) Consistent with Prediction from Preclinical Modeling



Subject ID	Mean Max Degradation* Post-doses 1&2 (Range)
DL1-1	**-79.8 %** (-75.6 % to **-84.1 %**)
DL1-2	**-67.8 %** (-73.5 % to **–62.0 %**)
DL1-3	**-50.0 %** (-47.4 % to **-52.6 %**)
DL1-4	**-66.7 %** (-47.7 % to **-85.8 %**)
Cohort Average	-66.0 %

*Max degradation as measured across timepoints sampled

- Observed STAT3 degradation of 50-80% in PBMCs at Dose Level 1 is consistent with the range predicted for tumor based on preclinical modeling of SUDHL1 xenograft PK-PD data
- Maximal degradation in DL1 patients is observed between 24-96 hours post infusion in Cycle 1 weeks 1 & 2, with recovery of STAT3 levels between doses, as seen in preclinical models

Demonstration of Initial Proof-of-Mechanism (POM) for KT-333

- Accrual to first dose level completed
- STAT3 degradation in blood at first dose level consistent with preclinical predictions, with mean maximum degradation following first 2 doses of Cycle 1 averaging 66%, with maximum knockdown of up to 86%
- At least 48h of target degradation observed that in preclinical species led to robust antitumor activity in STAT3 sensitive preclinical models
- DL1 level generally well-tolerated with no DLTs or treatment-related SAEs
- DL2 currently enrolling patients
- DL3-4 expected to be clinically active doses

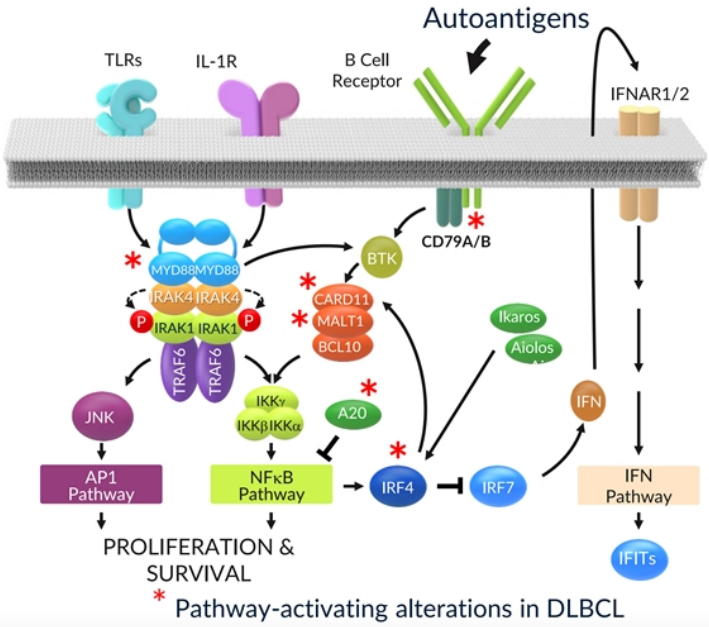

IRAKIMiD (KT-413)
KYMERA

IRAKIMiDs are Potent Degraders of IRAK4 and IMiD Substrates Targeting Redundant Pro-survival Pathways in MYD88^{MT} DLBCL

- Single-agent therapies targeting activated NFκB signaling in DLBCL show limited activity
- Redundant NFκB pathway activation and downregulation of Type 1 IFN common in MYD88^{MT} lymphoma
- Simultaneous degradation of IRAK4 and IMiD substrates Ikaros and Aiolos shows synergistic activity in MYD88^{MT} models

	U.S.		R.O.W.	
	Prevalence	Incidence	Prevalence	Incidence
MYD88 MT DLBCL	~8k	2.8 / 100k	~10k	1.2 / 100k
MYD88 MT Waldenström's Macroglobulinemia	~9k	0.3 / 100k	~26k	0.7 / 100k
MYD88 MT PCNS Lymphoma	~2k	0.6 / 100k	~10k	0.6 / 100k

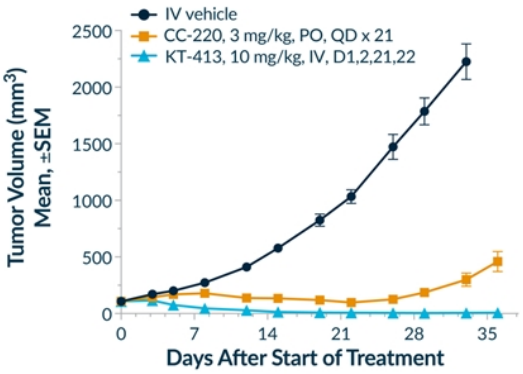
Source: Bionest and Global Data. ROW includes E.U., U.K. and Japan.



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

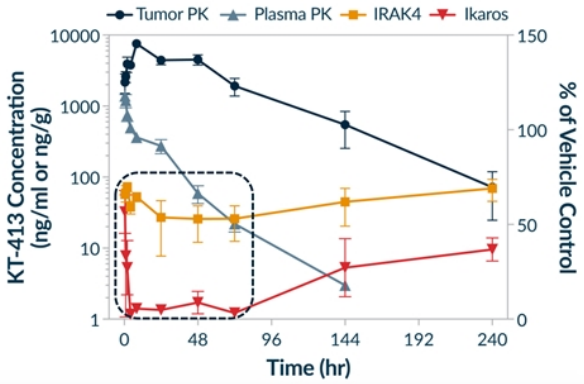
KT-413 Highly Active on Intermittent Dosing in Preclinical Models

Complete Tumor Regressions Associated with Robust IRAK4 and Ikaros/Aiolos Degradation for ~72h



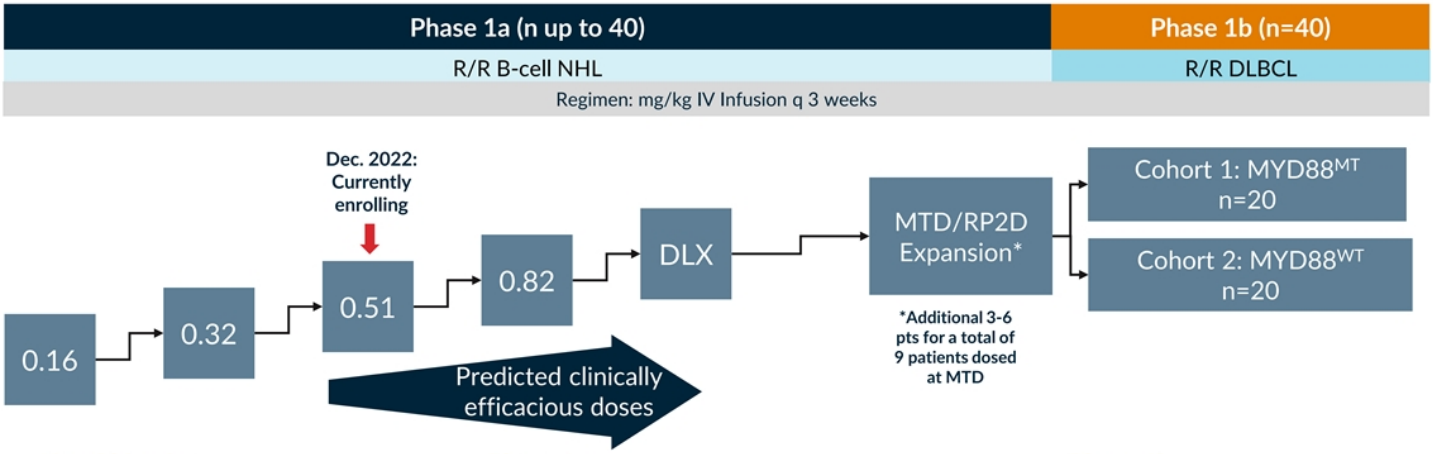
Drug (Day 33)	T/C% (REG%)	CR	PR	SD	PD
CC-220	9	0	0	0	7
KT-413 10 mg/kg	(94)	5	2	0	0

- In the OCI-LY10 MYD88^{MT} xenograft model, intermittent dosing of KT-413 induced strong antitumor activity, including complete regressions.
- **Superior activity compared to IMiD CC-220 alone**



- Single 10 mg/kg dose showed extended tumor exposure and strong degradation of both IRAK4 and IMiD substrates that was maintained for least 72hr in preclinical models
- **Target PD 80-90% Ikaros KD and 50-70% IRAK4 KD *in tumor* for ≥72 hrs to achieve robust anti-tumor activity**

KT-413: Phase 1, Multicenter, Dose-Escalation and Expansion Trials to Evaluate KT-413 in Patients with R/R DLBCL



Key Objectives	Phase 1a	Phase 1b
Primary	• Safety/Tolerability and MTD and RP2D	• Safety/Tolerability at RP2D in Patients with DLBCL
Secondary	• PK Parameters of KT-413 • Preliminary Estimates of Activity	• Preliminary Clinical Activity (ORR, DoR, PFS, DCR, OS) • PK Parameters of KT-413
Exploratory	• PD Effects of KT-413	• PD Effects of KT-413

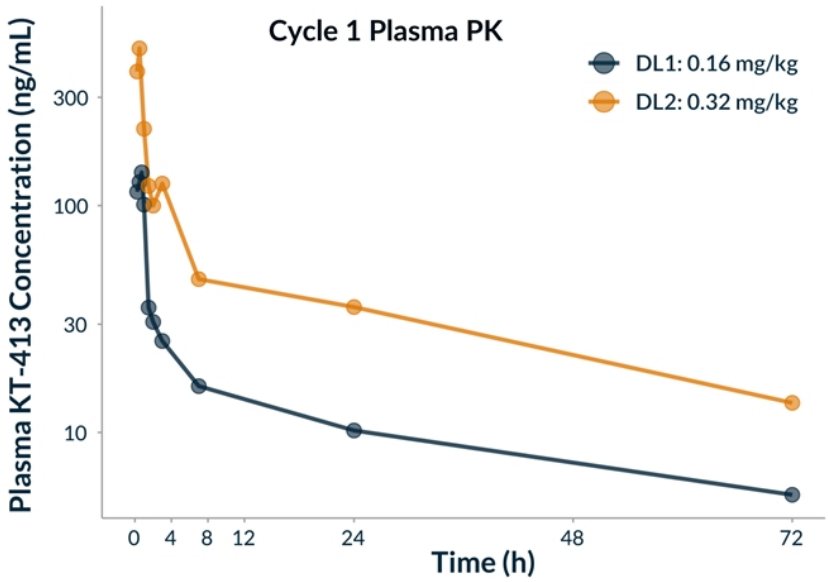
MTD: Maximum Tolerated Dose. RP2D: Recommended Phase 2 Dose. ORR: Overall Response Rate

