INVENTING NEW MEDICINES

WITH TARGETED PROTEIN DEGRADATION

May 2023

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Overview

KYMERA

Recognized **leader in Targeted Protein Degradation** (TPD)

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

Initial I/I and Oncology focus, but a **disease-agnostic platform**

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

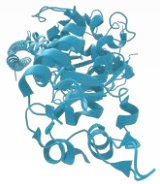
Key Accomplishments

- Advanced **four programs to clinical stage**
- Developed a **deep pipeline** positioned to deliver **≥1 IND/year**
- First to advance degrader (KT-474/SAR444656) in **healthy volunteers and patients** with HS and AD
- Demonstrated degrader vs. small molecule inhibitors (SMI) **biological and clinical 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
- **Unique target selection strategy** based on using TPD to unlock high value, undrugged targets
- **Well-capitalized with $516m of cash**, enabling expansion of clinical impact into areas with large clinical and commercial opportunities

Kymera's Differentiated Approach to TPD

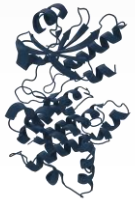
TARGET SELECTION

Undrugged (**UD**) or inadequately drugged (**ID**) targets



UD

Transcription Factors (e.g. **STAT3)**



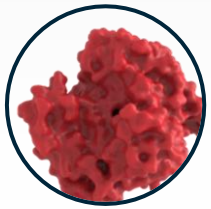
ID

Degrader Advantage Over SMI (e.g. **IRAK4, MDM2)**

Strong genetic validation within clinically validated pathway

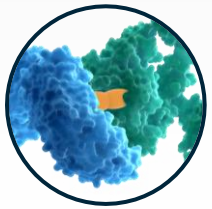
PLATFORM

Significantly **differentiated** investments



Tissue-selective E3 Ligases

- Enabling a whole new generation of clinical programs

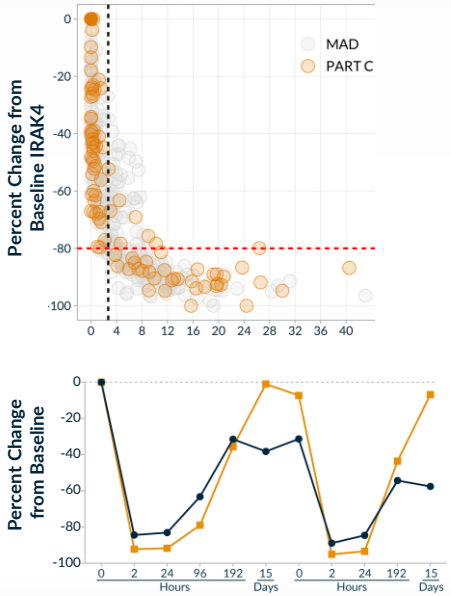


New Molecular Glue Approach

- Novel strategy to address undrugged/ un-ligandable targets

CLINICAL TRANSLATION

Fidelity of translation of **PK, PD** and **safety** now in **3 programs** in immunology and oncology



TPD "FIRSTS"

Accomplished several **"firsts"** in TPD:

- **FIRST** randomized, placebo-controlled trial in healthy volunteers with **KT-474 (IRAK4)**
- **FIRST** heterobifunctional degrader with clinical activity, outside of oncology, in patients with HS and AD with **KT-474 (IRAK4)**
- **FIRST** demonstration of biological and clinical differentiation of degrader vs SMI with **KT-474 (IRAK4)**
- **FIRST** heterobifunctional degrader against an undrugged transcription factor in clinic with **KT-333 (STAT3)**

What Our Recent Accomplishments Mean for Kymera and TPD

Validated Platform and Discovery Engine

- Demonstrated predictable translation of PK, PD and Safety in 3 oncology and immunology programs

Successfully Applied TPD to Unmet Needs Outside of Oncology

- Reported clinical impact in complex inflammatory diseases such as HS and AD

Demonstrated TPD Can Lead to Differentiated Clinical Activity Compared to Small Molecule Inhibitors

- Initial KT-474 data in HS and AD validates Kymera's unique target selection strategy

Kymera is Building Franchises in Both Immunology and Oncology

- Focus is on areas of high unmet needs and large commercial opportunity, in targets with clear degrader rationale

Building Franchises in Immunology and Oncology in Diseases with Large Unmet Needs and Commercial Opportunities

Immunology Franchises

DERM.	GI	RHEUM.	RESP.		
●	●	●	●		**IRAK4** KT-474
●	●	●	○	Scaffolding Kinase	**Undisc.**
●	●	○	●	Transcript-ion Factor	**IL4/13 Pathway**
●	●	●	●		**STAT3**
●	●	●	○	Transcrip-tional Regulator	**Novel Molecular Glue**

Oncology Franchises

SOLID TUMORS	LEUKEMIA	LYMPHOMA		
○	○	●		**IRAKIMiD** KT-413
●	○	○	Scaffolding Complex	**Undisc.**
●	●	●		**MDM2** KT-253
●	●	●		**STAT3** KT-333

Kymera's Commitment to Solving Real Clinical Problems with TPD Where Other Technologies Have Failed

Immunology Franchises

Oncology Franchises

Scaffolding Proteins

IRAK4
KT-474

Undisc.

Scaffolding Kinase

- Scaffolding proteins with clinically validated SMI's

- Protein degradation affords superior biological and clinical effect

IRAK-IMiD
KT-413

Scaffolding Complex

Undisc.

Transcription Factors

IL4/13 Pathway

Transcript-ion Factor

STAT3

Novel Molecular Glue

Transcript ional Regulator

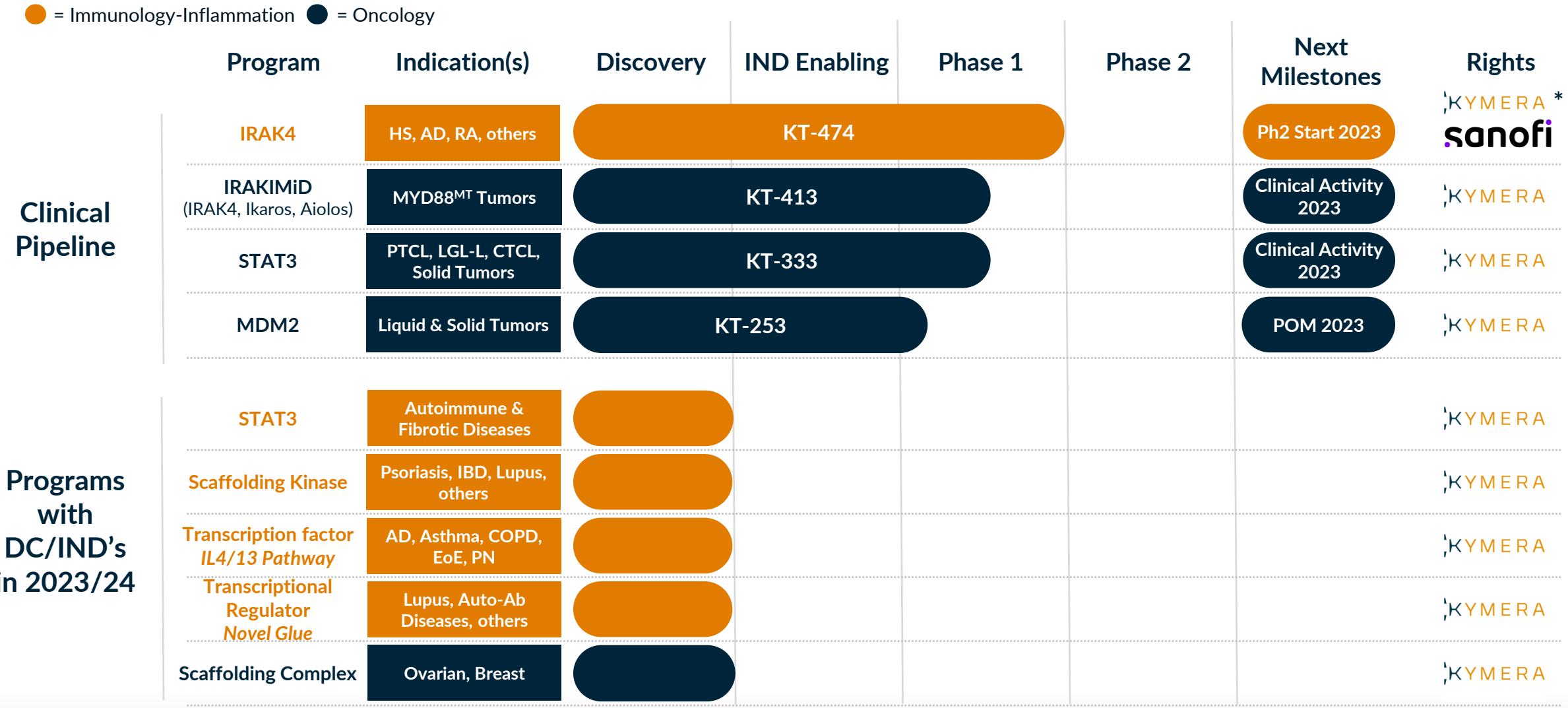
- Undrugged transcription factor with strong genetics validation

- Protein degradation only/best approach to deliver effective drug

MDM2
KT-253

STAT3
KT-333

Kymera's Pipeline of Novel Protein Degraders



*Option to participate equally in the development and commercialization of Sanofi-partnered programs in the US

Kymera's 2023 Objectives

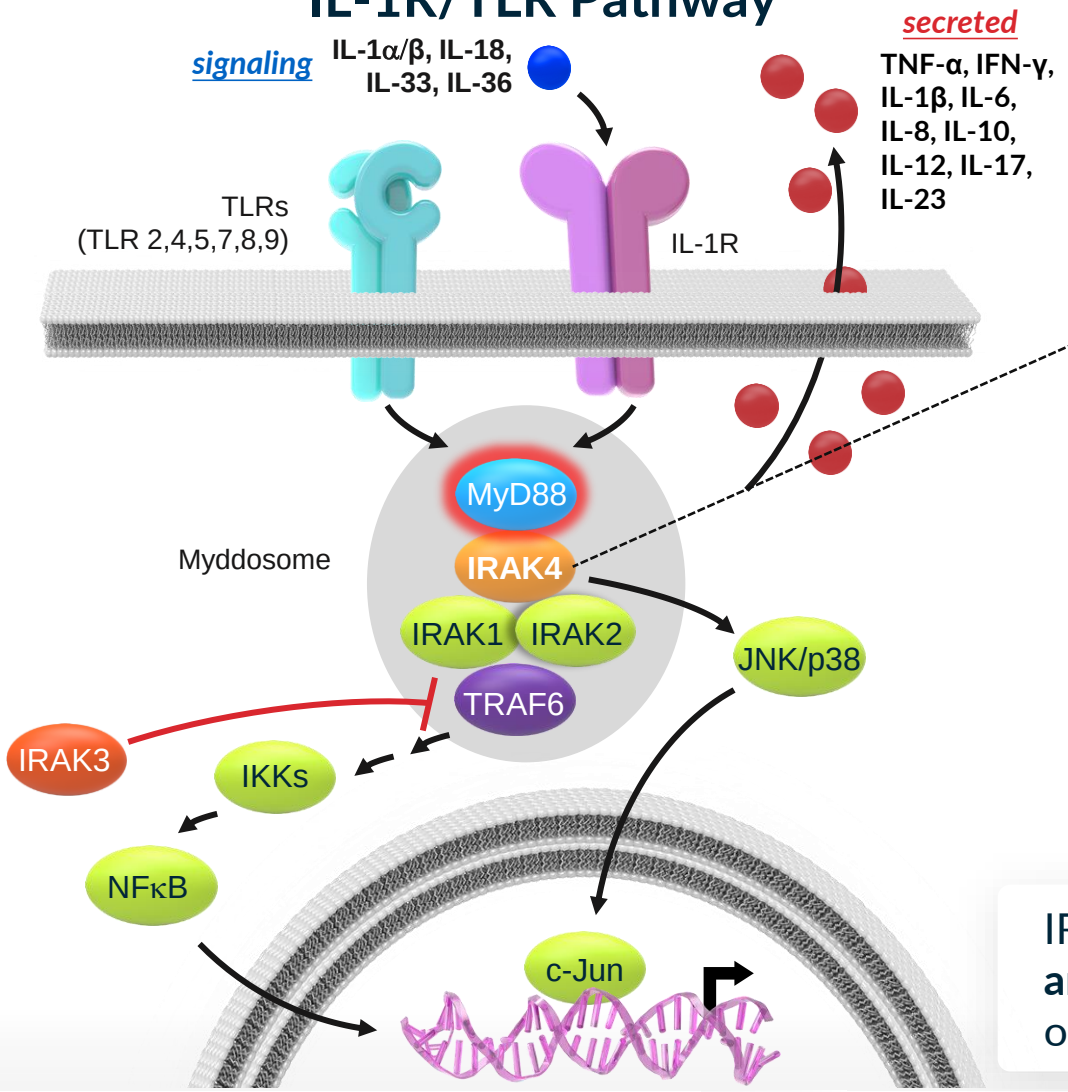
- Collaborate with Sanofi to **initiate KT-474 Phase 2 Trials**
- **Publish results of KT-474** Phase 1 Trial including patient cohort
- Demonstrate **KT-413 clinical anti-tumor activity** in patients
- Demonstrate **KT-333 clinical anti-tumor activity** in patients
- **Initiate KT-253 Phase 1 Trial** in solid and heme tumors
- Establish **KT-253 clinical proof-of-mechanism** in patients
- Deliver at least **2 new DC/IND** from the preclinical pipeline
- Expand **novel molecular glue franchise**

IRAK4

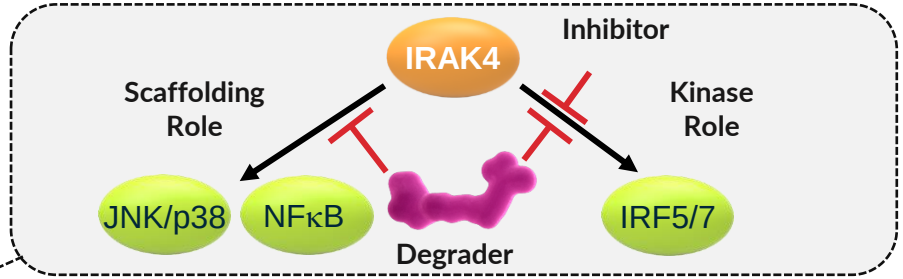
KYMERA

Degrading IRAK4: Best 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

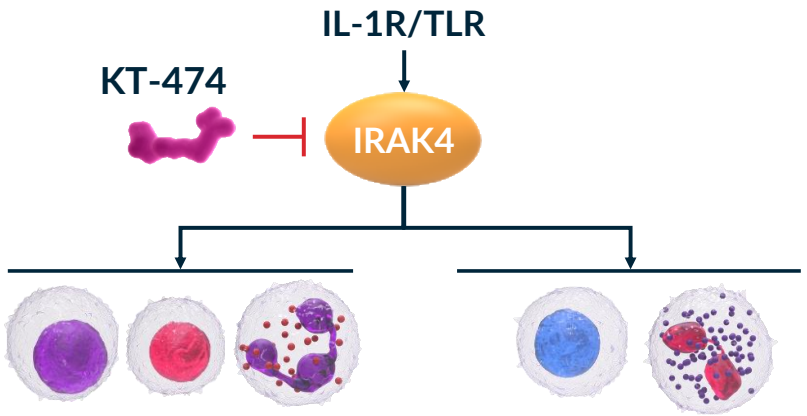
Human Genetics

Adult humans with **IRAK4 Null Mutation are healthy**

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

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 and Summary

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)

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

Summary of Key Findings in Healthy Volunteers

- IRAK4 **reduction to near lower limit of quantification** with Mass Spectrometry
- Degradation 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**

Summary of Key Findings in Patients

- Safety, **PK and PD comparable to healthy** volunteers
- **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
- Results support **advancing KT-474 into Phase 2** placebo-controlled trials; Sanofi has committed to start Ph2 clinical trials, initially in HS and AD

Key KT-474 Phase 1 Accomplishments

- Healthy volunteer SAD and MAD cohorts demonstrated:
  - Robust and **sustained IRAK4 degradation in blood and skin** with single and multiple daily doses
  - Broad **inhibition of *ex vivo* TLR-mediated cytokine induction**
  - **Generally well tolerated**
- Patient cohort demonstrated:
  - **PK, PD and safety comparable** to healthy volunteers
  - Modest, non-adverse **QTcF prolongation spontaneously resolved back to baseline** during dosing
  - Robust IRAK4 degradation in blood and skin associated with **systemic anti-inflammatory effect** in HS and AD patients, validating pathway and target relevance in HS and AD
  - **Promising clinical activity** exceeding benchmark placebo rates and comparing favorably to SOC biologics **in both HS and AD**
- **Sanofi has committed to start Ph2 clinical trials, initially in HS and AD**