Interim Safety Data Summary

Dose Levels 1-2

- All patients with heavily pretreated B-cell lymphoma (up to 3 prior lines of therapy)
- Follicular lymphoma, DLBCL (all wild-type MYD88)
- No DLTs, no treatment-related SAEs or AEs leading to discontinuation, no neutropenia in first two dose levels

Plasma PK Showing Dose-Proportional Increase in Exposure

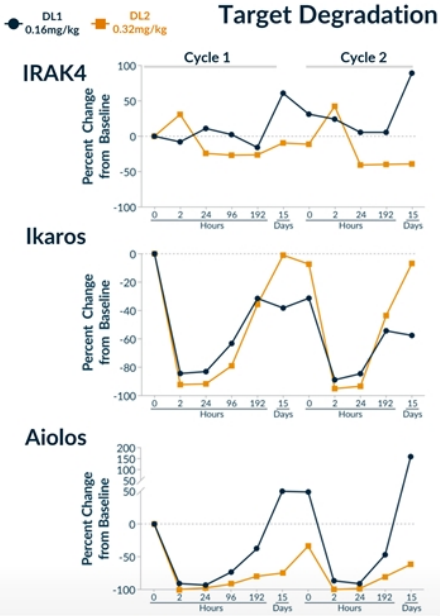


PK Parameter	0.16 mg/kg (DL1)	0.32 mg/kg (DL2)
	Cycle 1	Cycle 1
C_{max} (ng/mL)	140	493
AUC_{inf} (ng.h/mL)	1360	3490
Vd (L/kg)	10.1	3.99
CL (L/h/kg)	0.118	0.092
$t_{1/2}$ (h)	59.3	30.2

Degradation Profile of IRAK4, Ikaros and Aiolos in DL1/DL2 Consistent with Preclinical Models in Blood and Tumor

At least 72h of Target Degradation Observed with Once Every Three-week Dosing

Target Degradation in PBMC by FLOW



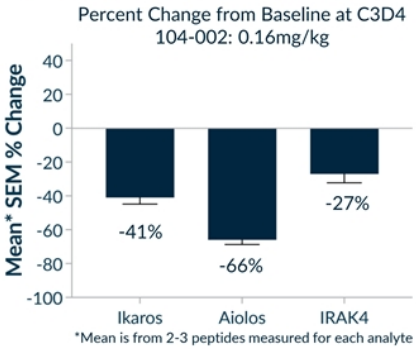
Dose Level	Cycle 1	Cycle 2
DL1	-16%	0
DL2	-27%	-40%

Dose Level	Cycle 1	Cycle 2
DL1	-84%	-88%
DL2	-92%	-95%

Dose Level	Cycle 1	Cycle 2
DL1	-93%	- 91%
DL2	-100%	-100%

- Up to 40% KD of IRAK4 and 95/100% KD of Ikaros and Aiolos in PBMC at DL1-2

Target Knockdown in Tumor by Targeted MS



*Mean is from 2-3 peptides measured for each analyte

Demonstration of Initial POM for KT-413

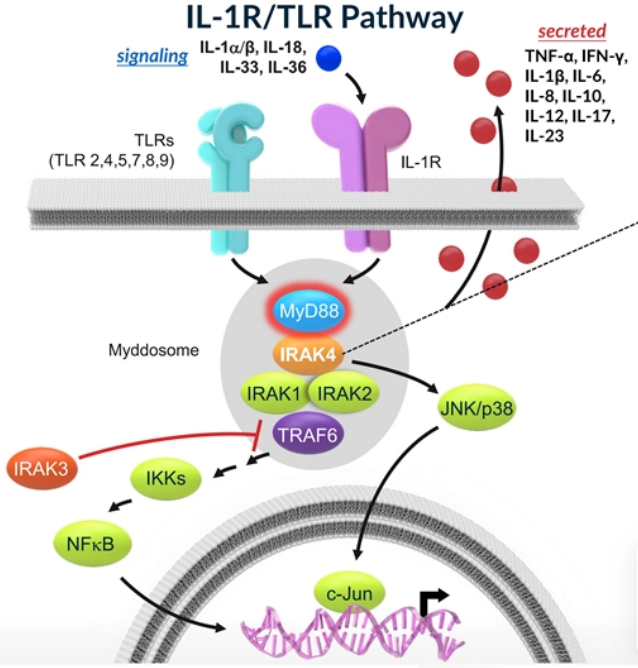
- First two dose levels completed
- PK and PD profiles in DL1 and DL2 consistent with preclinical data supporting once every three-week dosing regimen
  - Up to 95/100% KD of Ikaros/Aiolos and 40% KD of IRAK4 in blood
  - Consistent degradation in blood and tumor
  - At least 72h target degradation observed, a profile that in preclinical species led to robust antitumor activity in MYD88 mutant tumors
- First 2 dose levels generally well-tolerated with no DLTs, treatment-related SAEs or neutropenia observed
- DL3 currently enrolling patients
- DL3/4 expected to be clinically active doses


IRAK4 (KT-474)
KYMERA

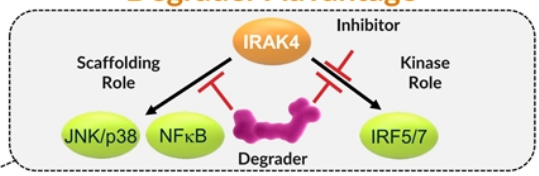
Degrading IRAK4

Superior Approach to Block IL-1R/TLR-driven Inflammation

IL-1R/TLR Pathway



Degrader Advantage



Clinical Pathway Validation

IL-1α/IL-1β : Rheumatoid Arthritis, CAPS, Hidradenitis Suppurativa
IL-1α: Atopic Dermatitis
IL-1β: Gout; CANTOS Outcomes Data in Atherosclerosis and Lung Cancer
IL-18: Macrophage Activation Syndrome
IL-36: Generalized Pustular Psoriasis, Atopic Dermatitis
IRAK4 SMI: Rheumatoid Arthritis

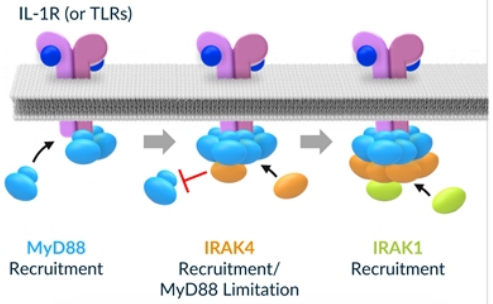
Human Genetics

Adult humans with **IRAK4 Null Mutation have no clinical phenotype**

IRAK4 degrader has potential to achieve a **broad, well-tolerated anti-inflammatory effect,** providing multiple development opportunities in autoimmune inflammatory diseases

IRAK4 Degradation but Not Inhibition is Required to block IL1R/TLR Pathway

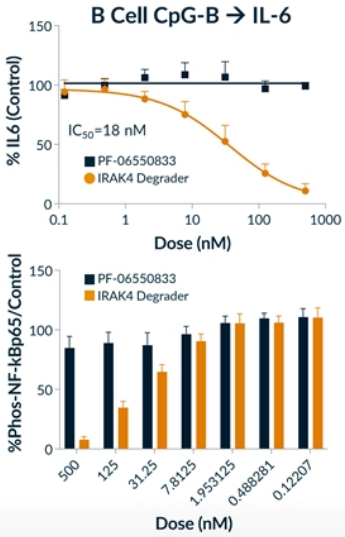
IRAK4 **Scaffolding Function** is Critical in Myddosome Formation and Pathway Signaling



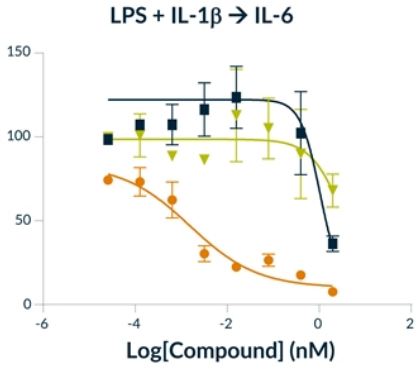
- IRAK4 scaffolding role functions to limit MYD88 oligomer size and trigger myddosome formation

Source: Deliz-Aguirre, et al. *J. Cell Biol.*, 2021

IRAK4 Degradation, but not Kinase Inhibition, can **Block TLR-induced NF-κB Translocation**



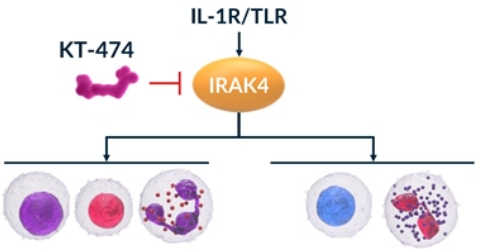
IRAK4 Degradation, but not Kinase Inhibition, can **block IL1R+TLR activation**



Compound	IL-6 IC_{50} (nM)
IRAK4 Degrader	0.8
Negative Control	450
IRAK4 SMI (PF-06550833)	N/A

IRAK4 Degrader Best-in-class Potential in Immune-inflammation

Potential for Broad Activity Across Th1-Th17 and Th2 Diseases



Th1-Th17/Neutrophils

- **Hidradenitis Suppurativa**
- **Rheumatoid Arthritis**
- Lupus
- IBD
- Gout
- Psoriasis

Th2/Eosinophils

- **Atopic Dermatitis**
- Asthma
- COPD
- CRSwNP

$ 150B Combined global drug sales

Indication	2021 Prevalence US/EU5/JP	2021 Global Sales
AD	~82.5 M	$5,760 M
HS	~785 K	$1,106 M
RA	~4.6 M	$27,634 M
SLE	~580 K	$1,333 M
IBD	~3.2 M	$21,710 M
Gout	~18.2 M	$1,319 M
Psoriasis	~15.8 M	$23,268 M
Asthma	~87.3 M	$15,664 M
COPD	~61.7 M	$9,960 M
CRSwNP	~20.4 M	$2,622 M

Limitations of Current Therapies

- **Anti-Cytokine/Cytokine Receptor Antibodies**
  - Target only 1-2 cytokines
  - Require injection
- **Small Molecule Inhibitors**
  - Limited pathway blockade (IRAK4 SMI)
  - Safety issues (JAK family)

Source: EvaluatePharma; GlobalData; Dash. Allied Market Research. 2021; Koto. Modern Rheumatology. 2021; Ahn. JAMA Otolaryngol Head Neck Surg. 2016; UC: Ulcerative Colitis; CD: Crohn's Disease.