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

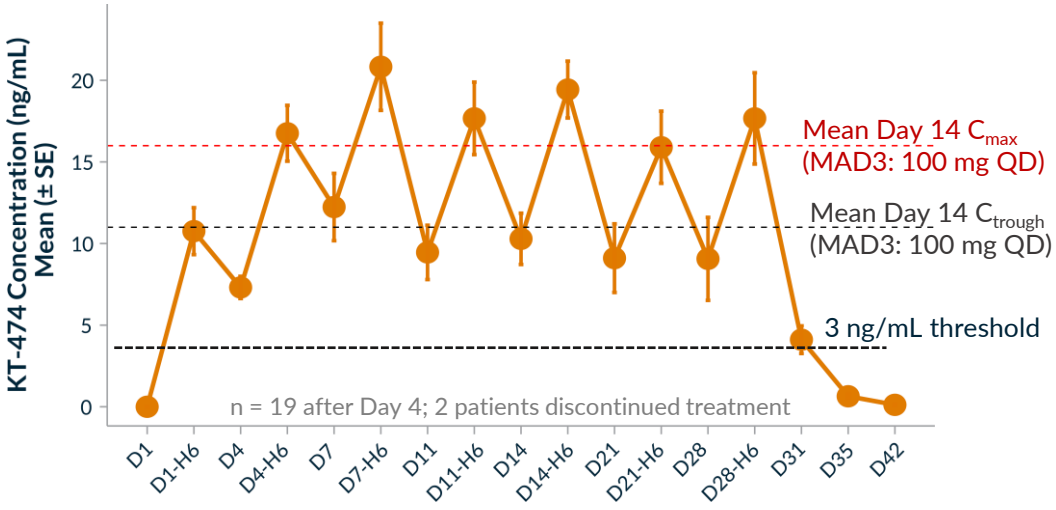
Patient Disposition

	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

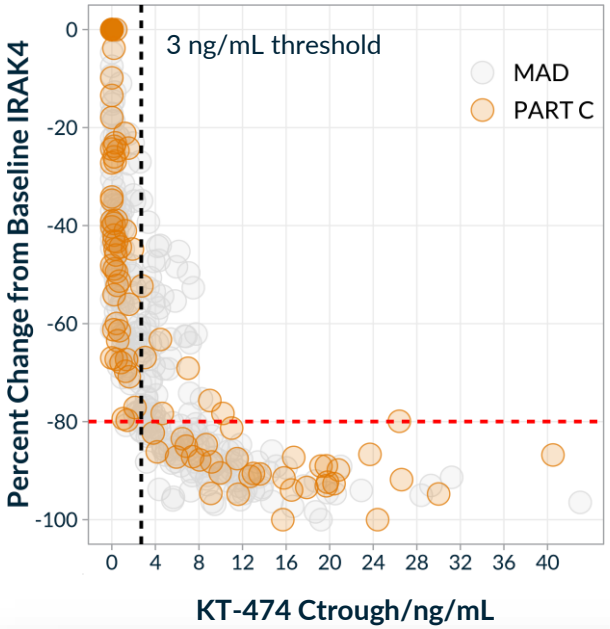
* Withdrew treatment after 4 doses for personal reasons
** Withdrew treatment after 5 doses for personal reasons

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

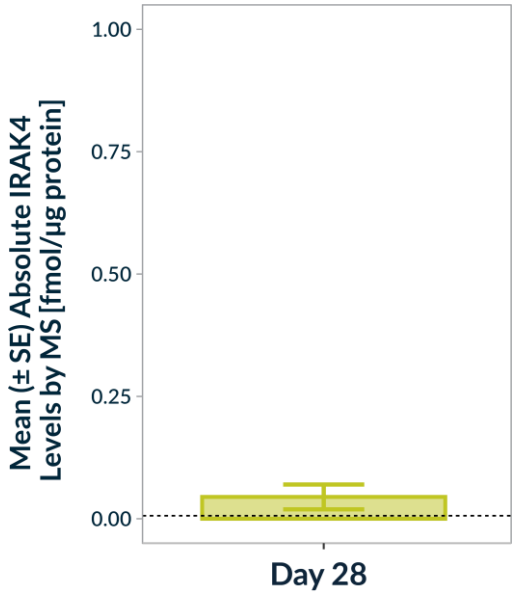
Part C KT-474 Plasma PK



PK/PD Correlation in Plasma/Monocytes (FLOW)



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



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

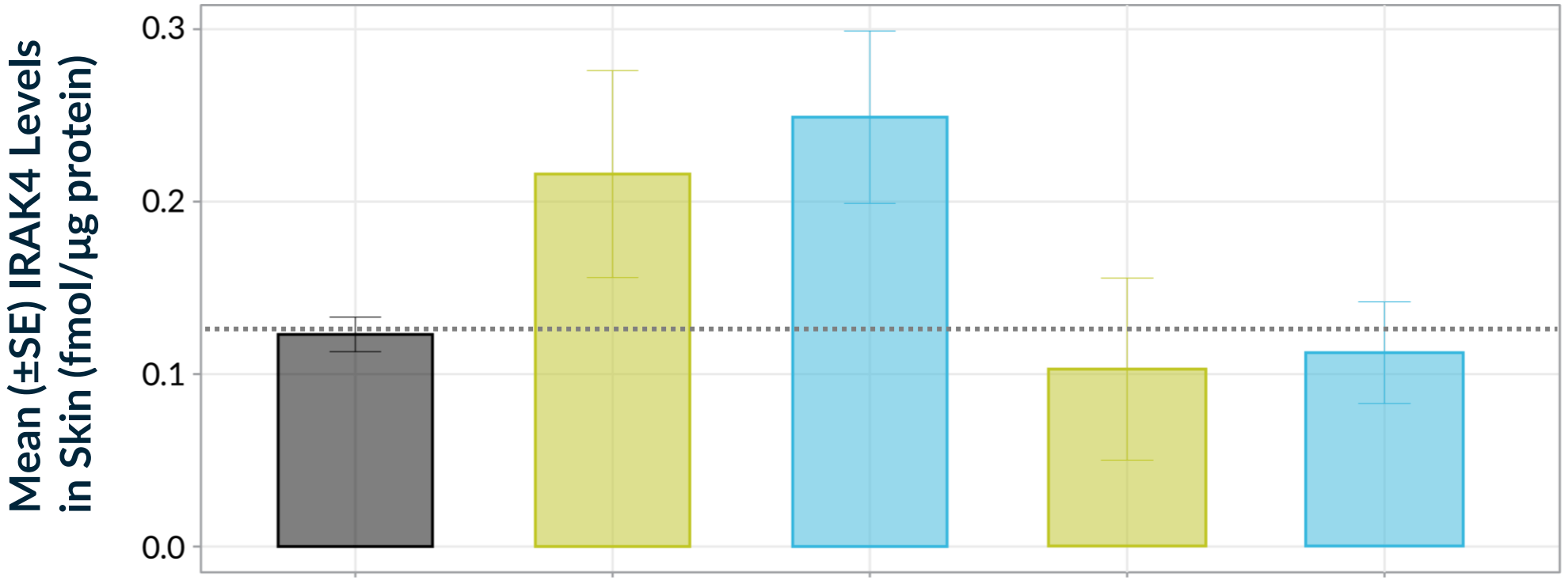
- Mean C_{max} and C_{trough} levels at steady state in Part C are in line with MAD3 levels at Day 14
- Mean half-life of 44 hours is within the range observed in MAD (34-59 hours)

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

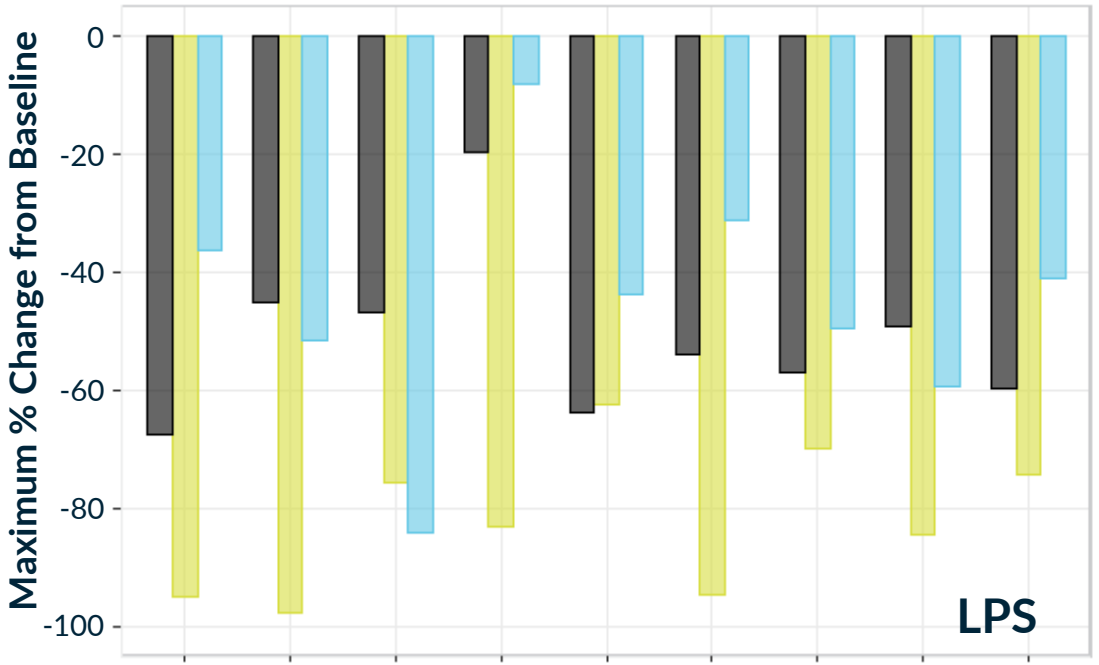
HS and AD Patients **IRAK4 Levels at Day 28 (n=4) near LLOQ**

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)**

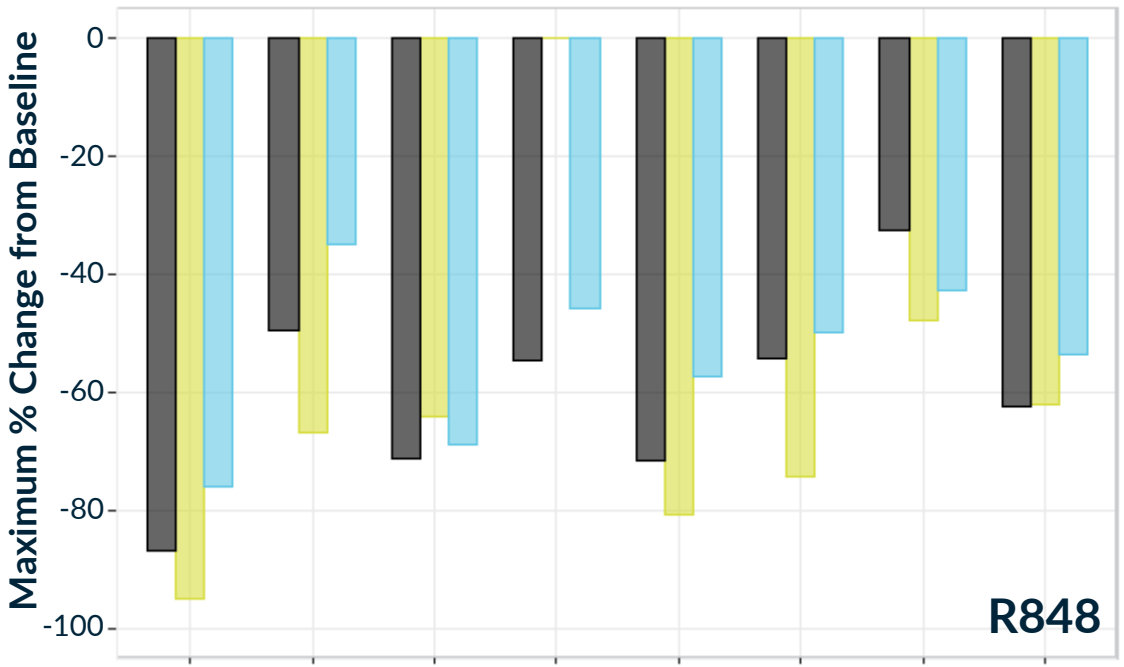
Up to 98% Inhibition of 9 Disease-Relevant Cytokines *Ex Vivo* in both HS and AD Patients



MAD 3
Healthy Subjects
100 mg QD (n = 9)

Part C
AD Patients (n=7)

Part C
HS Patients (n=9)



	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%

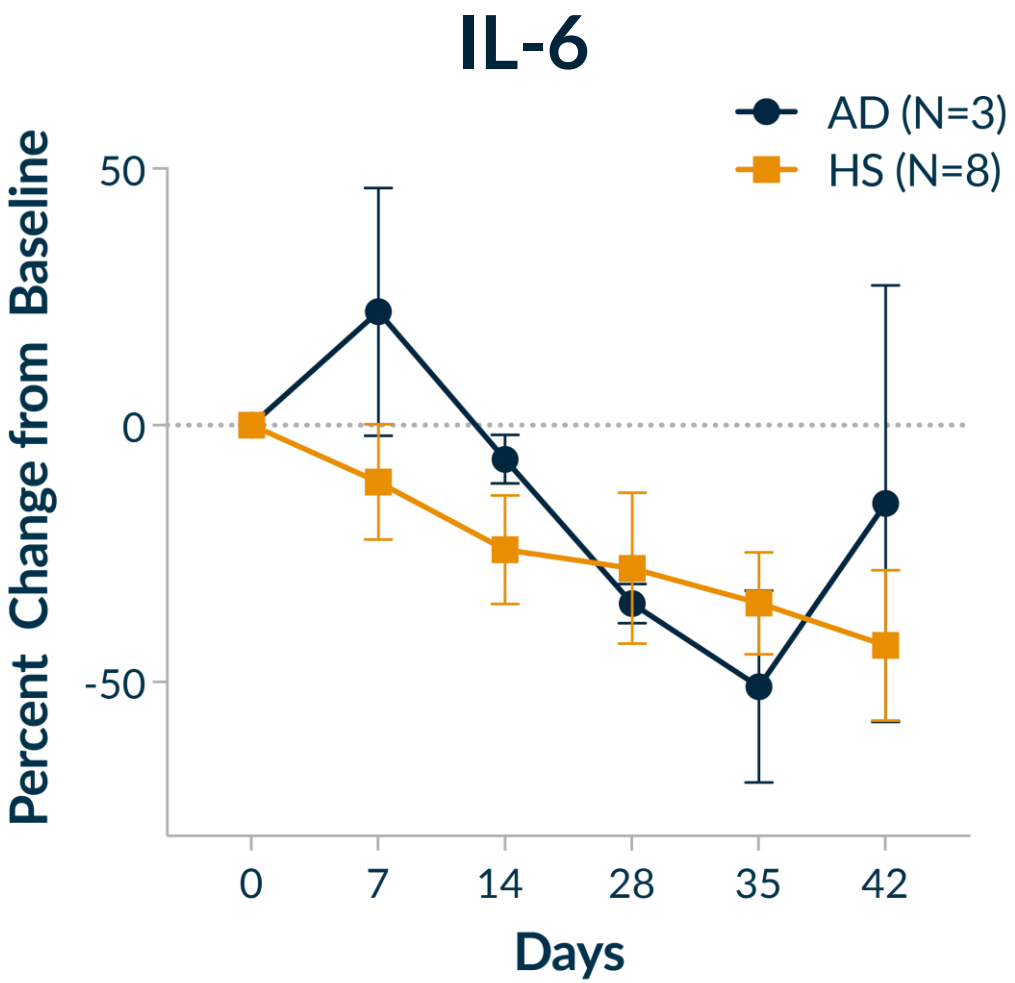
	IFNγ	IL10	IL12	IL17	IL1b	IL6	IL8	TNFα
HV (MAD3)	-87%	-50%	-71%	-55%	-72%	-54%	-33%	-62%
AD	-95%	-67%	-64%	0%	-81%	-74%	-48%	-62%
HS	-76%	-35%	-69%	-46%	-57%	-50%	-43%	-54%

* 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

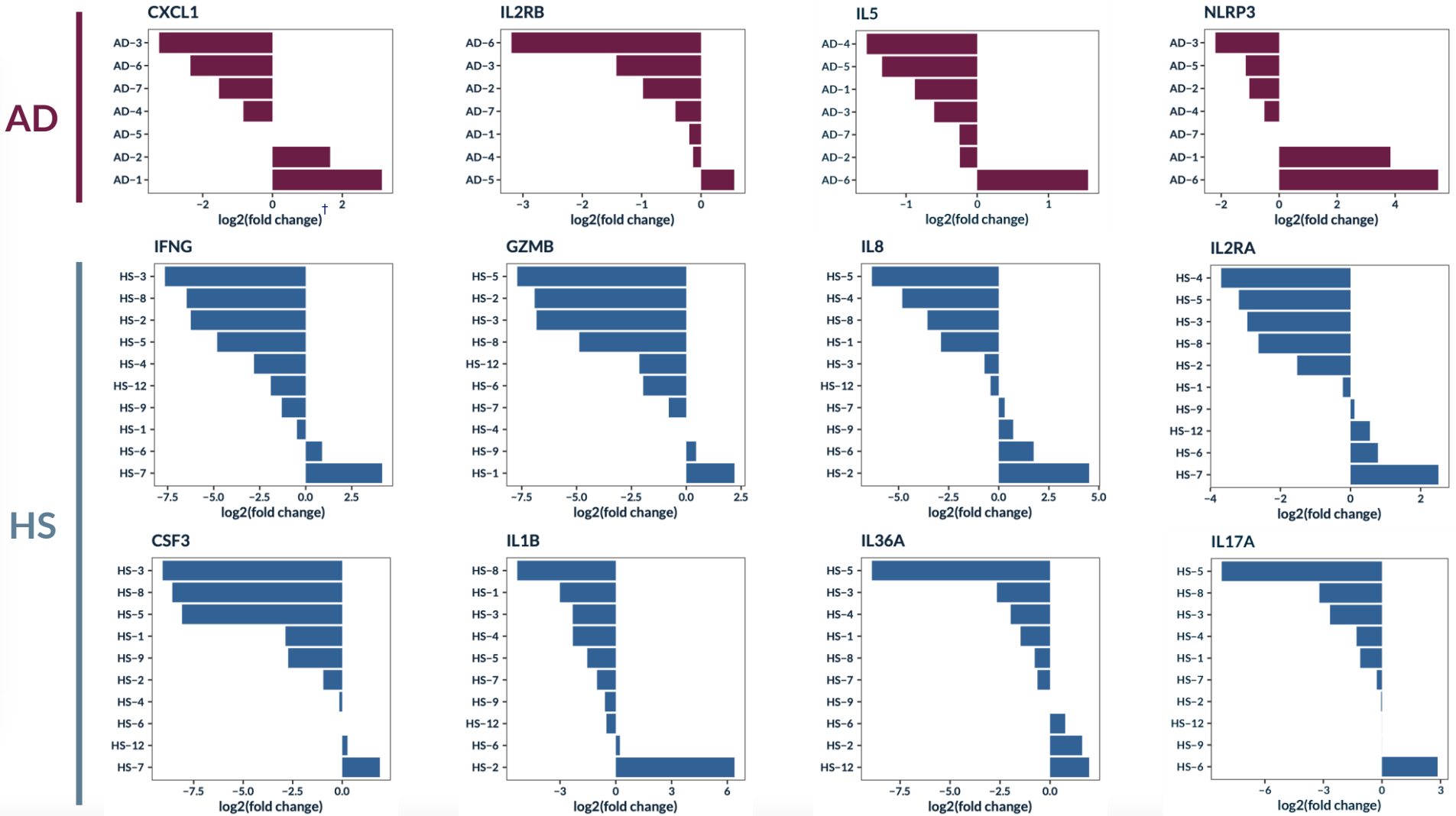
Analyte	Mean Max* AD (n)	Mean Max* HS (n)
IL-6†	-56% (3)	-63% (8)
CRP†	NA	-58% (5)
IL-1β	-36% (7)	-48% (8)
SAA†	-51% (4)	-41% (10)

*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

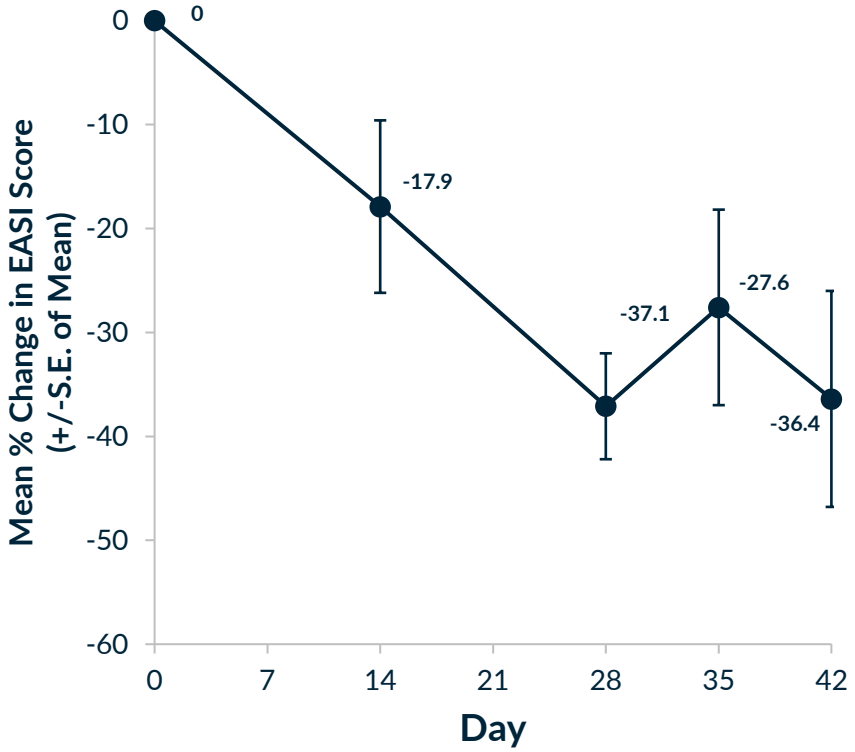


†log2(fold change): -1 = 50% decrease, -2 = 75% decrease, -3 = 87.5% decrease

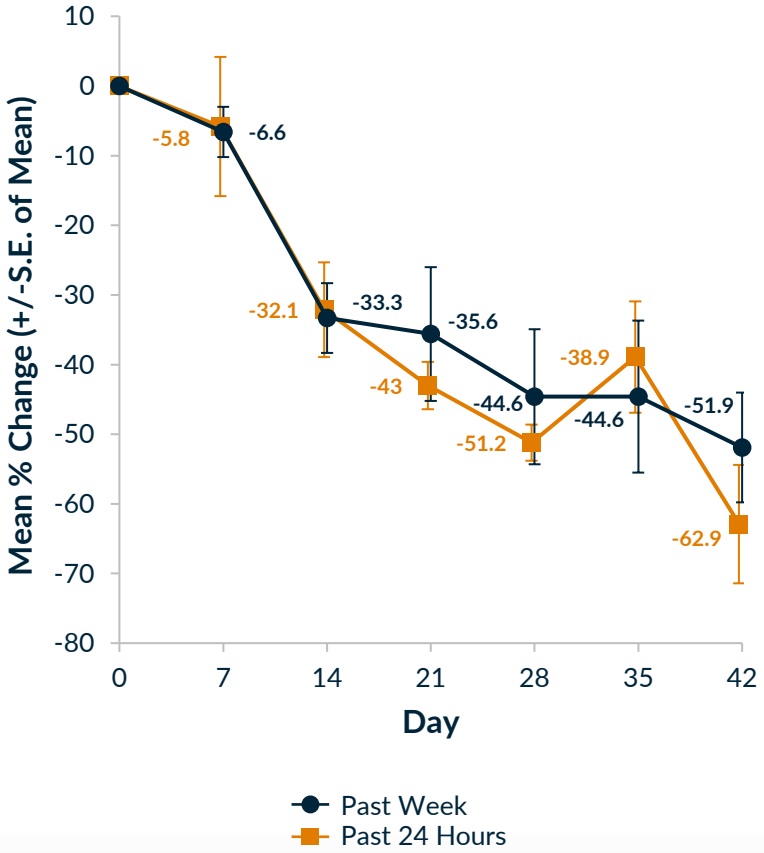
*Evaluable patients for whom the samples were of sufficient quality for analysis.

AD: Significant Reduction in EASI Score and Pruritus

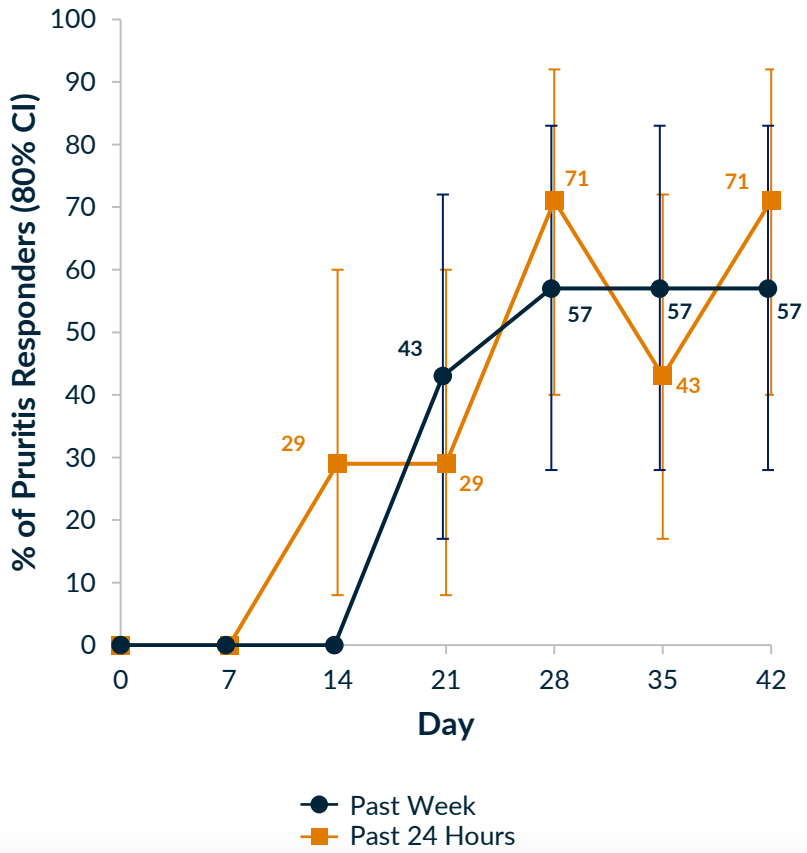
Mean % Change in EASI Score Over Time (N=7)



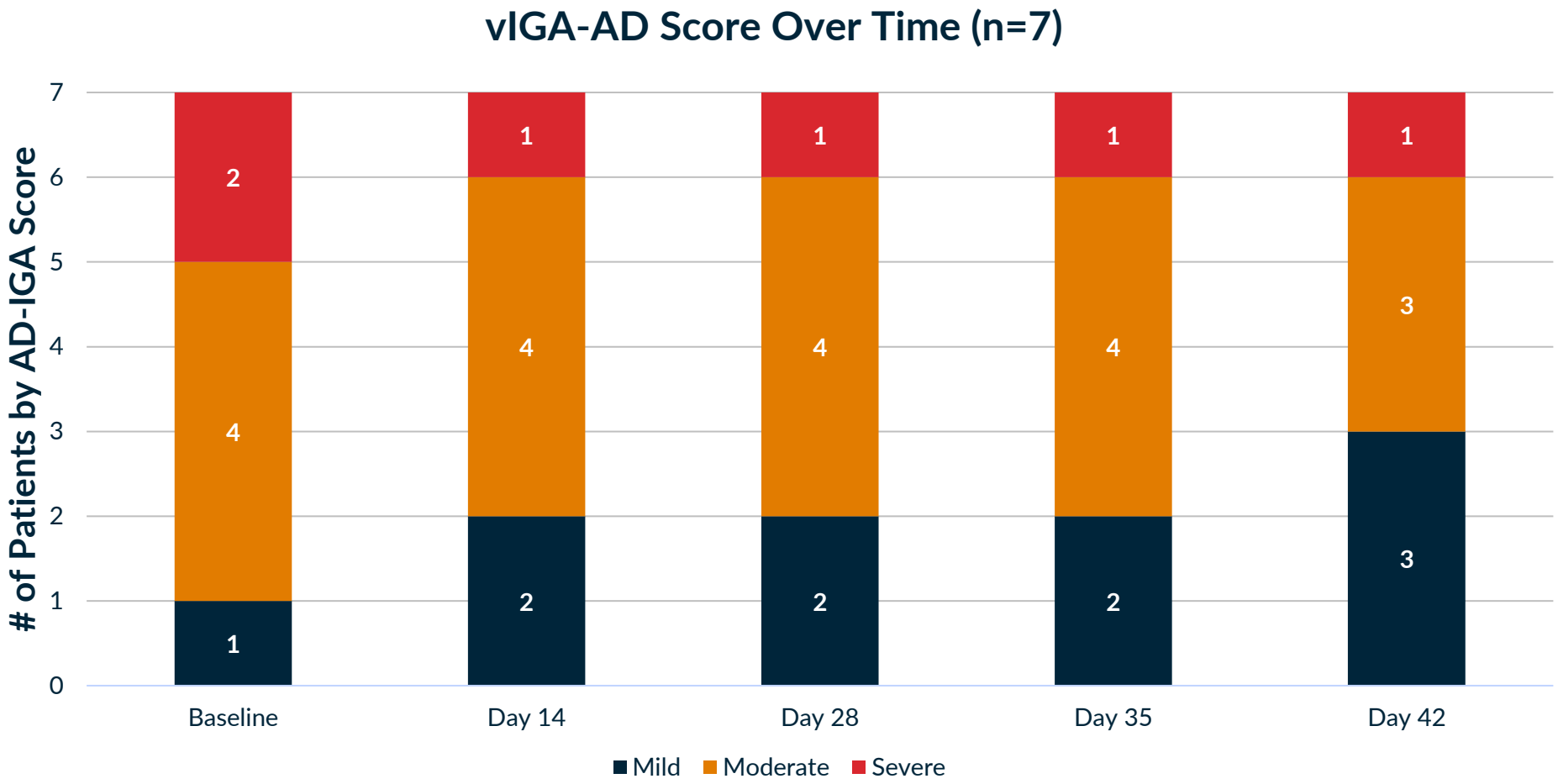
Mean % Change of Worst Pruritus Over Time (N=7)



Patients with ≥4 Unit Reduction from Baseline in Worst Pruritus (N=7)



Investigator's Global Assessment (vIGA-AD)



- IGA scores remained stable or improved in all patients

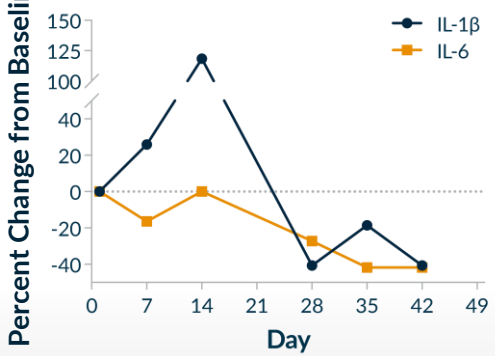
AD Case Study: Patient AD-3

Improvement in Disease Severity from Severe to Mild

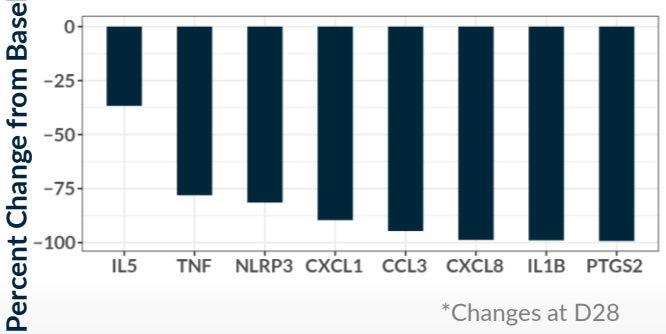
- 51-year-old Hispanic/Latino male with severe AD (vIGA-AD) and EASI score of 28.2 at baseline
- Previously treated with topical betamethasone 2018-2020

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**)

Plasma Cytokines

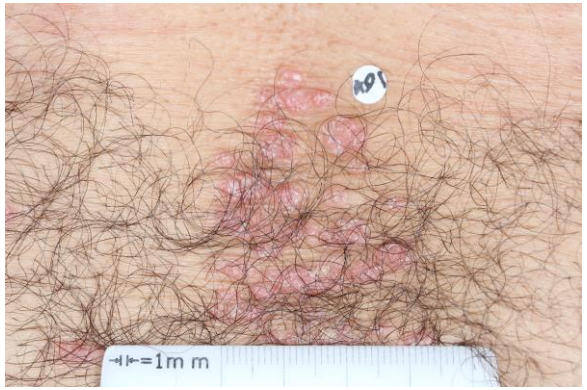


Skin Inflammation Biomarkers* (RNAseq)