KT-474 Phase 1 Trial Design

Double-blind, Placebo-controlled SAD and MAD in Adult HV; Open Label Patient Cohort in HS & AD Patients

Parts A & B

Healthy Volunteers (HV)
SAD and MAD

9 SAD cohorts
- 8 subjects per cohort (6:2 randomization) including 2 food-effect cohorts
- 72 adult healthy subjects dosed
  Single dose (25-1600 mg)

5 MAD cohorts
- 12 subjects per cohort (9:3 randomization)
- 60 adult healthy subjects dosed
  14x daily doses (25-200 mg, MAD 1-4);
  5x twice-weekly doses (200 mg, MAD5)

Summary of Key Findings in MAD

- IRAK4 degradation of 80-90% in PBMC using Flow Cytometry; reduction to near lower limit of quantification with Mass Spectrometry
  - Associated with up to 85% inhibition of multiple disease-relevant cytokines and chemokines in *ex vivo* TLR stimulation assay at 100 mg dose
- Dose-dependent IRAK4 degradation in skin of >50%
- Generally well tolerated at doses up to 200 mg with no SAEs
- Non-adverse, self-limiting QTcF prolongation in 10-20 msec range was neither dose- nor exposure-dependent

Todays' Focus

Part C

HS and AD Patients

1 cohort
21 HS and AD patients

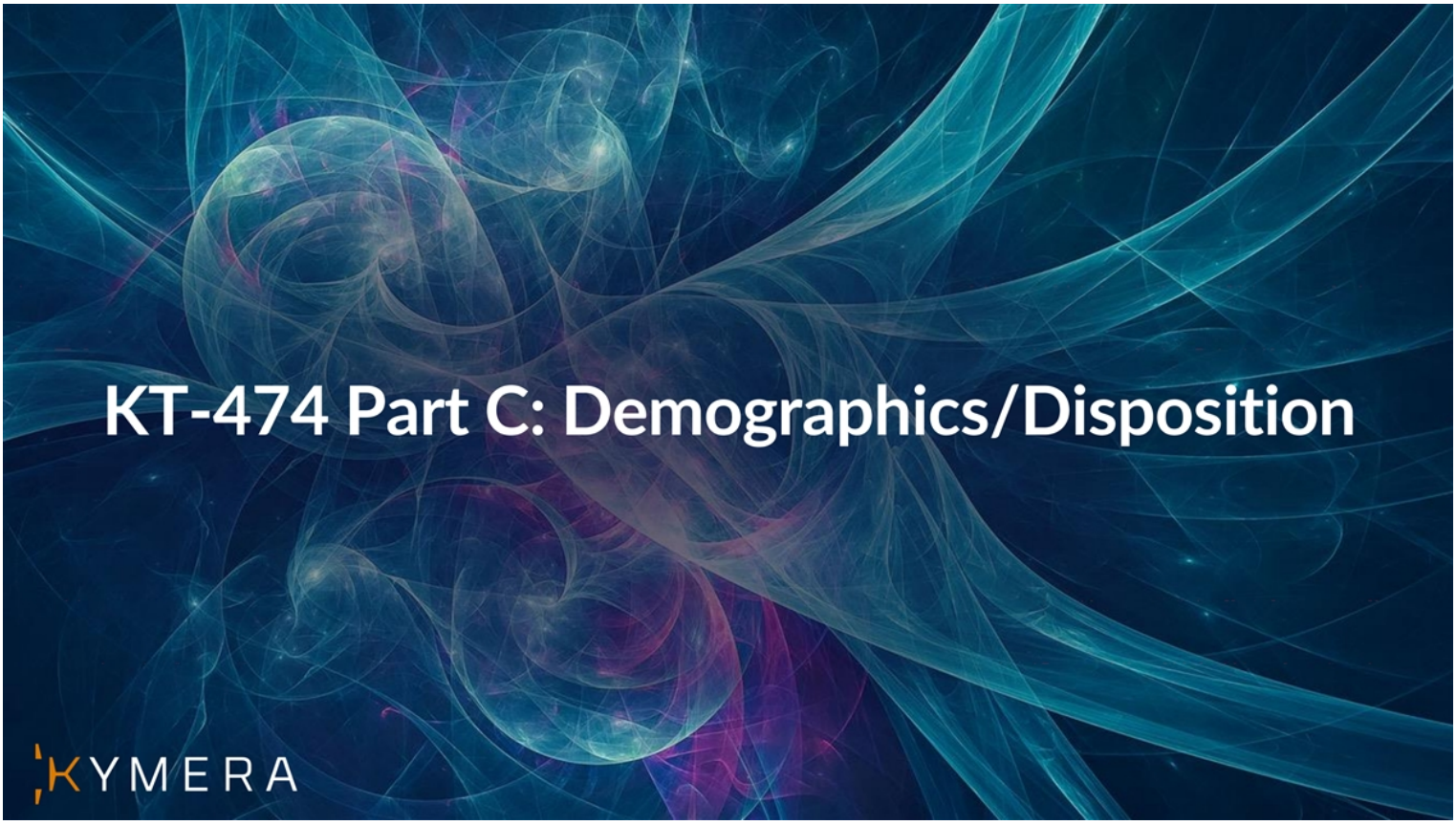
75 mg (fed state)
(~equivalent exposure to 100mg fasted MAD cohort dose level)

Open-label

28x daily doses

Primary
- Safety & tolerability

Secondary/ Exploratory
- Pharmacokinetic measures (half-life, bioavailability)
- IRAK4 knockdown in PBMC and skin
- Change in systemic inflammatory biomarkers and proinflammatory gene transcripts in skin
- *Ex vivo* response of whole blood to TLR agonists
- Clinical endpoints: EASI (AD), Total AN Count (HS), symptom scores and global assessments


KT-474 Part C: Demographics/Disposition
KYMERA

Patient Demographics

	HS (n=13)	AD (n=8)
Gender, n		
Female	10	3
Male	3	5
Median age, years (range)	40 (21-53)	31 (23-55)
Race/Ethnicity		
White / Hispanic, Latino	7	6
White / Non-Hispanic, Latino	1	0
Black / Hispanic, Latin	0	1
Black / Non-Hispanic, Latino	5	0
Other*	0	1

*Native American or Alaskan Native/ Hispanic, Latino

Baseline Disease Characteristics

	HS (n=13)	AD (n=8)
Disease Severity	**(HS-PGA)**	**(vIGA-AD)**
Mild	--	1
Moderate	10	5
Severe	1	2
Very Severe	2	--
Extent of Disease	**Mean (min, max)**	**Mean (min, max)**
AN Count	8 (5, 18)	--
Fistula Count	4 (0, 15)	--
Pain-NRS*	7 (3, 10)	--
Pruritus-NRS*	5 (0, 10)	8 (4, 10)
EASI Score	--	17.6 (4.4, 52.3)
Patients with any prior Therapy, n (%)	**8 (62)**	**7 (88)**
Antibiotics/Antibacterials**	6 (46)	1 (13)
Corticosteroids	0	7 (88)
Adalimumab	3 (23)[₴]	0
Other Biologics	1 (8)[₹]	0

*worst score over past week **includes clindamycin and chlorhexidine

[₴]includes 2 pts with very severe disease;
[₹]1 patient with very severe disease received infliximab and bimekizumab (and adalimumab)

AD=Atopic Dermatitis; AN=Abscess and Inflammatory Nodule Count; EASI=Eczema Area and Severity Index; HS=hidradenitis suppurativa; Min=minimum; Max=maximum; Pain-NRS=Skin Pain Numerical Rating Score; Pruritus-NRS=Peak Pruritus Numerical Rating Score; PGA-Physicians Global Assessment; IGA=Investigator Global Assessment

Patient Disposition

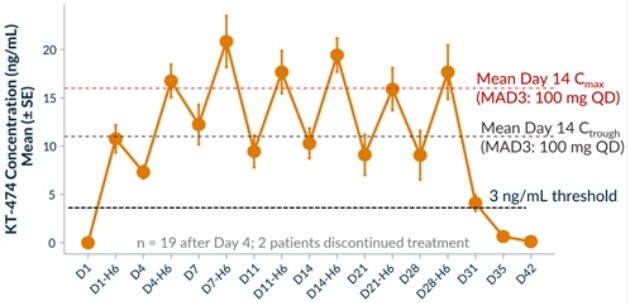
	HS	AD	Total
Enrolled patients	13	8	21
Primary reason for Treatment Completion			
Completed	12 • 9 Moderate • 1 Severe • 2 Very Severe	7 • 1 Mild • 4 Moderate • 2 Severe	19
Withdrawal by patient	1*	1**	2

* Withdrew treatment after 4 doses for personal reasons
** Withdrew treatment after 5 doses for personal reasons


KT-474 PK and Degradation
KYMERA

KT-474 Plasma PK and IRAK4 Degradation in Patients Dosed for 28 Days is Comparable to HV

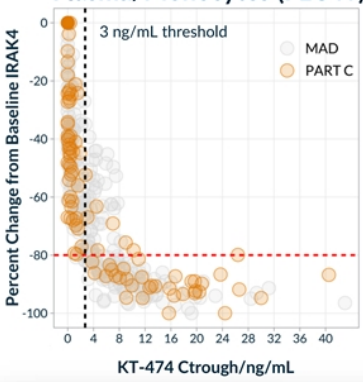
Part C KT-474 Plasma PK



KT-474 PK at the **75 mg QD dose (fed state) in patients is comparable to 100 mg QD (fasted state) in HV**