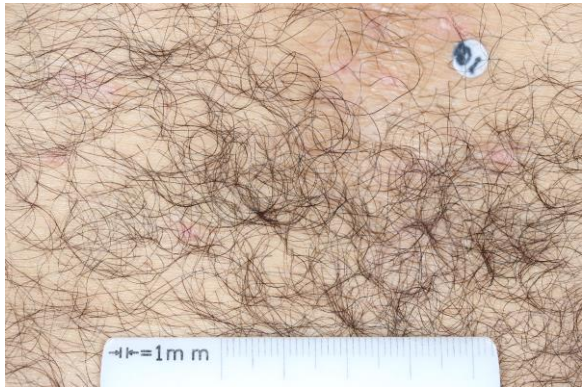


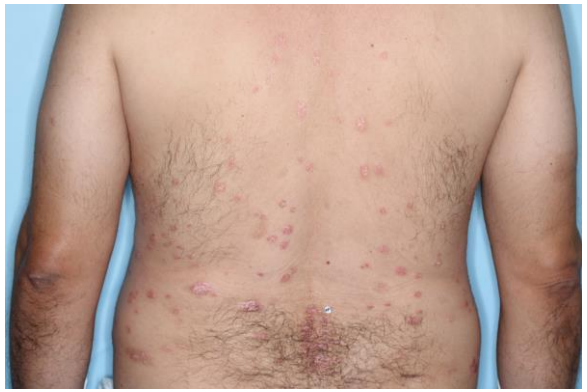
*Changes at D28

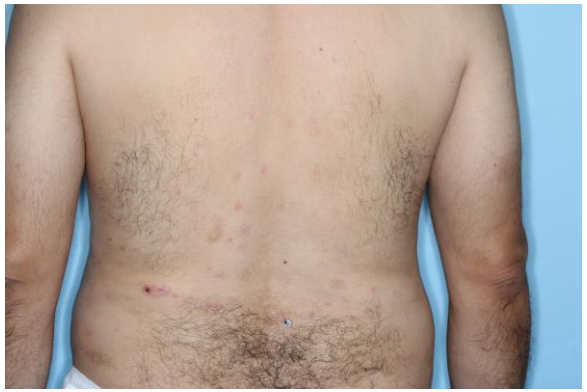
Day 1 - BL



Day 42







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

- **Encouraging initial EASI score reductions** sustained after cessation of dosing
- Peak pruritus reductions, and responder rates, **significantly greater than placebo and SOC benchmarks**
- Investigator Global Assessment **(IGA) scores improved in 2 of 7 patients** and remained stable in the others

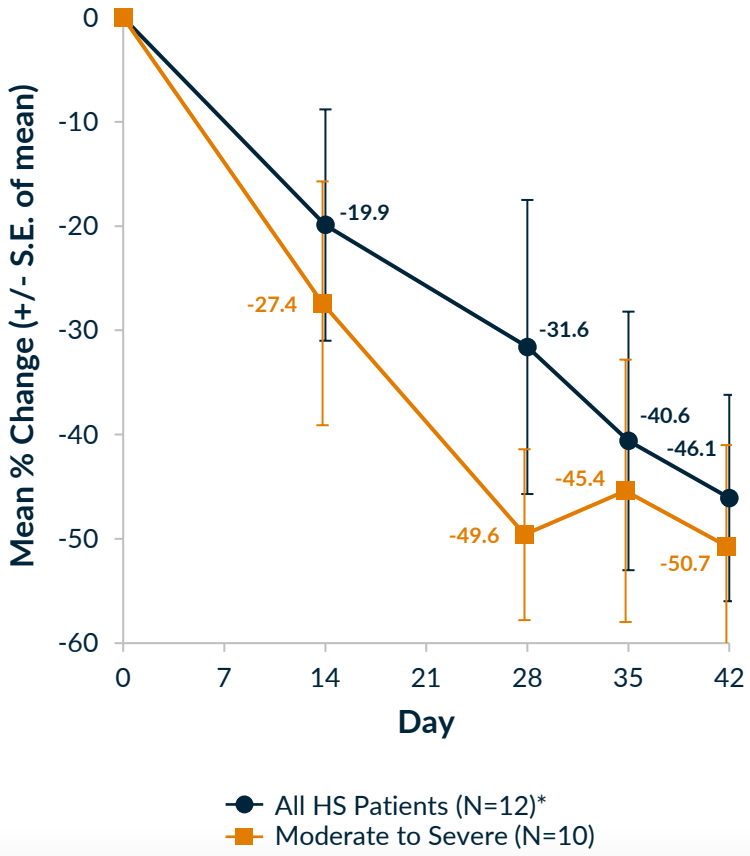
	KT-474 Part C		Placebo Benchmarks	Dupilumab Phase 3
	Day 28	Day 42	Week 4	Week 4
ΔEASI	**-37%**	**-36%**	-12 to -25%*	-52%[1]
ΔPeak Pruritus NRS	**-52%**	**-63%**	-11%[1]	-34%[1]
Peak Pruritus NRS Responder (week/24hrs)	**57%/71%**	**57%/71%**	4 to 17%**	23 to 40%[1,2]

*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;*

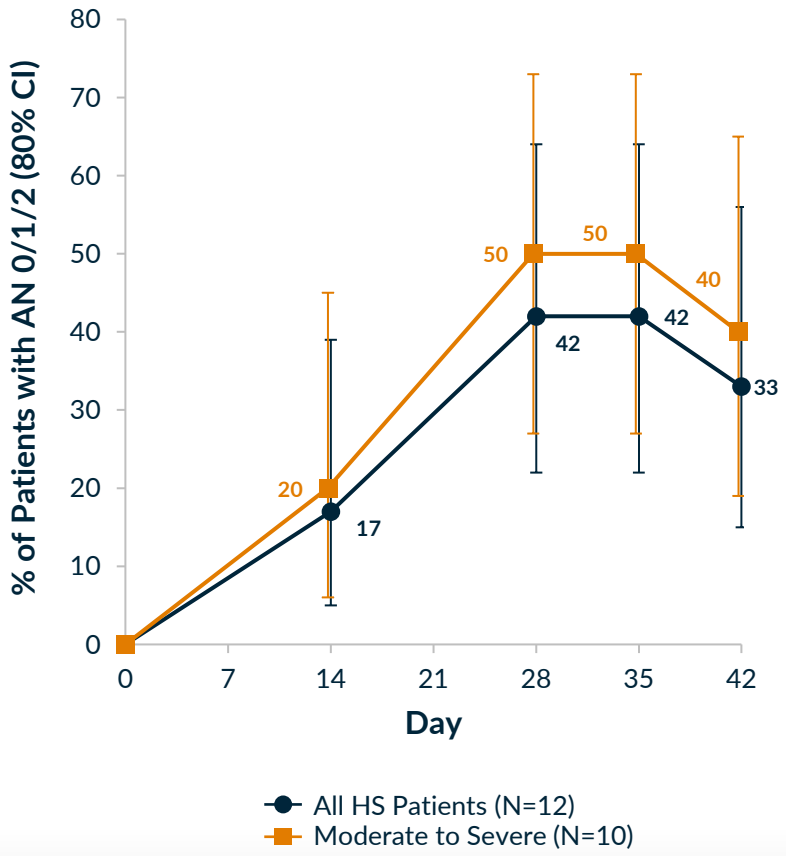
The Dupilumab clinical trial was conducted by other parties in a similar patient population with different enrollment criteria from Part 1C of our Phase 1 clinical trial evaluating KT-474. Results do not reflect a head-to-head trial and are shown for illustrative purposes only

HS: Significant Reductions in AN Counts Leading to HiSCR Responses

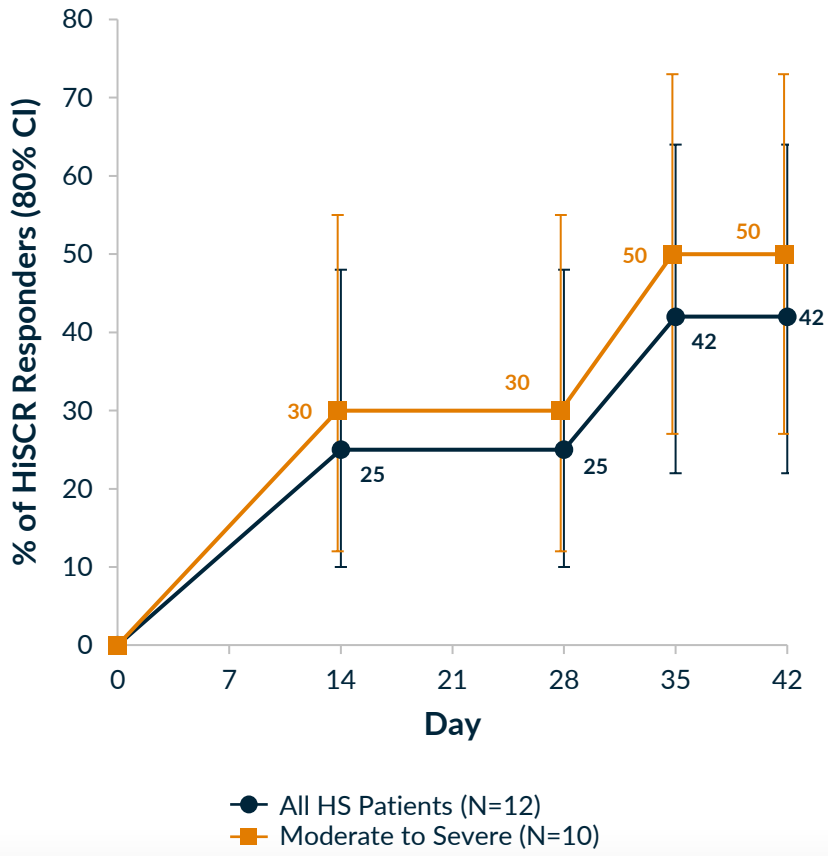
Mean % Change in Total AN Counts Over time



% of Patients with AN Count 0/1/2



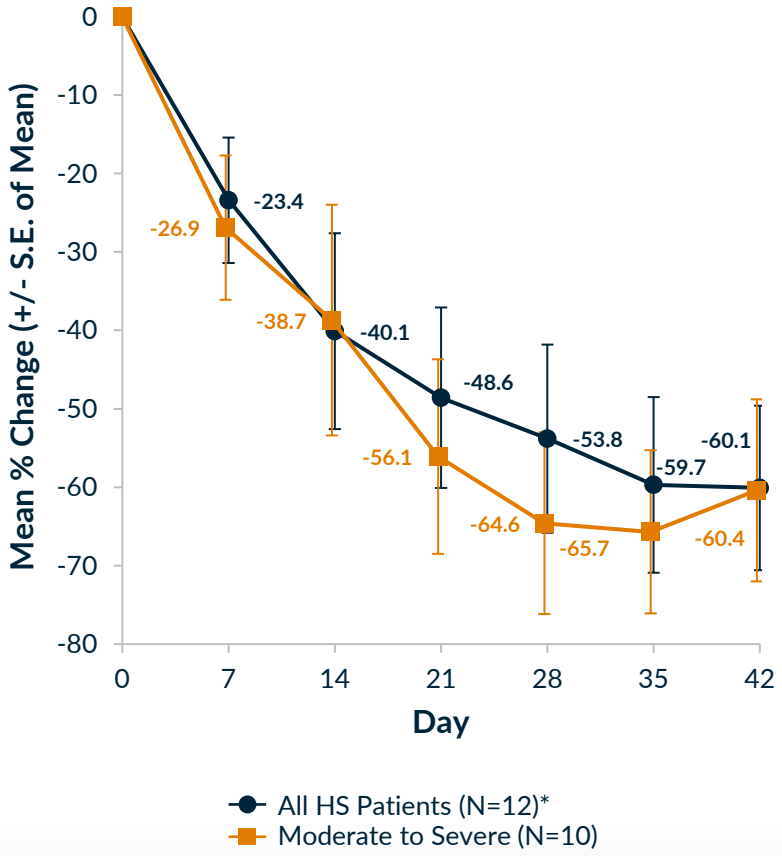
HiSCR50 Responders



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

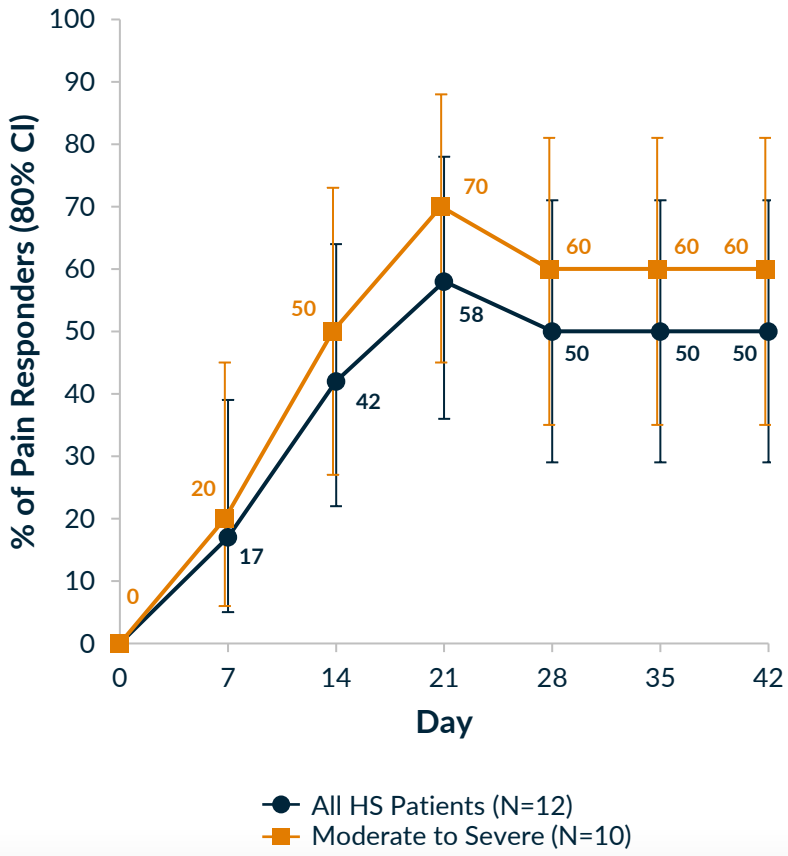
HS: Significant Reductions in Pain/Pruritus

Mean % Change in Average Pain Over Past Week



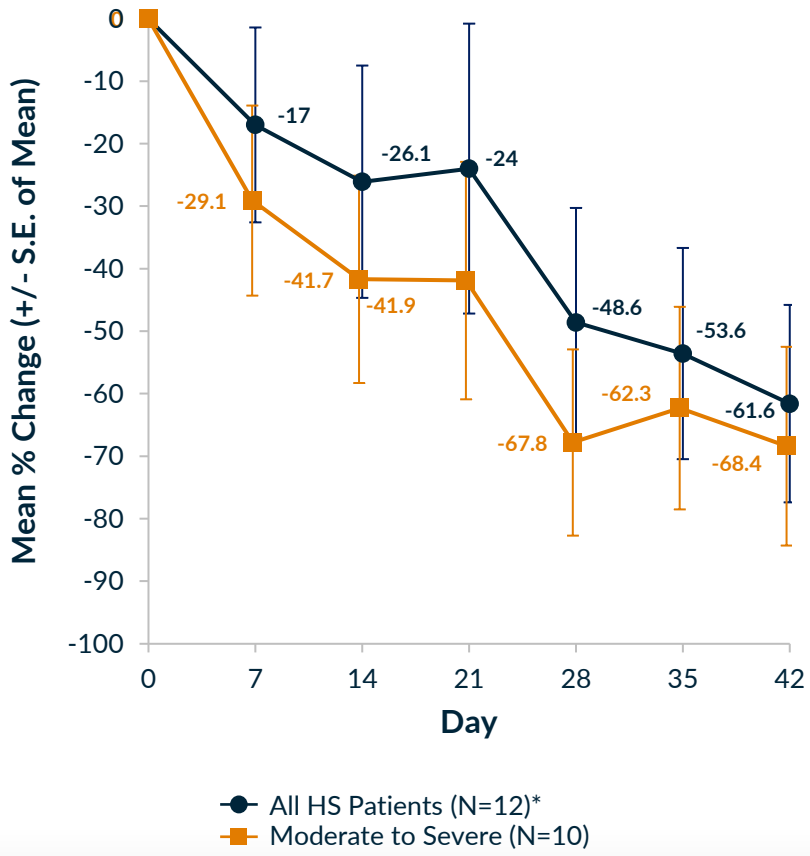
All HS Patients (N=12)*
Moderate to Severe (N=10)

% of Patients with ≥30% and ≥1 Unit Reduction in Worst Pain Over the Past Week



All HS Patients (N=12)
Moderate to Severe (N=10)

Mean % Change in Worst Pruritus Over Past Week

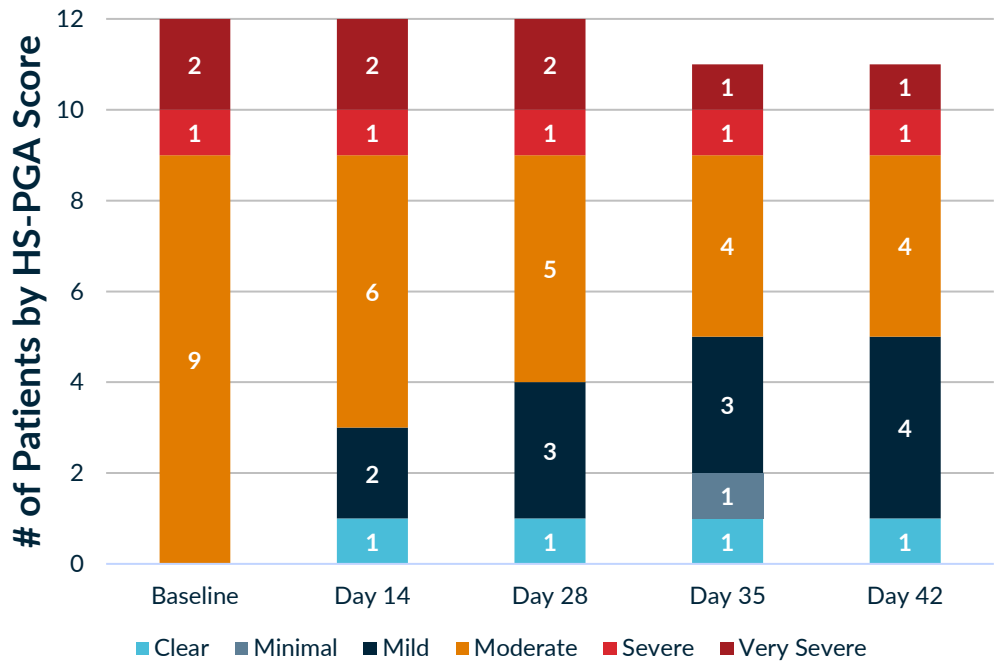


All HS Patients (N=12)*
Moderate to Severe (N=10)

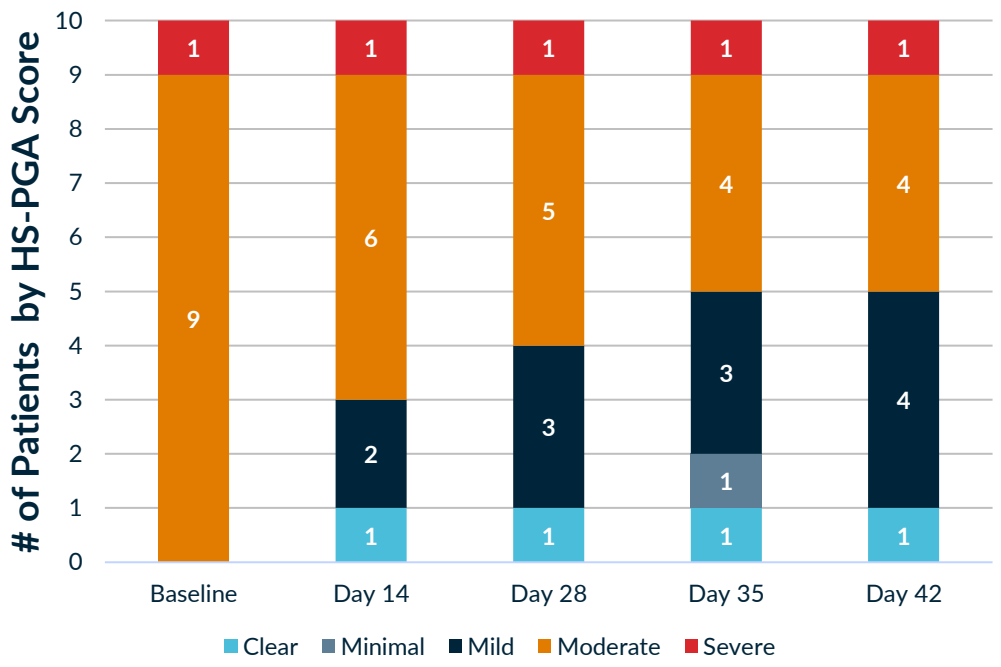
*One patient is censored for Day 35 and Day 42 since the patient started on ustekinumab, steroids and abx on Day 34.

Physician's Global Assessment (HS-PGA)

HS-PGA Score Over Time (N=12*)



HS-PGA Score Over Time Moderate to Severe Patients (N=10)



- 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.

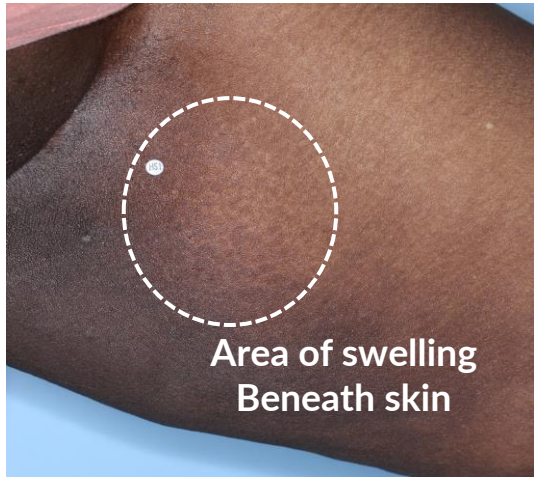
HS Case Study: Patient HS-3

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

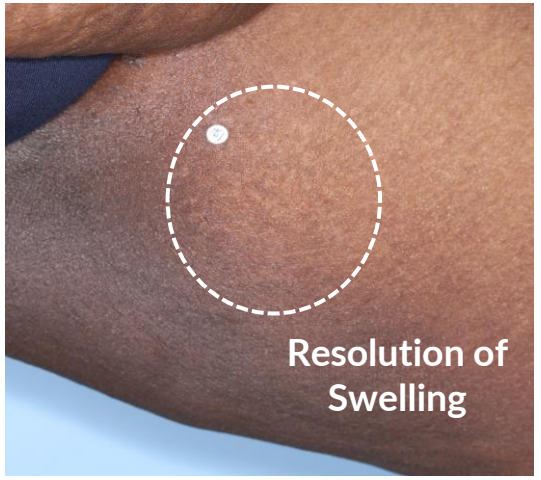
- 45 year old Black Female with Moderate HS (HS-PGA); Baseline AN count = 7
- Prior treatments: clindamycin (topical) and doxycycline

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**)

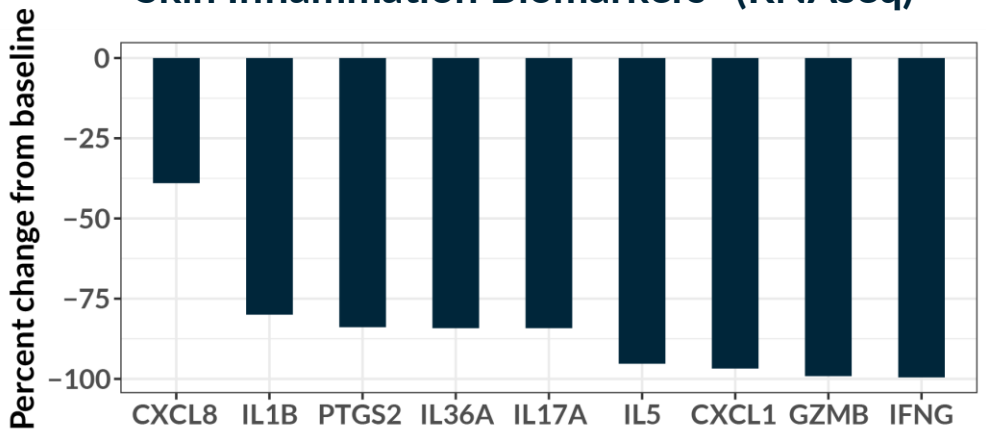
Day 1 - BL



Day 42



Skin Inflammation Biomarkers* (RNAseq)



*Changes at D28

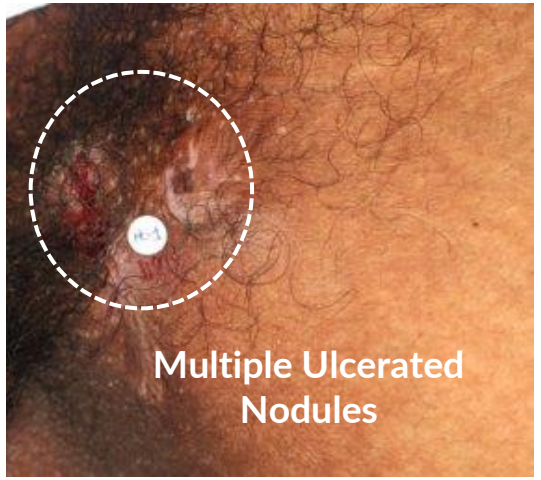
HS Case Study: Patient HS-10

Improvement in Disease Severity from Moderate to Mild

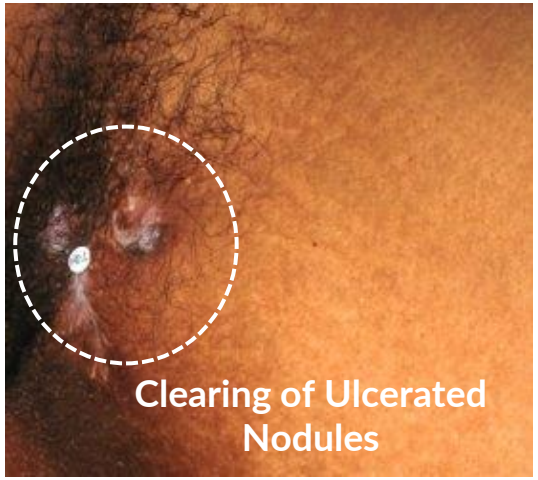
- 39 year old Black Female with Moderate HS (HS-PGA); Baseline AN count = 5
- Prior treatments: benzocaine ointment

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**)

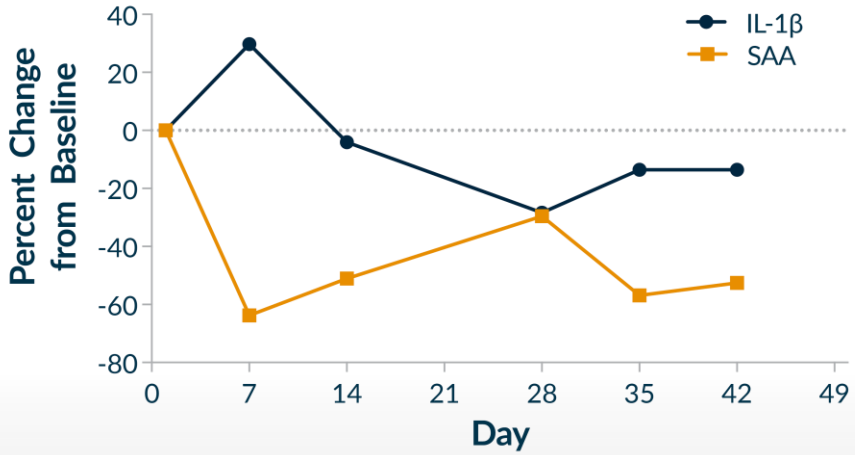
Day 1 - BL



Day 42



Plasma Cytokines/Acute Phase Reactants



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

- **AN Count reductions** most profound in moderate and severe patients
- **Highly competitive HiSCR response rates** continued to improve after cessation of dosing
- Pain and pruritus response rates and reductions **significantly higher than placebo and SOC benchmarks**
- 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 (All/Moderate to Severe)		**Placebo Benchmarks**	**Adalimumab Phase 2 and 3**
	Day 28	Day 42	Week 4	Week 4
ΔAN Count	**-32% / -50%**	**-46% / -51%**	-15%[1]	-31%[1]
AN Count 0/1/2	**42% / 50%**	**33% / 40%**	24 to 26%[3]	28 to 47%[2,3]
HiSCR50	**25% / 30%**	**42% / 50%**	19 to 30%[3,4]	29 to 51%[3,4]
HiSCR75	**8% / 10%**	**25% / 30%**	5%[4]	20%[4]
Pain NRS30 Responder	**50% / 60%**	**50% / 60%**	18 to 23%[3,5]	39 to 58%[2,3,5]

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

[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*

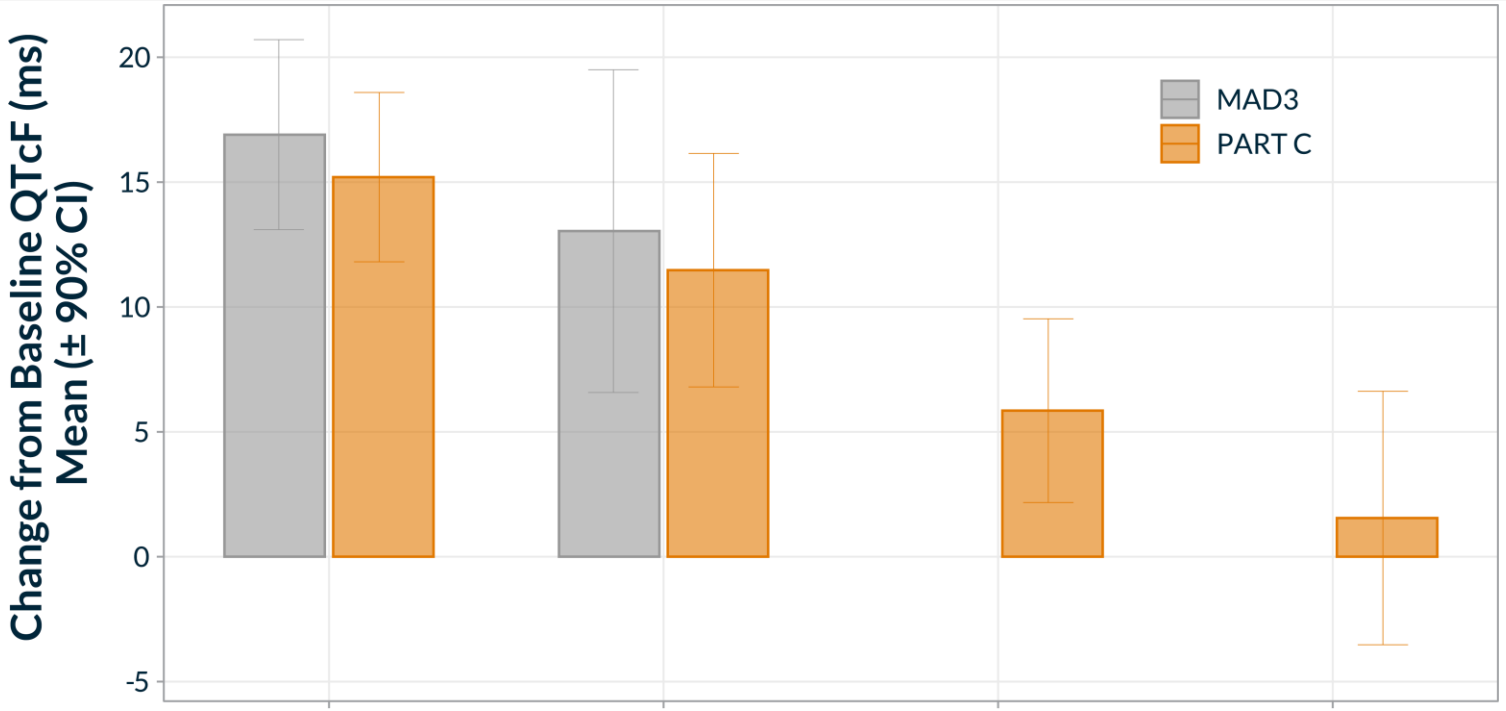
Adverse Events Related to Study Drug (Occurring in > 1 Patient)

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)