- Mean C_{max} and C_{trough} levels at steady state in Part C are in line with MAD3 levels at Day 14
- Mean half-life of 44 hours is within the range observed in MAD (34-59 hours)

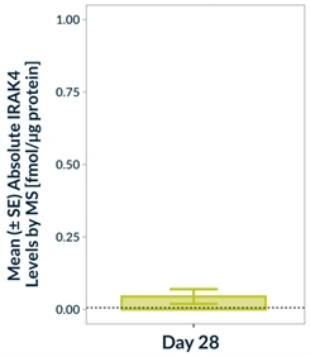
PK/PD Correlation in Plasma/Monocytes (FLOW)



KT-474 concentrations in plasma lead to **same level of IRAK4 degradation** in HV (n=48) and HS/AD (n=20) patients

- Concentrations above 3 ng/mL lead to same level of degradation (>80%) in HV and Patients

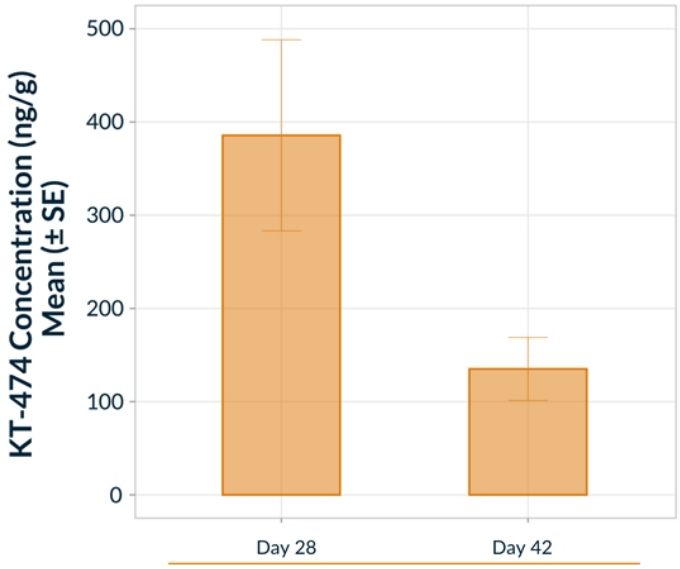
IRAK4 Levels in PBMC in Patients at Day 28 (MS)



HS and AD Patients **IRAK4 Levels at Day 28 (n=4) near LLOQ**

Skin PK: KT-474 Has High Skin Concentration In Patients at Day 28

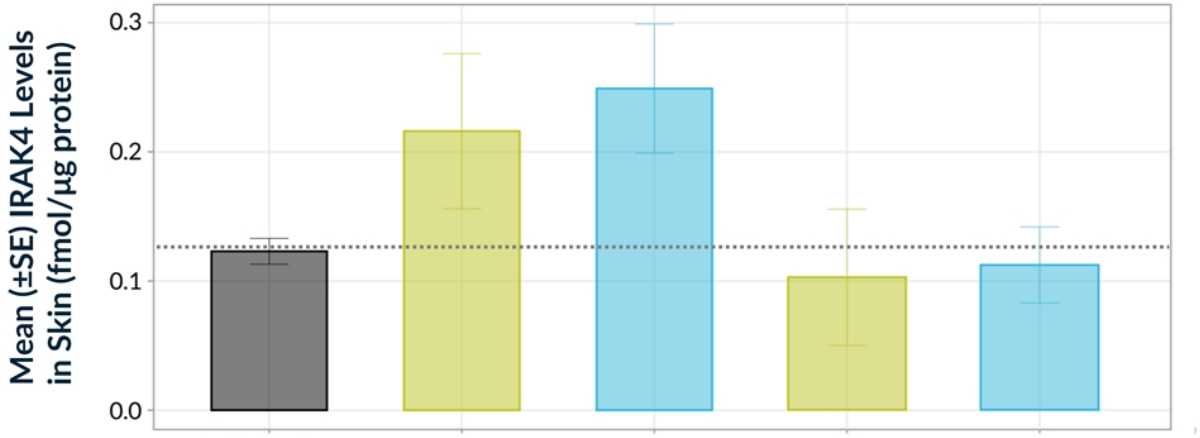
Higher than MAD3 HV



	Day 28	Day 42
Part C: 75 mg QD (fed)*	386 (± 103)	135 (± 33.8)

* n=11 for Day 28 and n=10 for Day 42

KT-474 Reduced IRAK4 in Skin Lesions of AD and HS Patients on Day 28 to at Least Same Level as Healthy Subjects



	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 (± SE)	0.123 (± 0.01)	0.216 (± 0.06)	0.236 (± 0.05)	0.103 (± 0.05)	0.112 (± 0.03)


KT-474 Safety
KYMERA

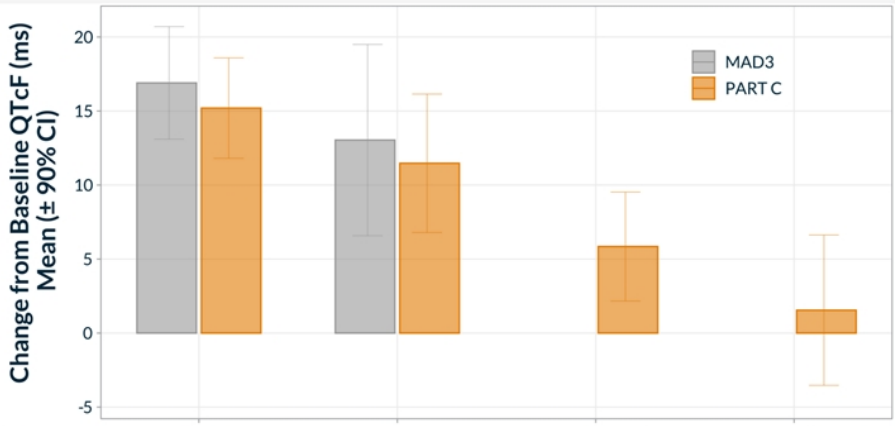
Adverse Events Related to Study Drug (Occurring in > 1 Patient)

Adverse Event (Preferred Term)	# of Patients	Severity (# of Pts)	Outcome (# of Pts)
Headache	6	Mild (5) Severe (1)	Recovered (6)
Fatigue	4	Mild (4)	Recovered (4)
Diarrhea	2	Mild (2)	Recovered (2)

No SAEs, no drug-related infections, and no AEs observed leading to dose interruption or discontinuation

QTc Prolongation Spontaneously Resolves to Baseline by Day 28

- ΔQTcF in Part C is in the range observed in MAD3 (100 mg QD) up to Day 14
- Declines to baseline with continued dosing and sustained plasma exposure through Day 28
- Profile is maintained through day 42 upon cessation of dosing after Day 28
- No QTc-related AEs observed

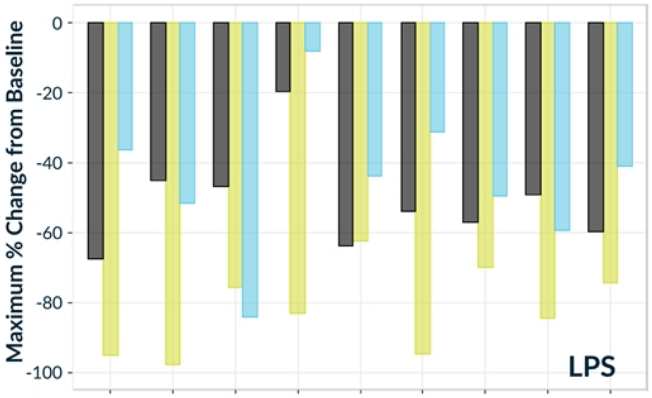


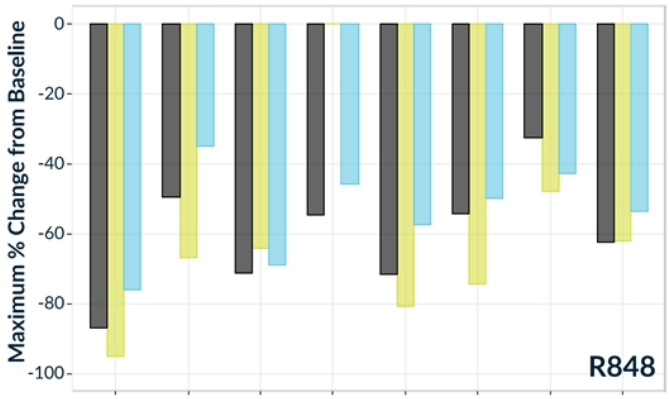
	Mean	Baseline	Day 7	Day 14	Day 21	Day 28
ΔQTcF	MAD3	-	17	13	--	--
	Part C	-	15	12	5.9	1.6
QTcF	MAD3	395	411	408	--	--
	Part C	403	419	416	410	405

* n=9 for MAD3 and n=20 for Part C, except day 14 (n=19)


KT-474 Pharmacodynamics
KYMERA

Up to 98% Inhibition of 9 Disease-Relevant Cytokines *Ex Vivo* in both HS and AD Patients





	IFNγ	IL10	IL12	IL17	IL1b	IL23	IL6	IL8	TNFα
HV (MAD3)	-67%	-45%	-47%	-20%	-64%	-54%	-57%	-49%	-60%
AD	-95%	-98%	-76%	-83%	-63%	-95%	-70%	-85%	-74%
HS	-36%	-52%	-84%	-8%	-44%	-31%	-50%	-59%	-41%

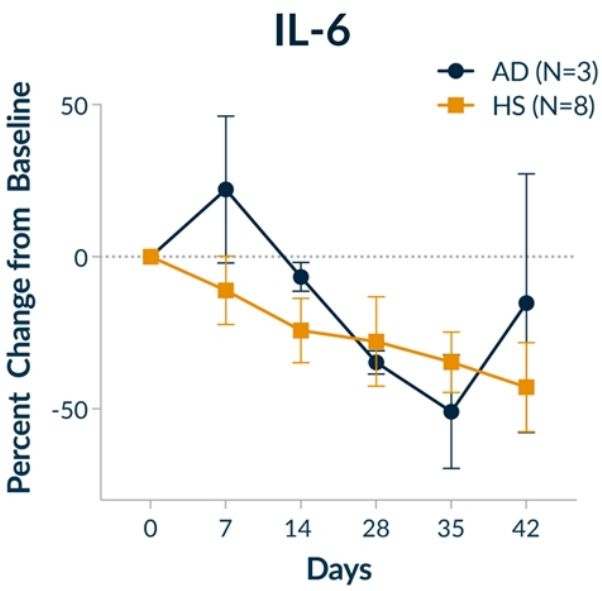
	IFNγ	IL10	IL12	IL17	IL1b	IL6	IL8	TNFα
HV (MAD3)	-87%	-50%	-71%	-55%	-72%	-54%	-33%	-62%
AD	-95%	-67%	-64%	0%	-81%	-74%	-48%	-62%
HS	-76%	-35%	-69%	-46%	-57%	-50%	-43%	-54%