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

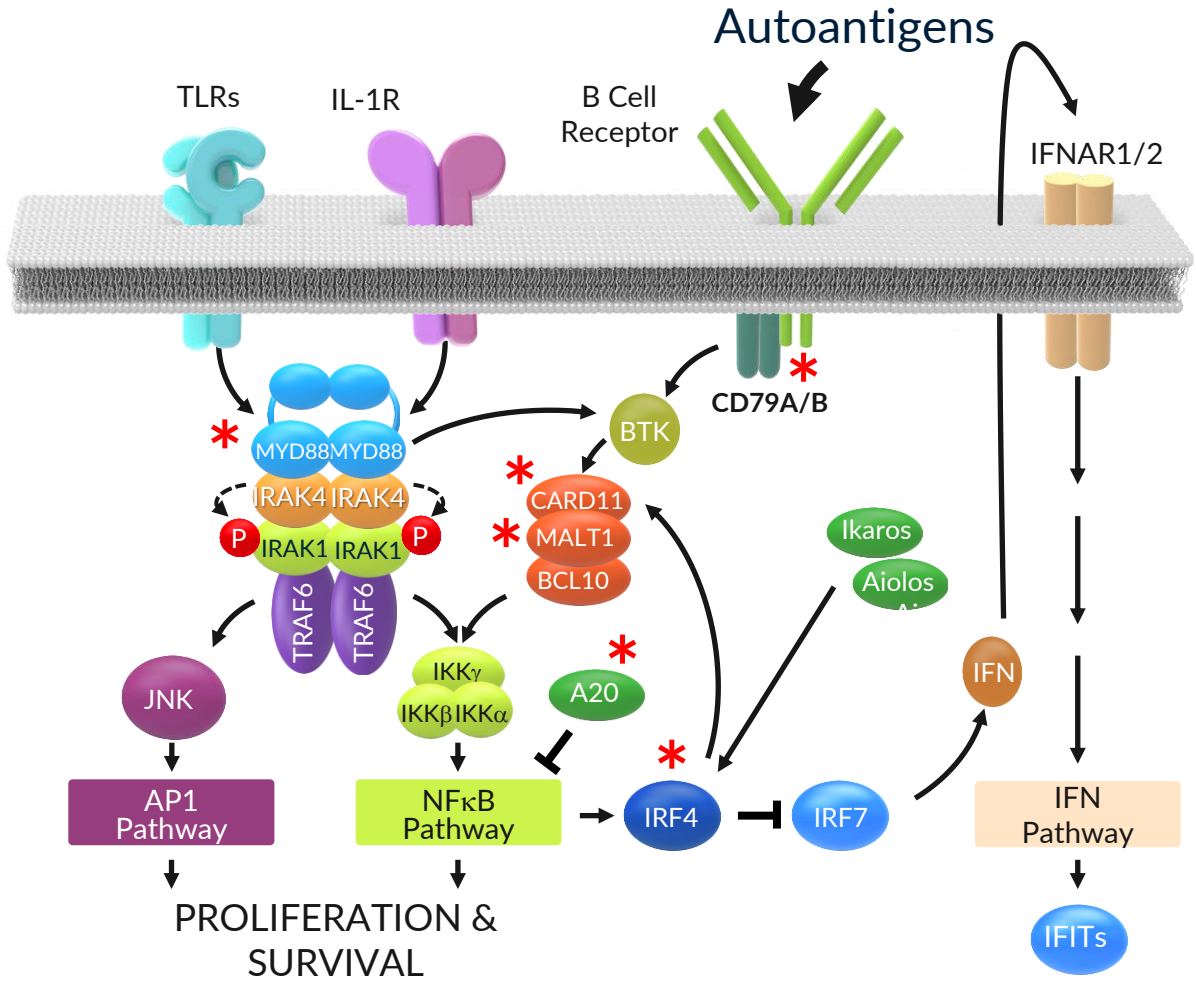

IRAKIMiD
KYMERA

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

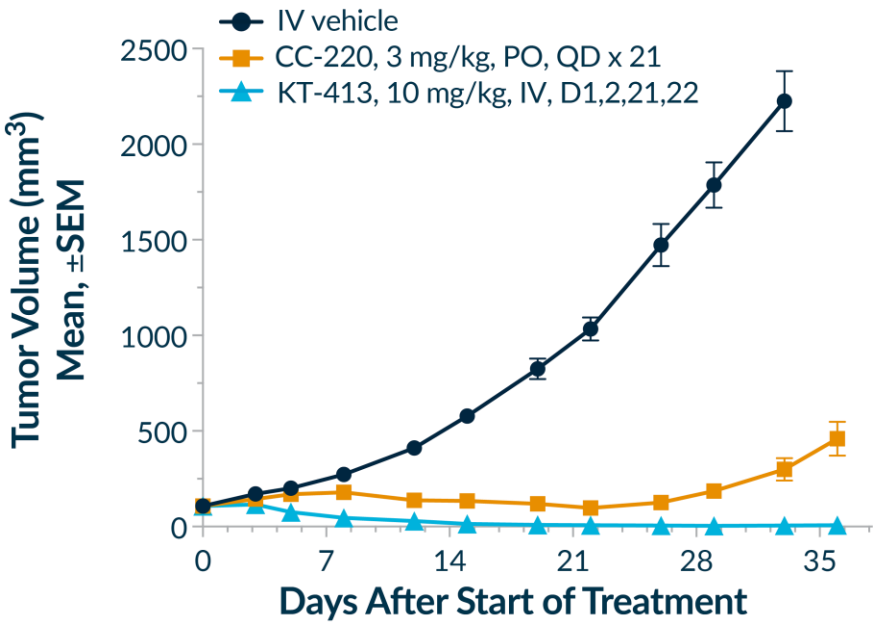
Source: Bionest and Global Data. ROW includes E.U., U.K. and Japan.

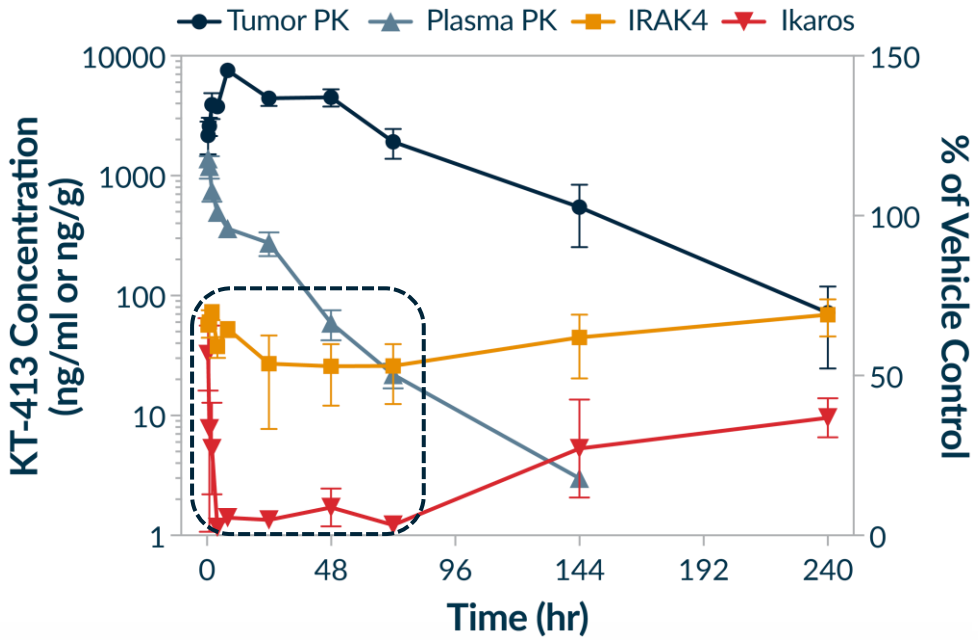


Adapted from Yang et al. (2012) *Cancer Cell* 21, 6, pp723-737

KT-413 Highly Active on Intermittent Dosing in Preclinical Models

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





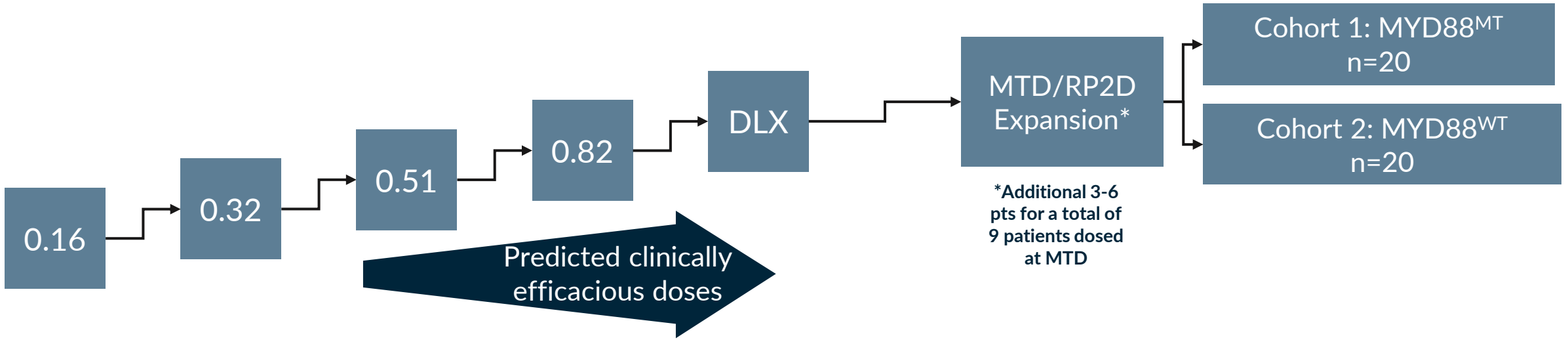
Drug (Day 33)	T/C% (REG%)	CR	PR	SD	PD
CC-220	9	0	0	0	7
KT-413 10 mg/kg	(94)	5	2	0	0

- 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

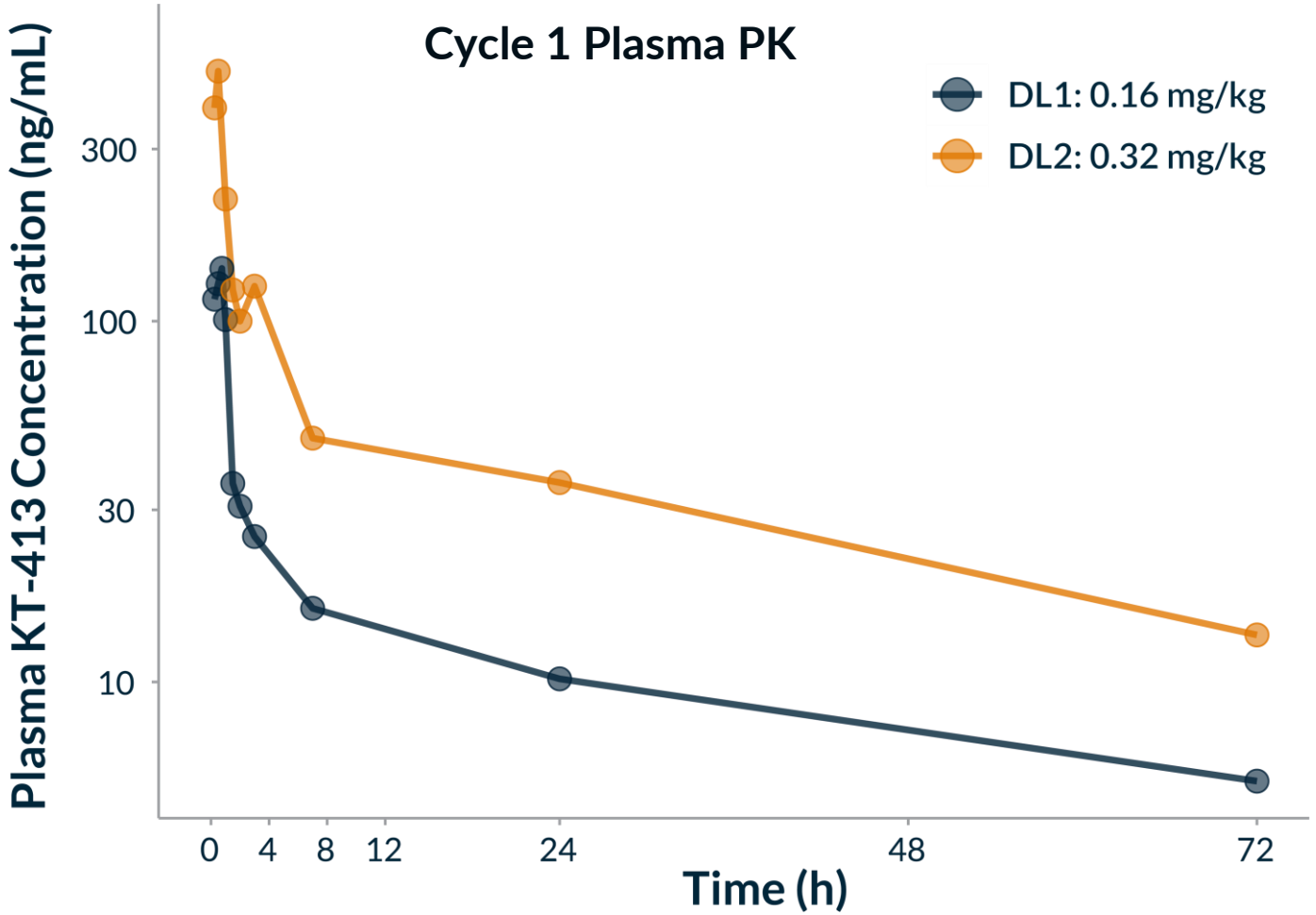
Phase 1a (n up to 40)	Phase 1b (n=40)
R/R B-cell NHL	R/R DLBCL
Regimen: mg/kg IV Infusion q 3 weeks	



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

Plasma PK Showing Dose-Proportional Increase in Exposure

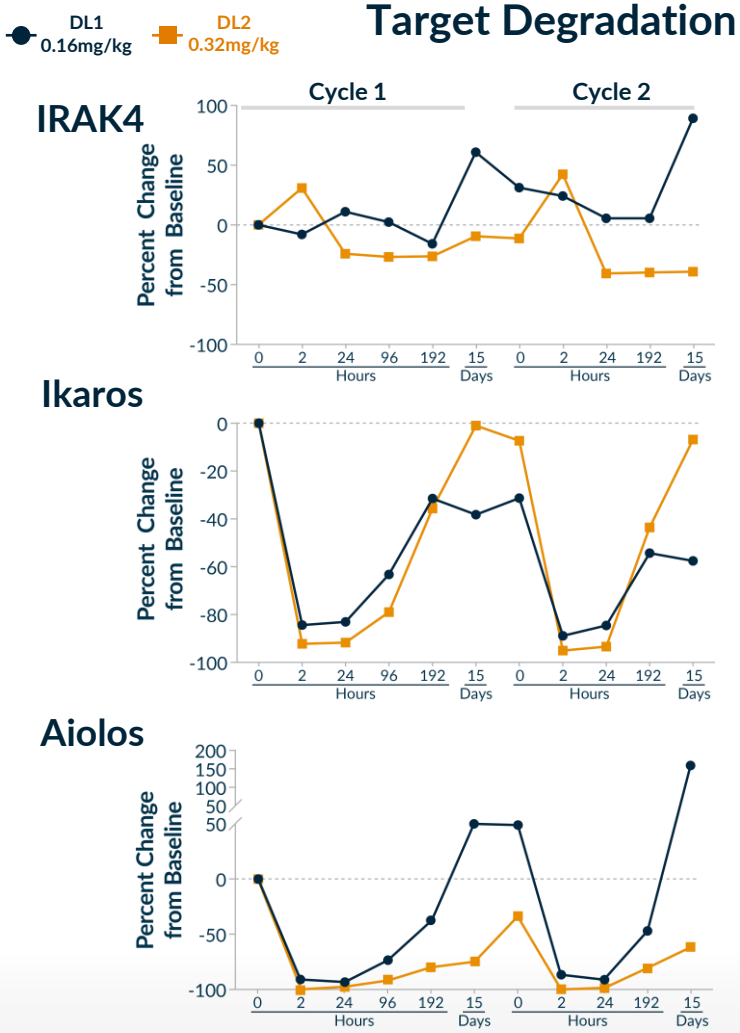


PK Parameter	0.16 mg/kg (DL1)	0.32 mg/kg (DL2)
	Cycle 1	Cycle 1
C_{max} (ng/mL)	140	493
AUC_{inf} (ng.h/mL)	1360	3490
Vd (L/kg)	10.1	3.99
CL (L/h/kg)	0.118	0.092
$t_{1/2}$ (h)	59.3	30.2

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%

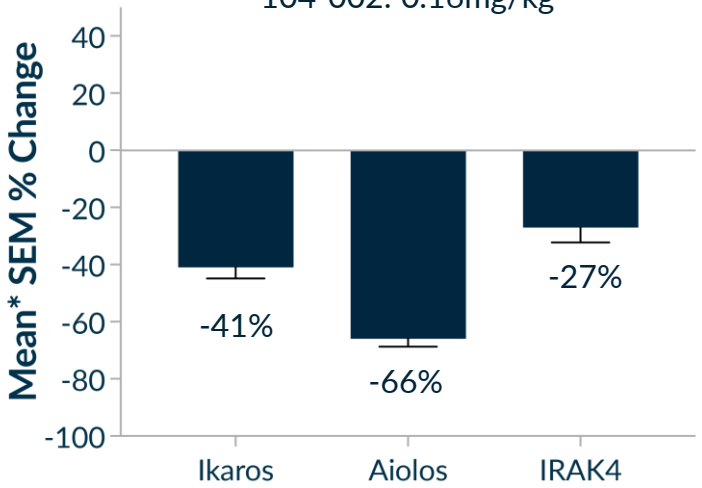
Dose Level	Cycle 1	Cycle 2
DL1	-84%	-88%
DL2	-92%	-95%

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

Percent Change from Baseline at C3D4
104-002: 0.16mg/kg



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

Demonstration of Initial POM for KT-413

- 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
- DL3/4 expected to be clinically active doses

Potential to be First Precision Medicine in DLBCL to Target a Genetically-defined Population (MYD88MT)

- Profound **antitumor activity** in preclinical models both **in single agent** and **combination**
- Clinical strategy in place to enable accelerated approval:

Monotherapy

- $MYD88^{MT}$ DLBCL for most direct path to registration
- Other $MYD88^{MT}$ lymphomas of interest include PCNSL, WM

Combinations

- With SOC agents in $MYD88^{MT}$ DLBCL to enable earlier line therapy

STAT3

KYMERA

STAT3 Degraders In Oncology: KT-333

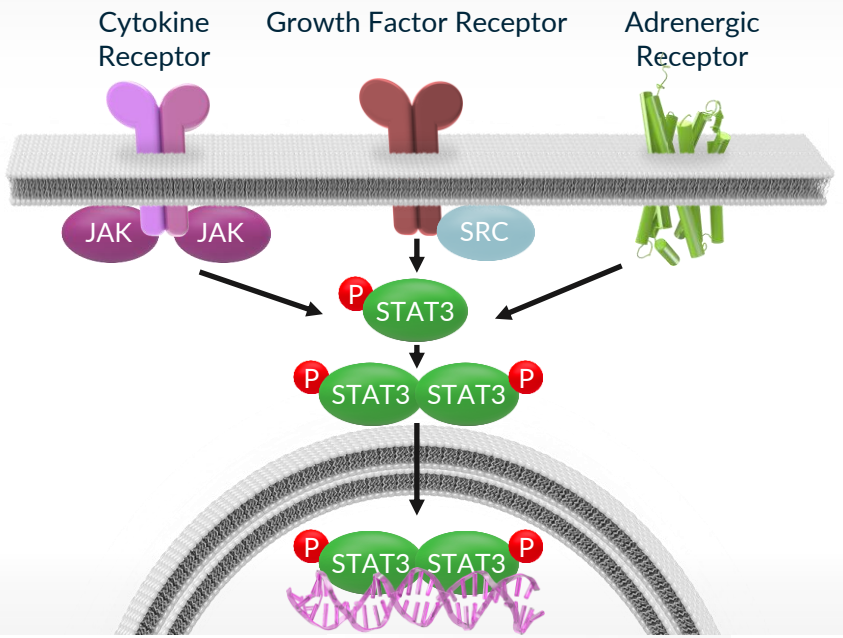
- High degree of validation of JAK-STAT pathway in oncology and immuno-oncology supported by >25k publications
- Traditionally undrugged target
- First-in-class opportunity to address STAT3 driven pathology across large and diverse indications

	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.

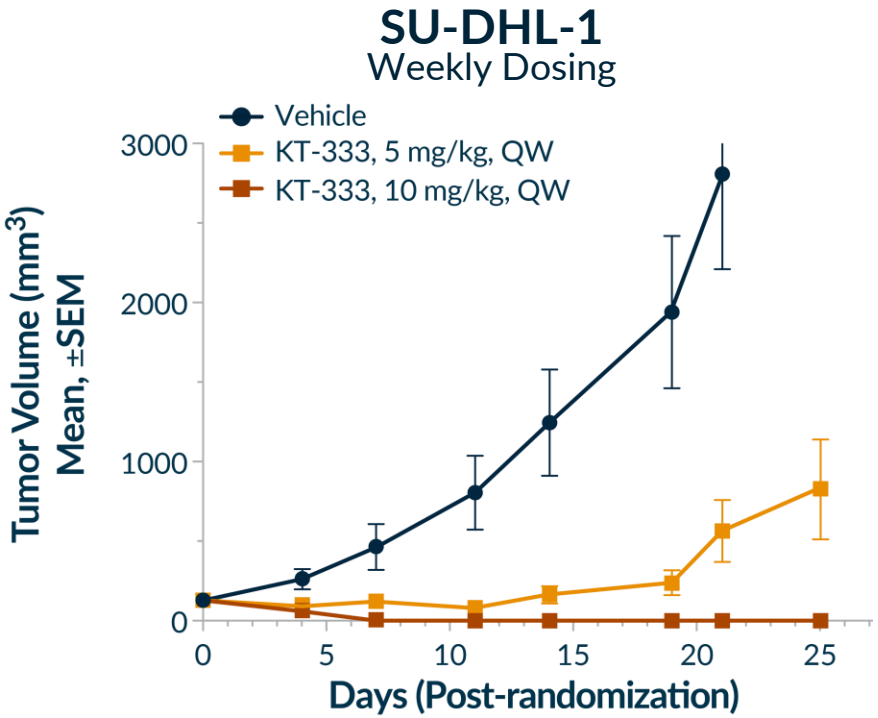
STAT3 Has Unique Tumor Cell Intrinsic and Extrinsic Mechanisms

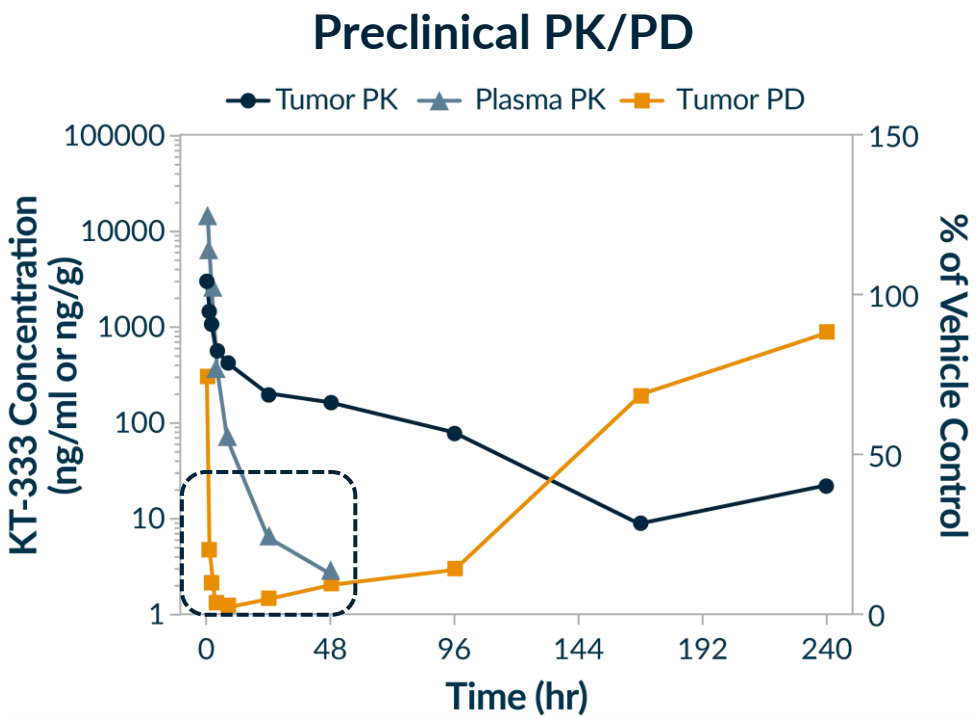
- **Intrinsic**: Hyperactivation of STAT3 via either receptor signaling, or hotspot mutations promotes gene expression programs involved with survival, proliferation, stemness and metastasis of tumor cells
- Opportunities in STAT3-dep. malignancies (e.g., T cell maligs., DLBCL, AML) and drug resistant 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

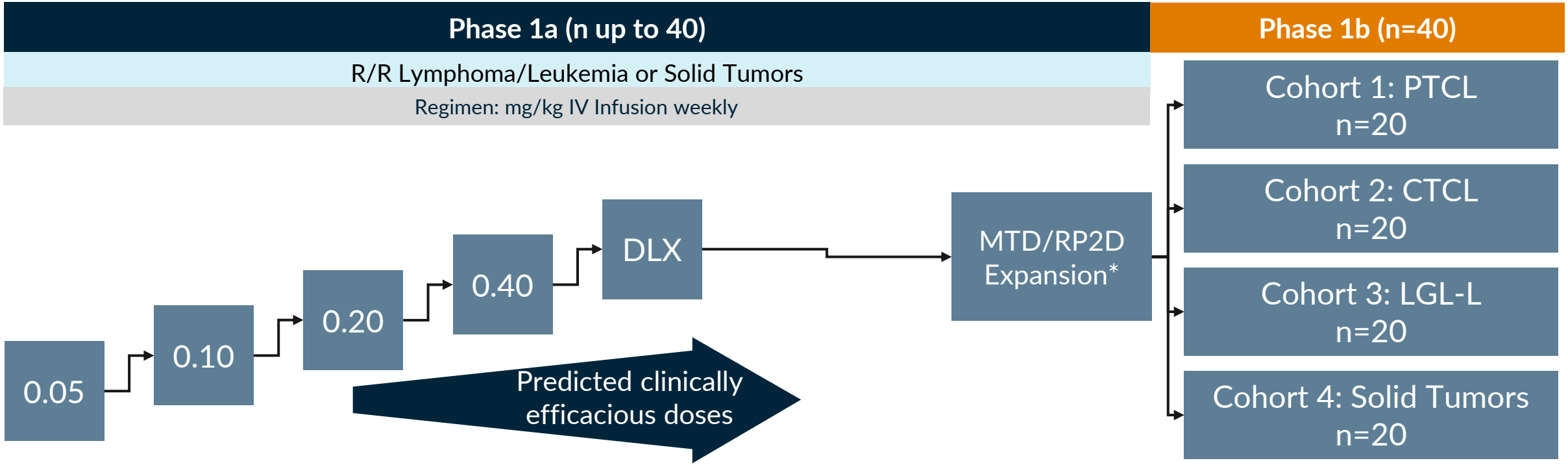




- Dose- and degradation-dependent tumor growth inhibition observed with once-weekly dosing in ALK+ ALCL
- 10 mg/kg sufficient to drive full tumor regression in SU-DHL- 1 that was durable for multiple weeks after the last dose (on day 14)

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

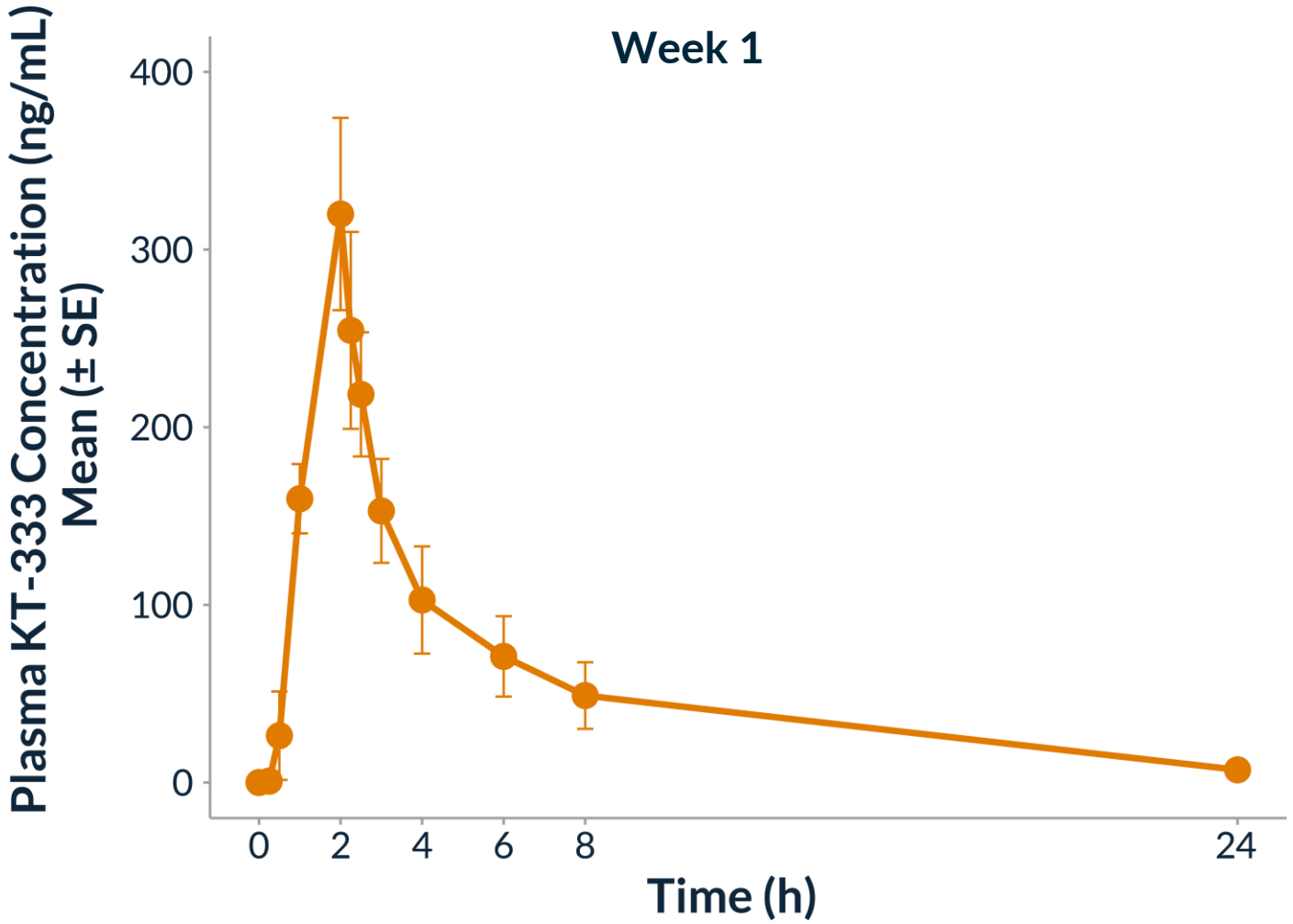
KT-333: Phase 1, Multicenter, Dose-Escalation and Expansion Trial to Evaluate KT-333 in Adult Patients with PTCL, CTCL, LGL-L, and Solid Tumors



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

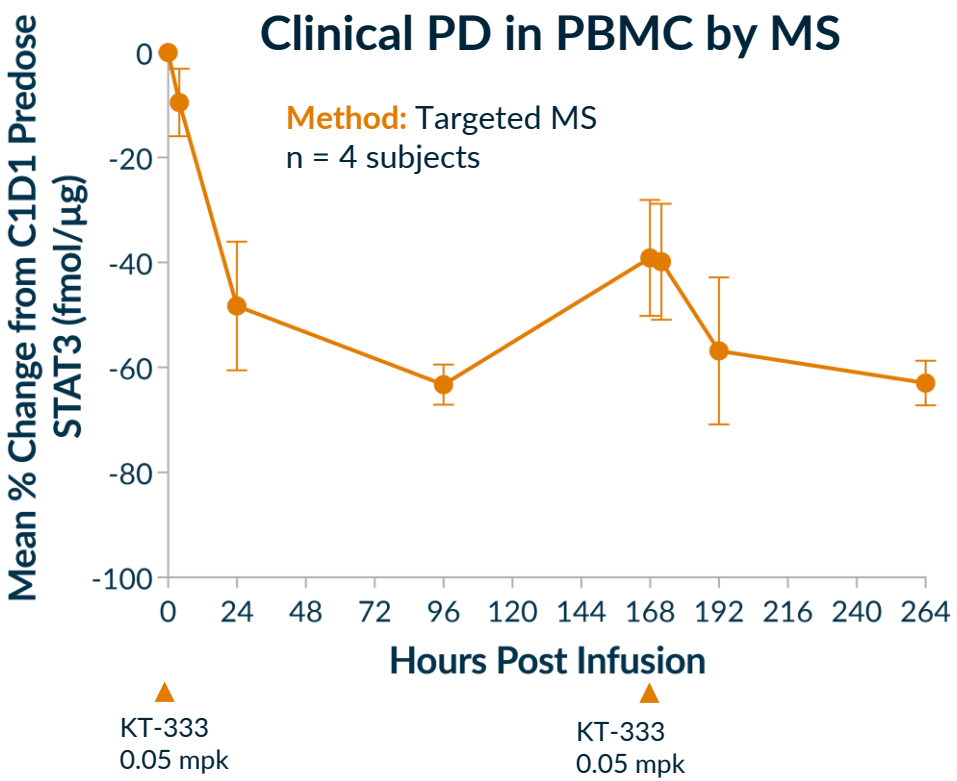
MTD: Maximum Tolerated Dose. RP2D: Recommended Phase 2 Dose. ORR: Overall Response Rate

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

- 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
- DL3-4 expected to be clinically active doses

First-in-class Opportunity to Address STAT3-driven Pathology Across Diverse Indications

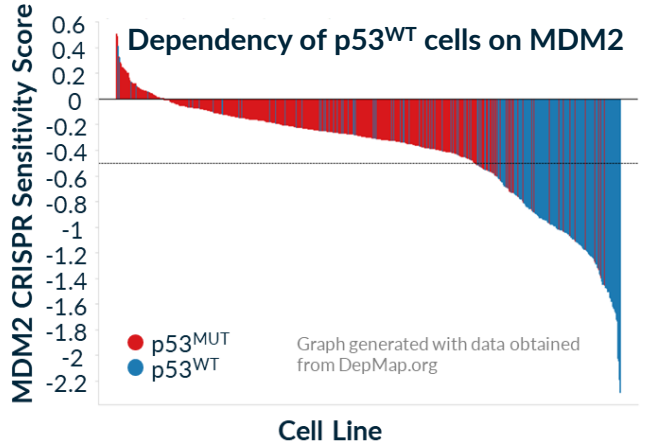
- First heterobifunctional degrader against an **undrugged target in the clinic**
- Clinical development strategy includes **monotherapy direct registrational path in STAT3 dependent T cell** malignancies
- Opportunity for **expansion into solid tumors** in combination with immune checkpoint inhibitors **informed by planned analysis of PDL1 and TME markers in solid tumor sample** from ongoing trial