* Plots show median of the maximum change from baseline between Days 7-14 in MAD3, and Days 14-28 in Part C

In Vivo Inhibition of Disease-Relevant Plasma Cytokines and Acute Phase Reactants by KT-474 in HS/AD Patients

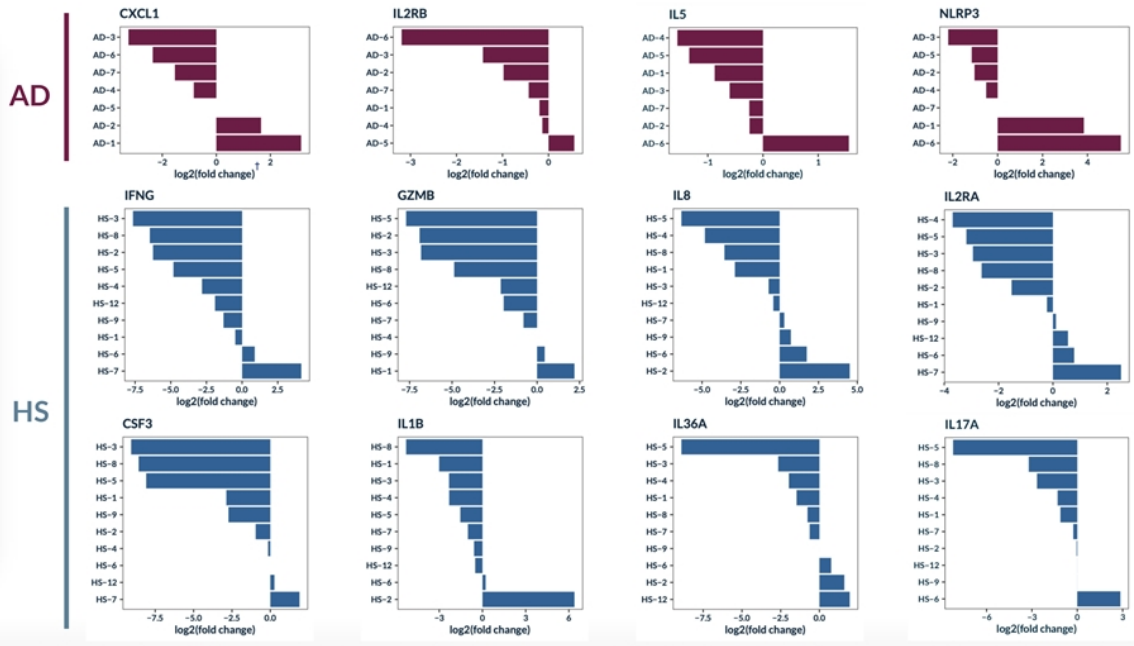
Analyte	Mean Max* AD (n)	Mean Max* HS (n)
IL-6†	-56% (3)	-63% (8)
CRP†	NA	-58% (5)
IL-1β	-36% (7)	-48% (8)
SAA†	-51% (4)	-41% (10)

*Max % reduction through Day 42
†Analysis performed only on patients with values >ULN at baseline
IL-6, IL-1β and CRP are high sensitivity assays



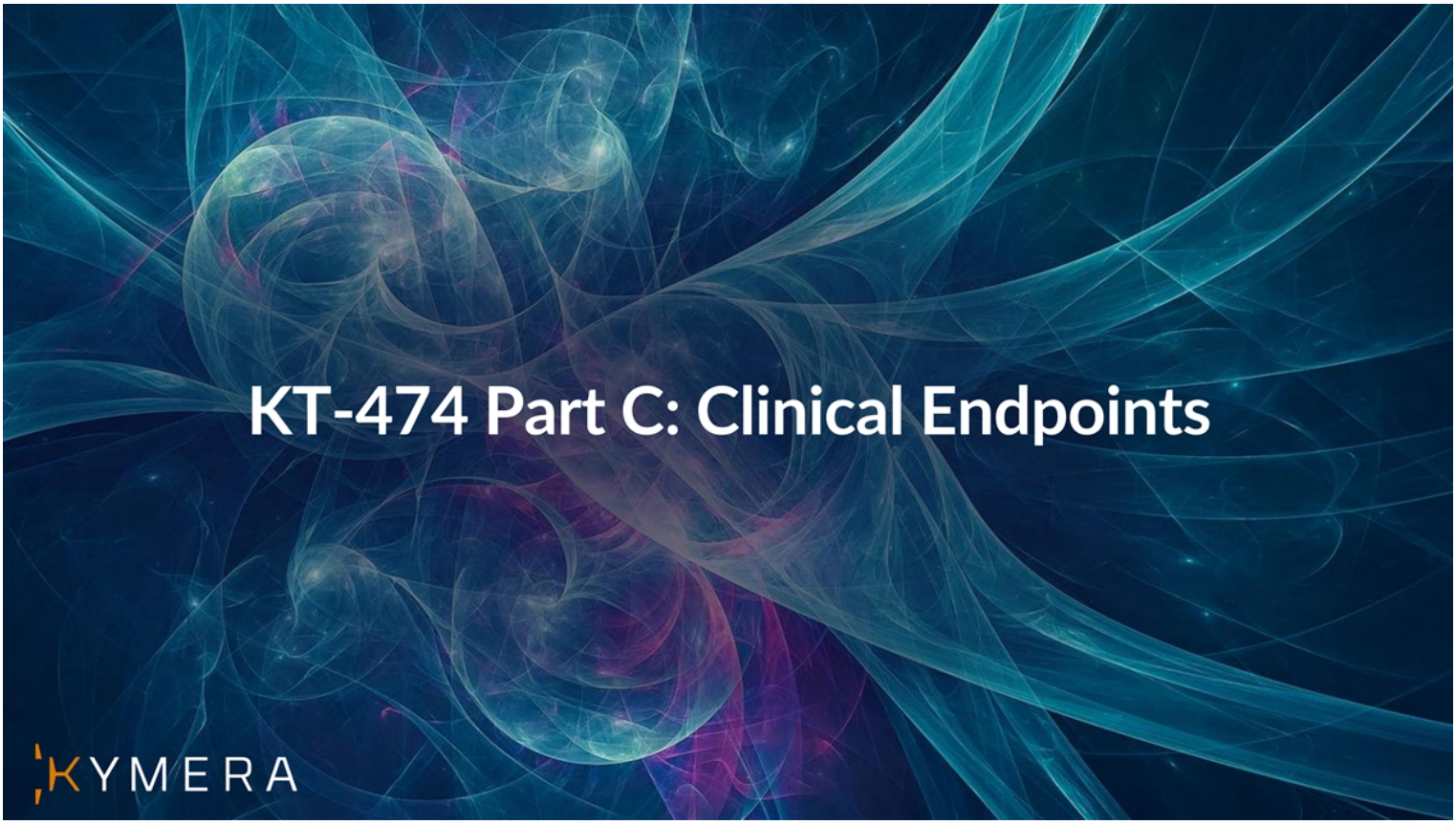
Disease-Relevant Genes Downregulated in Skin Lesions in ≥ 50% of Evaluable* AD (N=7) and HS (N=10) Patients at Day 28 (RNAseq)

- Substantial **downregulation of many disease relevant genes** in both HS and AD patients
- **Downregulation exceeded 90%** for many genes
- Broad **anti-inflammatory signature** with downregulation of genes responsible for:
  - ✓ IL1 family cytokines
  - ✓ Th1
  - ✓ Th17
  - ✓ Th2
  - ✓ Innate immunity



†log2(fold change): -1 = 50% decrease, -2 = 75% decrease, -3 = 87.5% decrease

*Evaluable patients for whom the samples were of sufficient quality for analysis.


KT-474 Part C: Clinical Endpoints
KYMERA

Clinical Endpoints

Included as Exploratory Endpoints

- Skin lesions and global assessments performed on Days 1, 14, 28, 35 and 42
- Symptom scores performed at additional time points

AD

- Change from baseline in Eczema Area and Severity Index (EASI)
- Peak pruritus NRS
- Investigator Global Assessment (vIGA-AD)
- Additional ad hoc analysis included: Peak Pruritus NRS Response (≥4-point improvement from baseline)

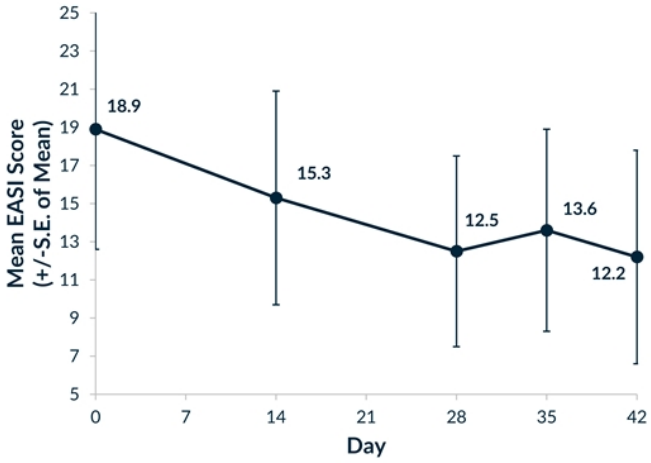
HS

- Change from baseline in Total Abscess and Inflammatory Nodule (AN) count
- Skin pain Numerical Rating Scale (NRS)
- Peak pruritus NRS
- HS-Physician's Global Assessment (HS-PGA)
- Additional ad hoc analyses included: AN0/1/2 Response, HiSCR50, HiSCR75, and Pain NRS30

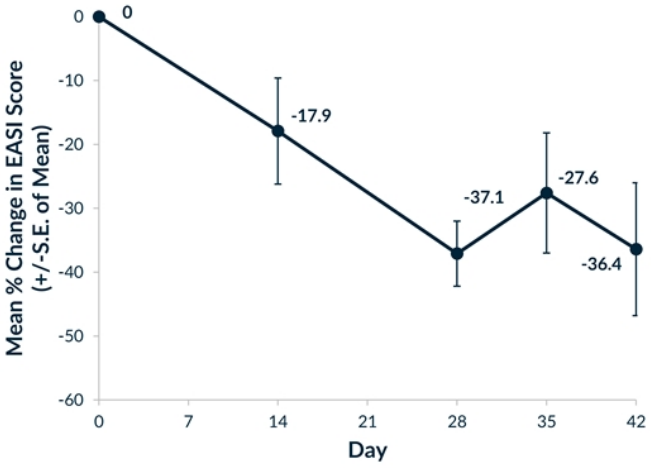

AD Clinical Endpoints
KYMERA

EASI Score: Mean 37% and Max 76% Reduction

Mean EASI Score Over Time (N=7)

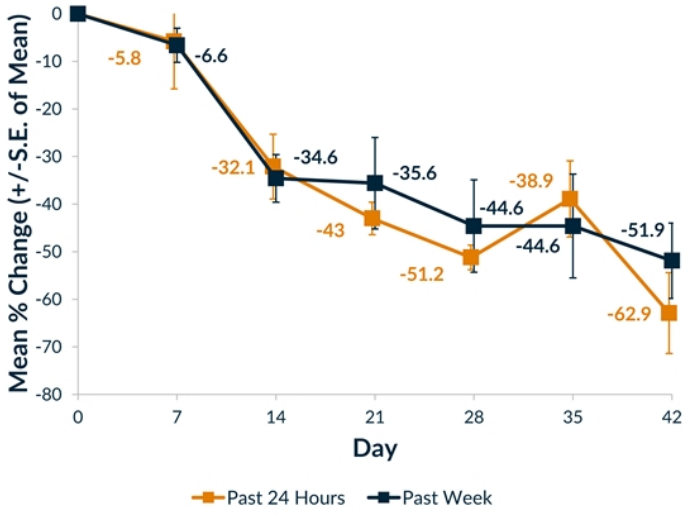


Mean % Change in EASI Score Over Time (N=7)

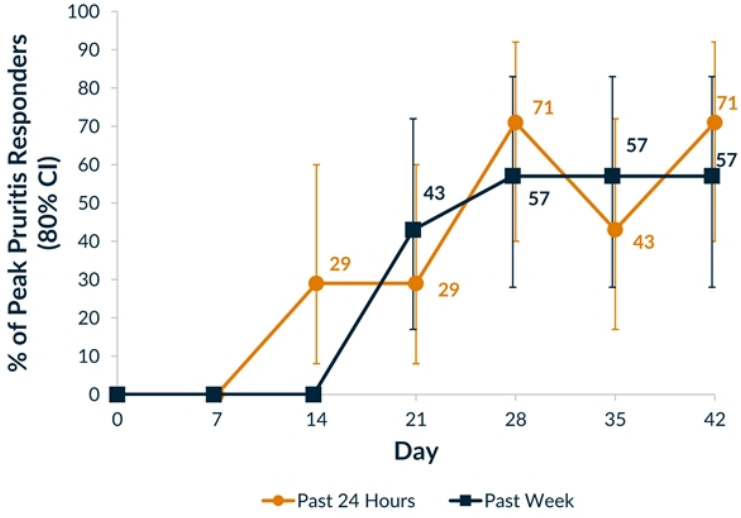


Peak Pruritus NRS: Mean 52 to 63% Reduction
Peak Pruritus NRS Responders: 57 to 71%

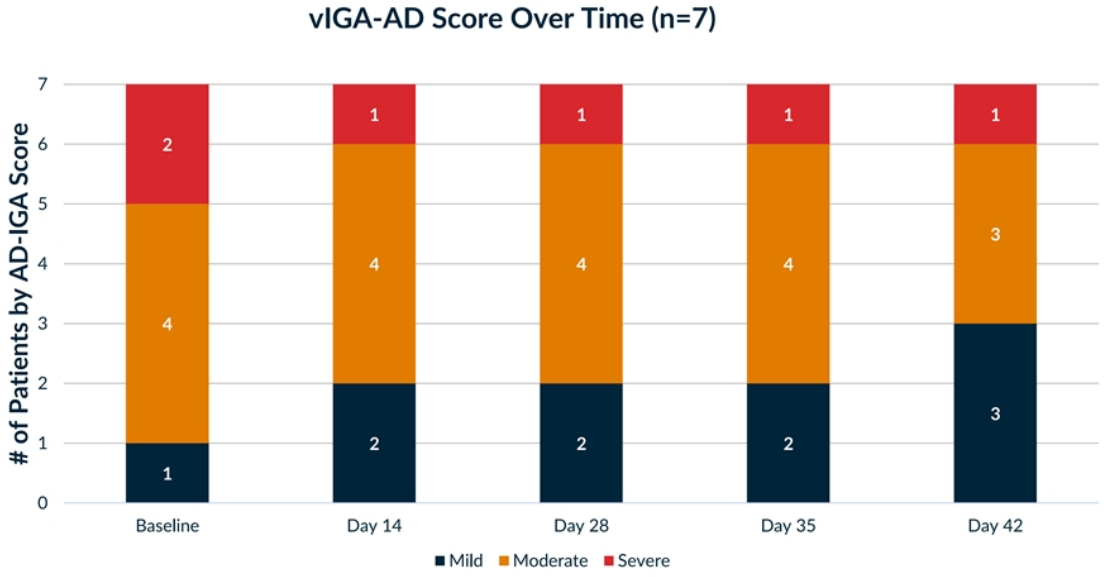
Mean % Change in Peak Pruritus Over Time (N=7)



% of Patients with ≥4 Unit Reduction from Baseline in Peak Pruritus (N=7)



Investigator's Global Assessment (vIGA-AD)



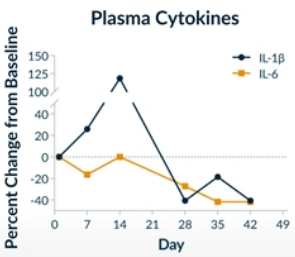
- IGA scores remained stable or improved in all patients

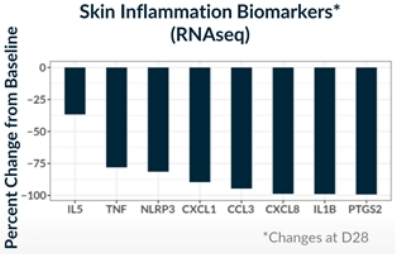
AD Case Study: Patient AD-3

Improvement in Disease Severity from Severe to Mild

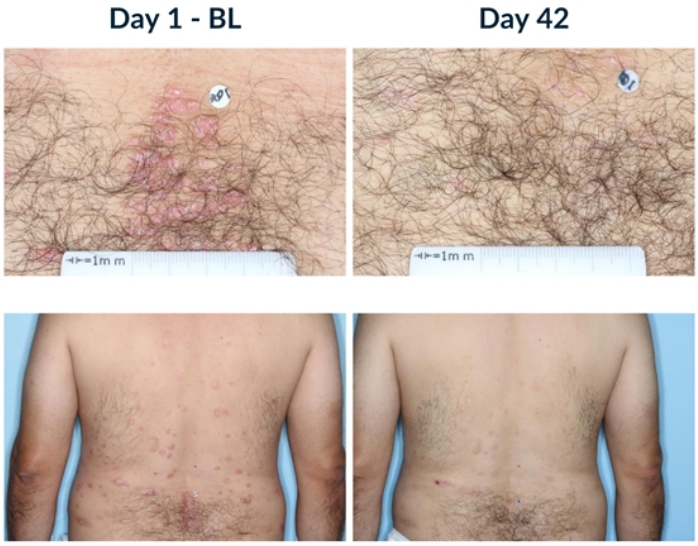
- 51-year-old Hispanic/Latino male with severe AD (vIGA-AD) and EASI score of 28.2 at baseline
- Previously treated with topical betamethasone 2018-2020

Efficacy Endpoints	BL	Day 28	Day 35	Day 42
IGA-AD Score	Severe	Moderate	Moderate	Mild
EASI Score (% Change)	28.2	14 (-50)	16.45 (-42)	9.2 (**-67**)
Peak Pruritis NRS - past week (% Change)	4	1 (-75)	1 (-75)	1 (**-75**)





*Changes at D28



KT-474 Showed Meaningful Signs of Clinical Activity in AD, Comparing Favorably to Placebo Benchmarks and SOC

Summary Results

- Mean EASI score reduction up to **37%,** with maximum reduction of up to **76%**
- Mean peak pruritus NRS reduction of **52** to **63%**
- Peak pruritus NRS Responder rate of **57** to **71%**
- Investigator Global Assessment (IGA) scores improved in **2 of 7** patients and remained stable in the others

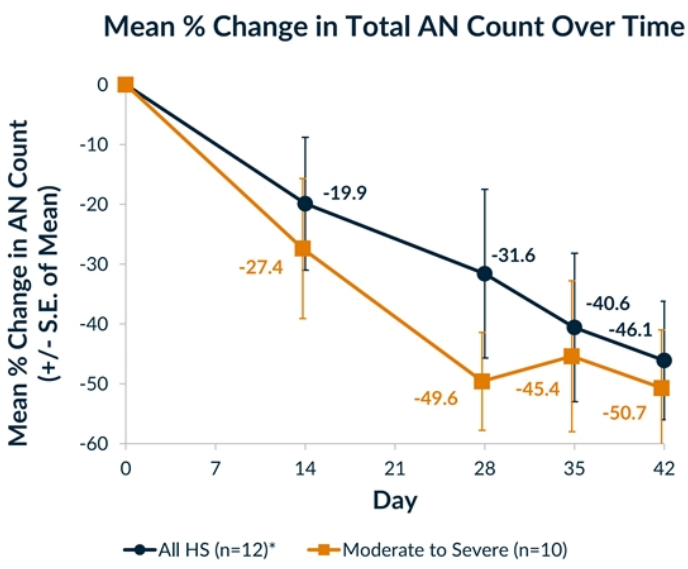
	KT-474 Part C	Placebo Benchmarks Week 4	Dupilumab Phase 3 Week 4
ΔEASI	**-37%**	-12 to -25%*	-52%[1]
ΔPeak Pruritus NRS	**-52 to -63%**	-11%[1]	-34%[1]
Peak Pruritus NRS Responder	**57 to 71%**	4 to 17%**	23 to 40%[1,2]

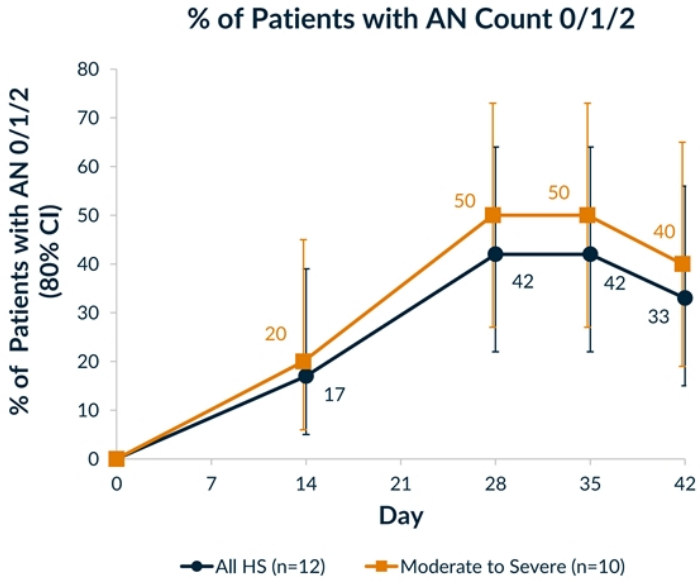
*Range from 7 different Phase 2 and Phase 3 trials; **Range from 10 different Phase 2 and Phase 3 trials; [1]Simpson EL, *et al. NEJM 2016;375:2335-2348;* [2]Bieber T, *et al. NEJM 2021;384:1101-1112;*

The Dupilumab clinical trial was conducted by other parties in a similar patient population with different enrollment criteria from Part 1C of our Phase 1 clinical trial evaluating KT-474. Results do not reflect a head-to-head trial and are shown for illustrative purposes only


HS Clinical Endpoints
KYMERA

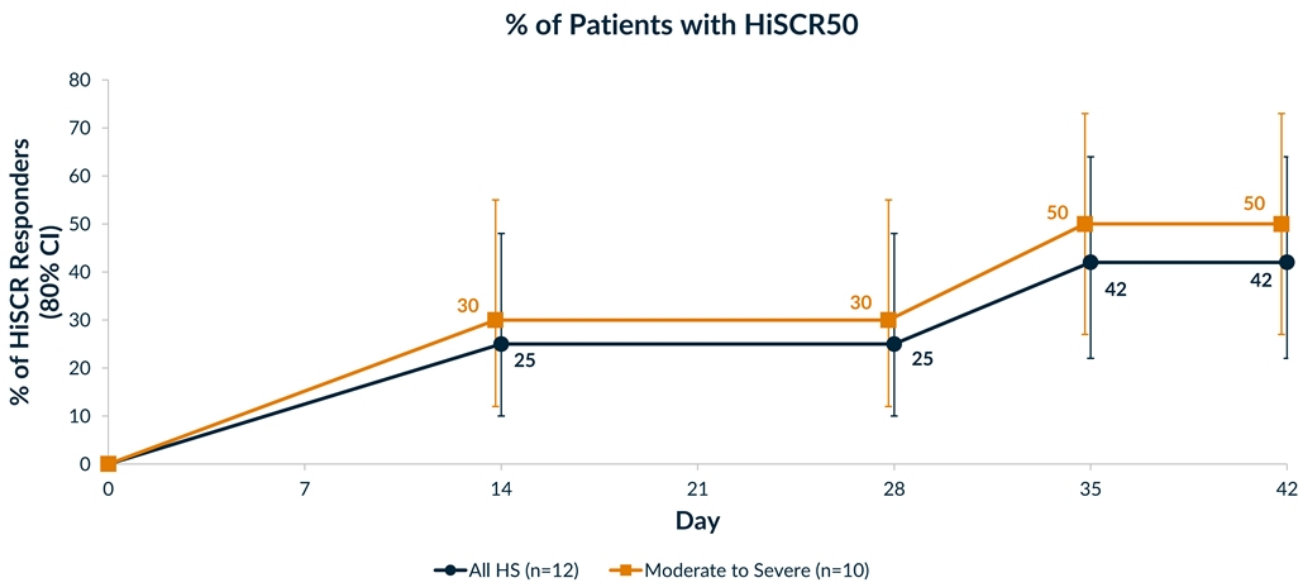
AN Count: Mean 46 to 51% and Max 100% Reduction
AN 0/1/2 Responders: 42 to 50% Response Rate



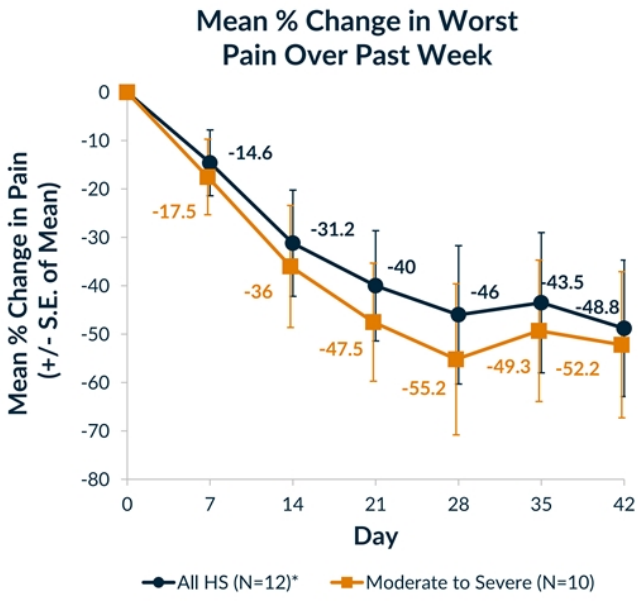


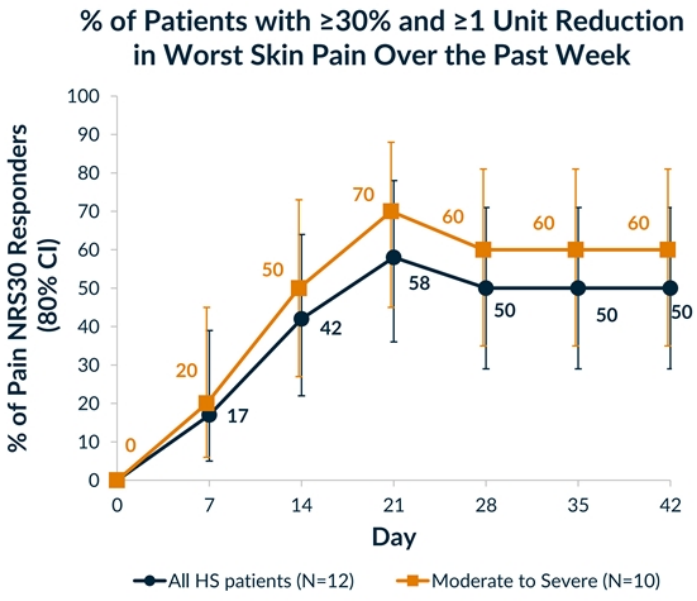
*One patient is censored for Day 35 and Day 42 since the patient started on ustekinumab, steroids and abx on Day 34.

HiSCR50: 42 to 50% Response Rate



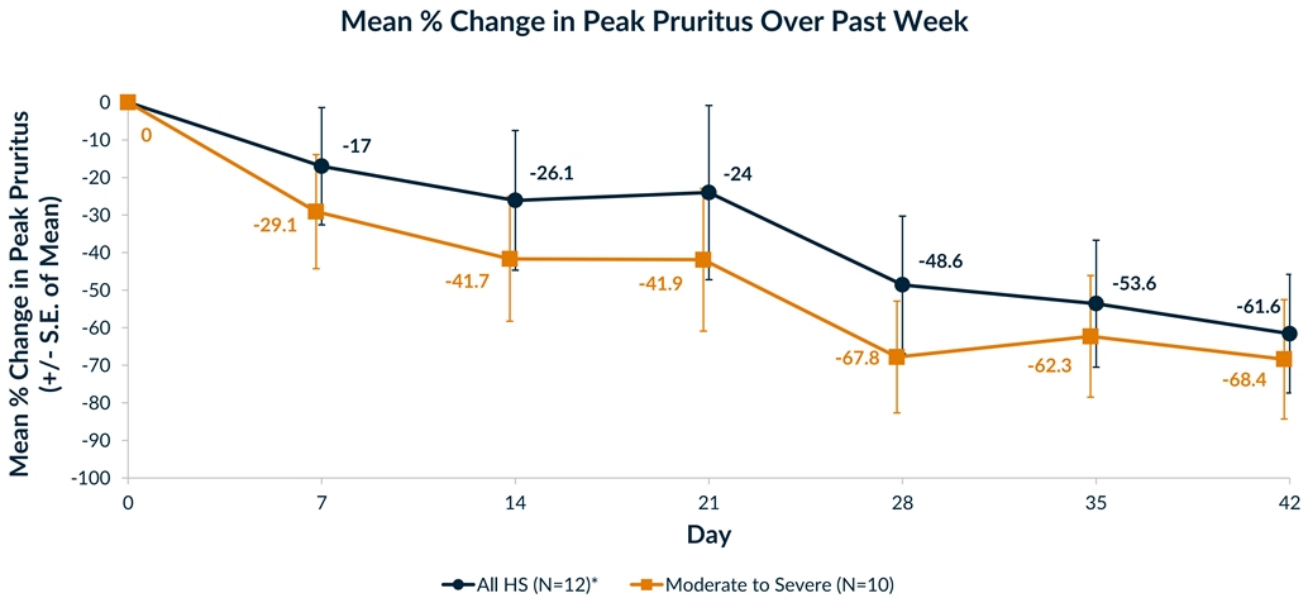
Pain NRS: Mean 49 to 55% Reduction
Pain NRS30: 50 to 60% Response Rate





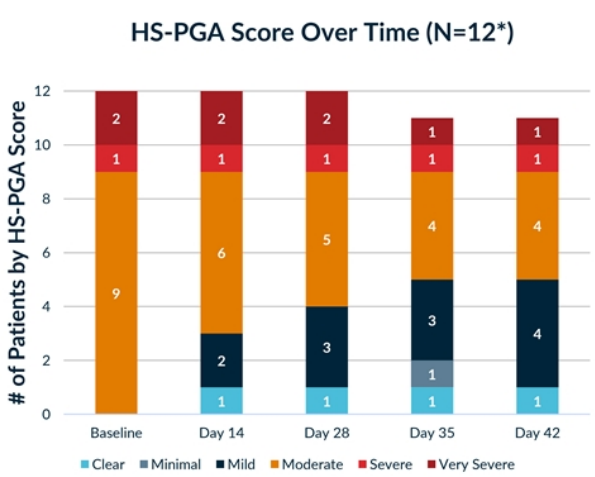
*One patient is censored for Day 35 and Day 42 since the patient started on ustekinumab, steroids and abx on Day 34.

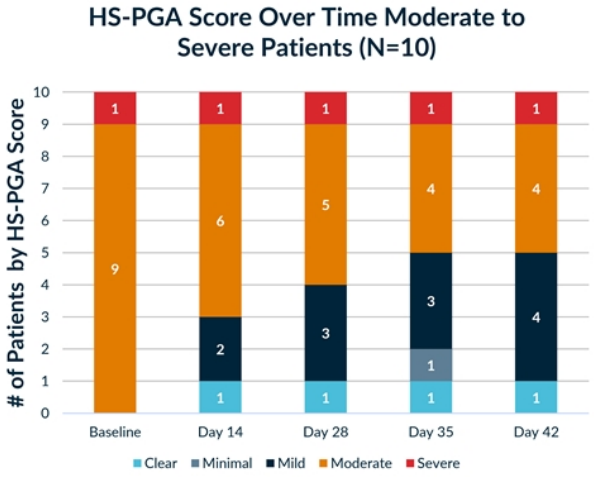
Peak Pruritus NRS: Mean 62 to 68% Reduction



*One patient is censored for Day 35 and Day 42 since the patient started on ustekinumab, steroids and abx on Day 34.

Physician's Global Assessment (HS-PGA)





- HS-PGA scores remained stable or improved in all patients
  - Disease cleared in 1 patient with moderate disease at baseline

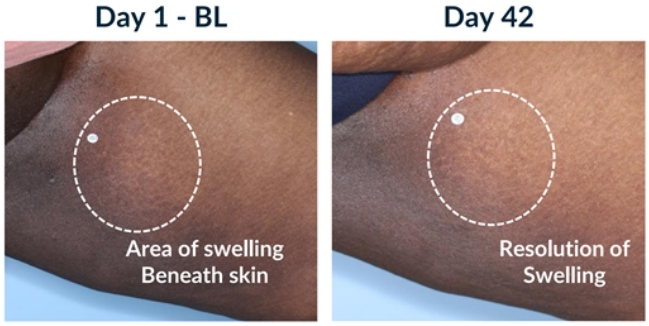
*One patient is censored for Day 35 and Day 42 since the patient started on ustekinumab, steroids and abx on Day 34.

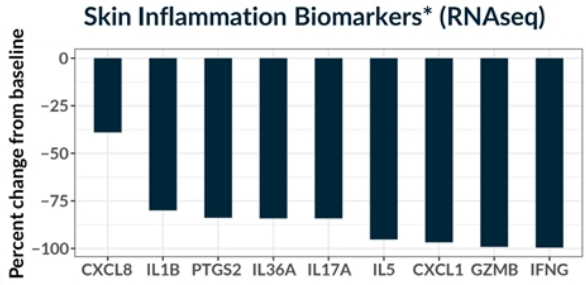
HS Case Study: Patient HS-3

Complete Clearing of Lesions and Symptoms in Patient with Moderate Disease at Baseline

- 45 year old Black Female with Moderate HS (HS-PGA); Baseline AN count = 7
- Prior treatments: clindamycin (topical) and doxycycline

Efficacy Endpoints	BL	Day 28	Day 35	Day 42
HS-PGA Score	Moderate	Clear	Clear	Clear
AN Count (% Reduction)	7	0 (-100)	0 (-100)	0 (**-100**)
Skin Pain NRS – Worst, past week (% Change)	7	0 (-100)	0 (-100)	0 (**-100**)
Peak Pruritis NRS – past week (% Change)	6	0 (-100)	0 (-100)	0 (**-100**)





*Changes at D28

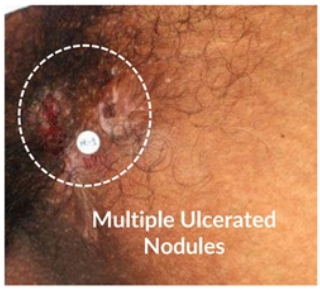
HS Case Study: Patient HS-10

Improvement in Disease Severity from Moderate to Mild

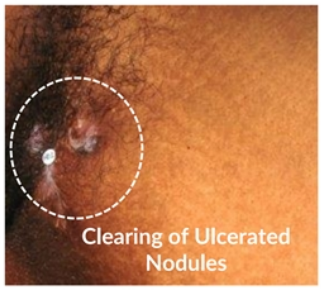
- 39 year old Black Female with Moderate HS (HS-PGA); Baseline AN count = 5
- Prior treatments: benzocaine ointment

Efficacy Endpoints	BL	Day 28	Day 35	Day 42
HS-PGA Score	Moderate	Mild	Mild	Mild
AN Count (% Reduction)	5	2 (-60)	2 (-60)	1 (**-80**)
Skin Pain NRS – Worst, past week (% Change)	8	3 (-63)	3 (-63)	1 (**-88**)
Peak Pruritis NRS – past week (% Change)	10	2 (-80)	0 (-100)	0 (**-100**)

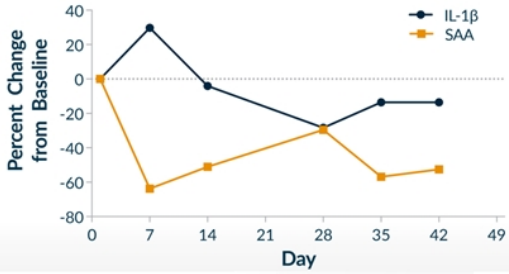
Day 1 - BL



Day 42



Plasma Cytokines/Acute Phase Reactants



KT-474 Showed Meaningful Signs of Clinical Activity in HS, Comparing Favorably to Placebo Benchmarks and SOC

Summary Results

- Mean total AN count reduction of **46** to **51%**, with maximum reduction up to **100%**
- AN count of 0/1/2 response rate of **42** to **50%**
- HiSCR50 response rate of **42** to **50%**
- HiSCR75 response rate of **25** to **30%**
- Pain NRS30 response in **50** to **60%** and mean peak pruritis reduction of **62** to **68%**
- Physician Global Assessment (PGA) scores improved in **5** of **12** patients, including 1 moderate disease patient with full disease clearance, and stable in the others

	KT-474 Part C	Placebo Benchmarks Week 4	Adalimumab Phase 2 and 3 Week 4
ΔAN Count	**-46 to -51%**	-15%[1]	-31%[1]
AN Count 0/1/2	**42 to 50%**	24 to 26%[3]	28 to 47%[2,3]
HiSCR50	**42 to 50%**	19 to 30%[3,4]	29 to 51%[3,4]
HiSCR75	**25 to 30%**	5%[4]	20%[4]
Pain NRS30	**50 to 60%**	18 to 23%[3,5]	39 to 58%[2,3,5]
ΔPeak Pruritus NRS	**-62 to -68%**	N/A	N/A

[1]Kimball AB, et al. *Ann Intern Med* 2012;157:846-55; [2]Morita A, *et al. J Dermatol* 2021;48:3-13; [3]Kimball AB, *et al. NEJM* 2016;375:422-434;[4]Glatt S et al. *JAMA Dermatol* 2021;157:1279-88; [5]Scheinfeld, *et al. Derm Online J 2016:22*

The Adalimumab clinical trial was conducted by other parties in a similar patient population with different enrollment criteria from Part 1C of our Phase 1 clinical trial evaluating KT-474. Results do not reflect a head-to-head trial and are shown for illustrative purposes only


Conclusions / Summary
KYMERA

Part C Summary

- KT-474 administered to HS and AD patients at 75 mg QD for 28 days shown to have safety, PK and PD **comparable to healthy volunteers**
- Modest, non-adverse QTcF prolongation observed **to spontaneously resolve back to baseline** during final 2 weeks of dosing in HS and AD patients
- Robust degradation of IRAK4 in blood and skin was associated with **systemic anti-inflammatory effect in HS and AD patients**
- Promising clinical activity observed in HS and AD **exceeding benchmark placebo rates** and **comparing favorably to SOC biologics**
- Data presented here **validate IRAK4 degradation as a potential best in class mechanism in inflammatory diseases and its superior clinical potential over SMI**
- Results support **advancing KT-474 into Phase 2 placebo-controlled trials, Sanofi has committed to start Ph2 clinical trials** initially in HS and AD

Meeting Summary

- Kymera **platform and discovery engine have been validated** across several programs in patients with cancer and inflammatory diseases, with fidelity of translation of PK, PD and safety
- Kymera's unique **target selection strategy**, using TPD to drug undrugged targets, **has been validated**, with initial demonstration of **IRAK4 degradation** providing a biologically and clinically differentiated/**superior profile than SMI**
- **KT-474 data positions this mechanism and drug as a potential best in class oral drug** in HS, AD and a broader variety of immune-inflammatory diseases with large market opportunity potential
- The successful target selection strategy, molecular design, discovery and clinical execution and insights **will allow acceleration and expansion of our pipeline in areas of high unmet need and large commercial opportunities**
- In 2023 Kymera expects to share **an expanded strategy to accelerate the path towards a disease agnostic global biotech**


Q&A
KYMERA