MDM2

KYMERA

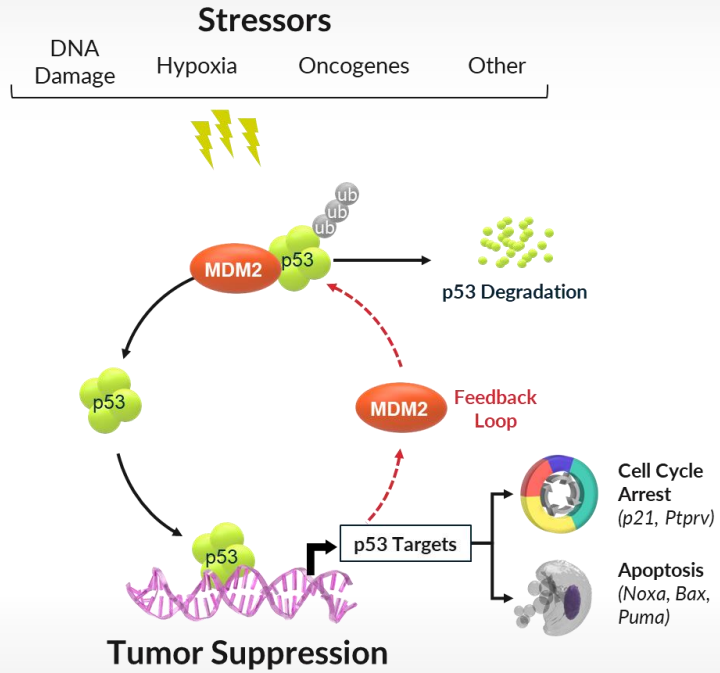
MDM2 Degraders In Oncology: KT-253

- MDM2 is the E3 Ligase that Modulates p53, the Largest Tumor Suppressor
- Cancer genetics: p53 is NOT mutated in almost 50% of tumors
- MDM2 overexpression and amplification can inactivate p53
- Large opportunity in wide variety of cancers

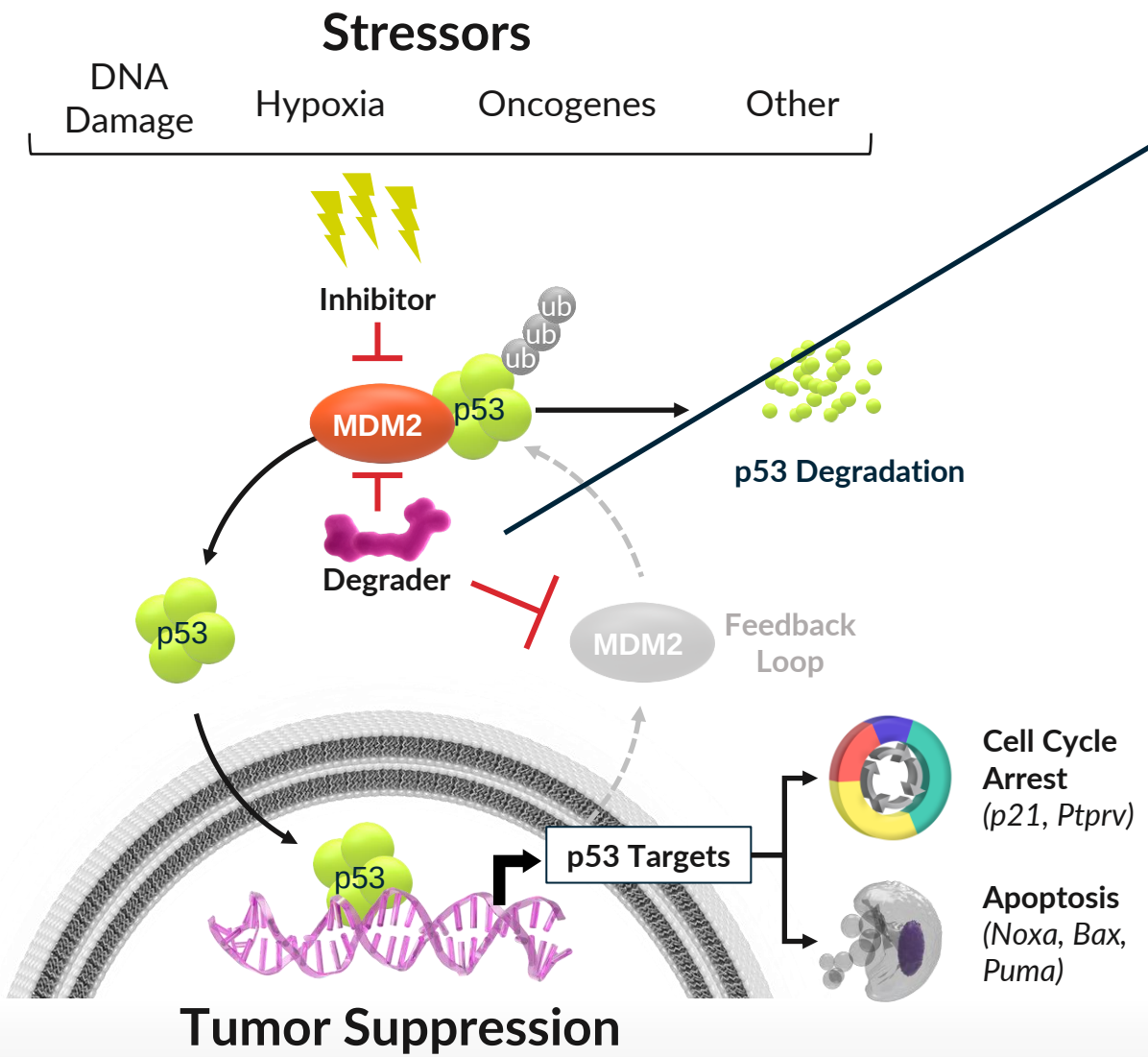


Benefits of MDM2 Degradation

- KT-253, unlike small molecule inhibitors, overcomes the feedback loop which up-regulates MDM2 production and in doing so more effectively stabilizes the tumor suppressor p53
- Broad franchise opportunities available for this mechanism (over 50% of tumors are p53 WT), Kymera is focused on indications with specific sensitivity to degrader mechanism, through a biomarker strategy
- Opportunity to translate profile into clinical superiority of degrader over SMI, as has been shown with IRAK4

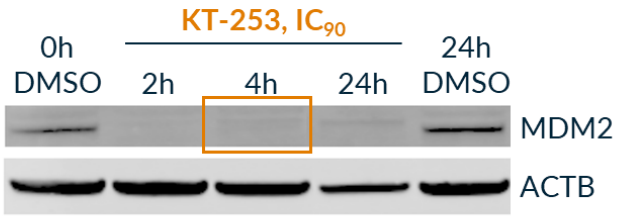


MDM2 Degradation, Not Inhibition, Efficiently Restores p53

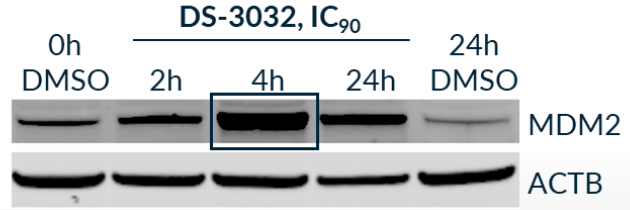


- MDM2 SMI's show activity, but can induce feedback loop, limiting impact on pathway
- MDM2 degraders remove the protein, can overcome the p53-dependent feedback loop that upregulates MDM2
- By inducing an acute apoptotic response in tumor cells, degraders can increase efficacy and therapeutic index vs a small molecule inhibitor

MDM2 levels are kept at undetectable levels with MDM2 degrader KT-253, leading to p53 stabilization

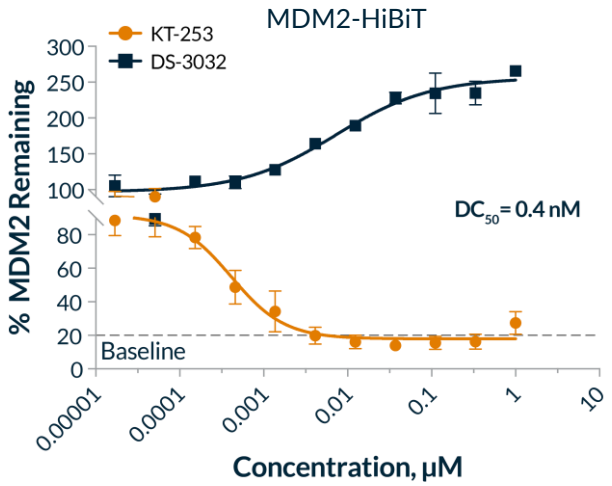


MDM2 levels are increased by the small molecule inhibitor (feedback loop), impairing p53 stabilization

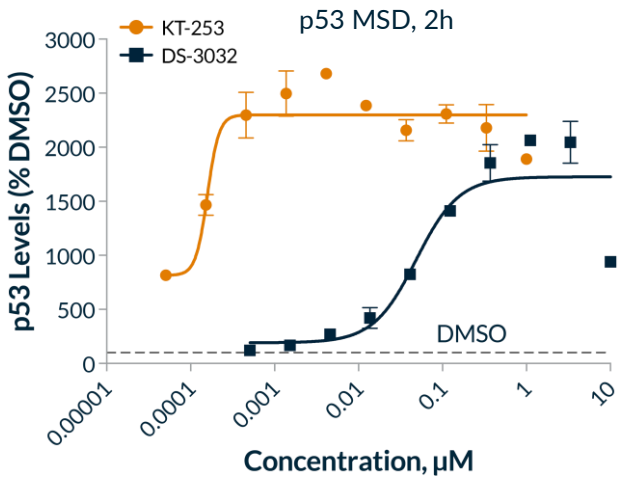


Kymera's MDM2 Degrader Investigational Drug, KT-253 is Superior to MDM2/p53 Small Molecule Inhibitors

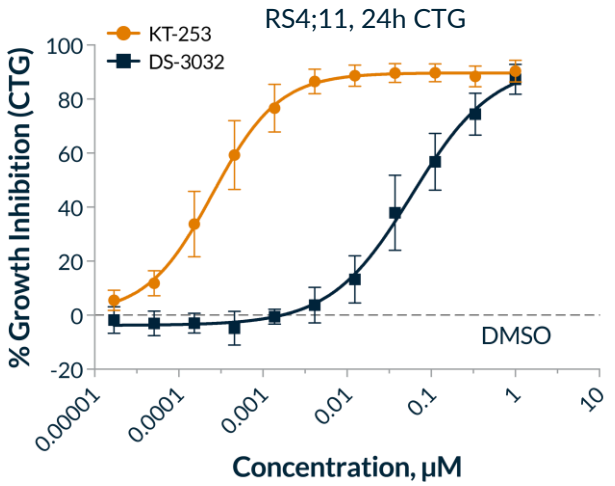
KT-253 is a potent MDM2 degrader



KT-253, unlike SMI's such as DS-3032, strongly stabilizes p53…



… which leads to superior tumor cell killing (pM range)



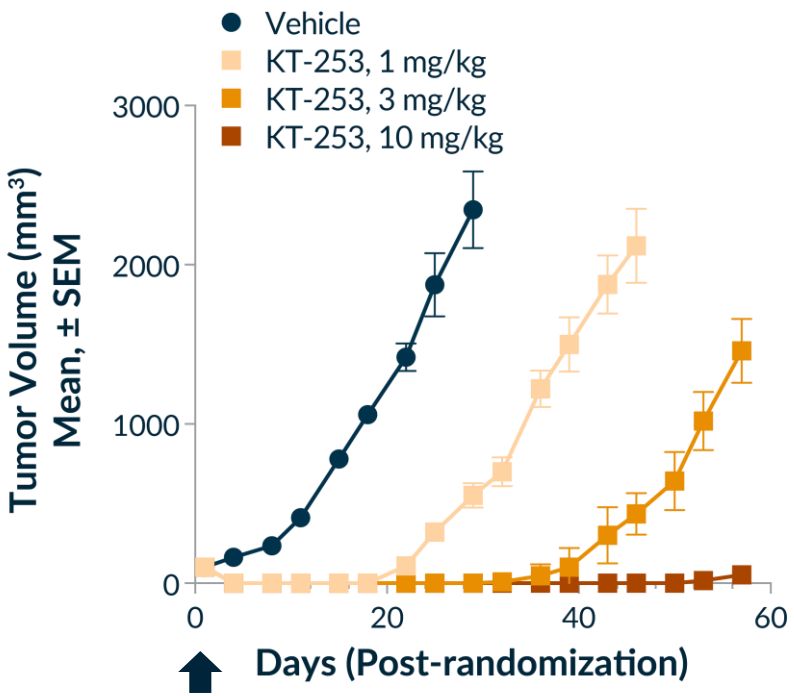
Compound	KT-253	DS-3032	RG7388	SAR405838	HDM201	AMG-232
Company	Kymera	Sankyo/Rain	Roche	Sanofi	Novartis	Amgen/Kartos
Clinical stage	IND enabling	Ph II / combo AML	Ph II / III	Paused	Ph I / II	Multiple Ph II; combo AML
RS4-11 IC_{50} (nM) (AML Cell Killing)	0.3	67	220	620	163	280
MDM2-HiBiT, DC_{50} (nM) (Degradation)	0.4	-	-	-	-	-

- KT-253 is **>200-fold more potent** in tumor cell killing assays than SMI's due to its mechanism of action
- Proteomics show selective degradation of KT-253

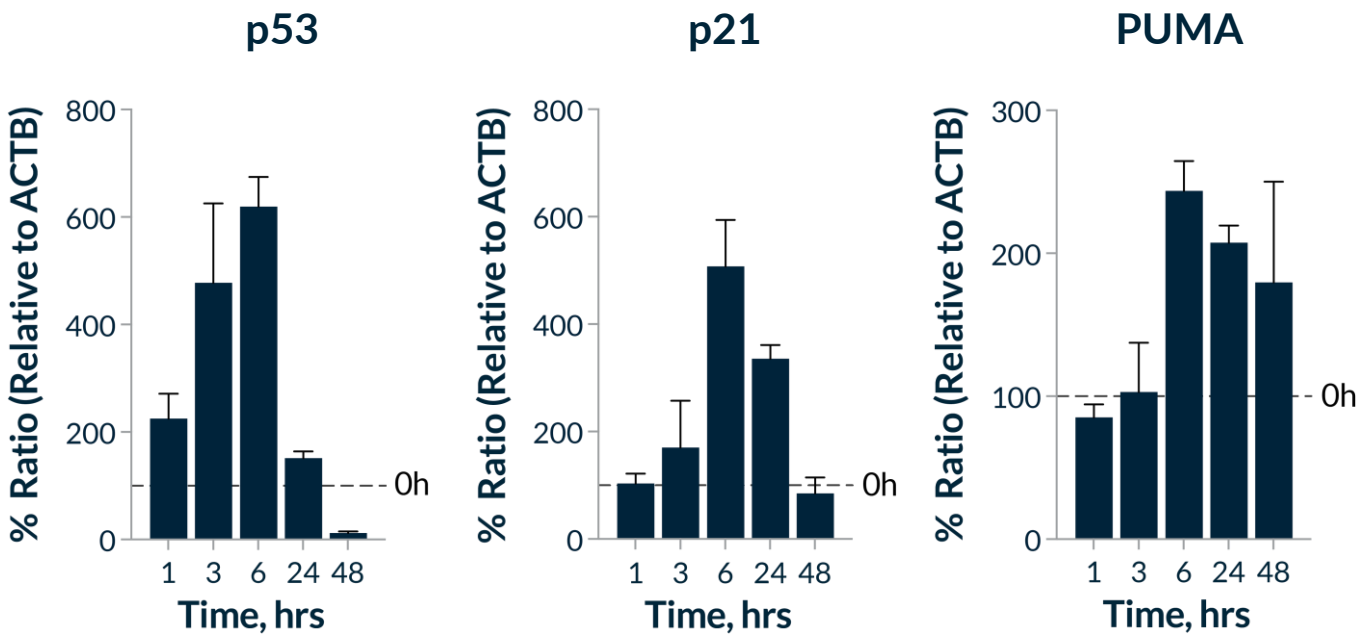
Single Dose of KT-253 Leads to Sustained Tumor Regression

Single Dose of KT-253 Achieves Sustained Tumor Regression

Rs4;11 XGs

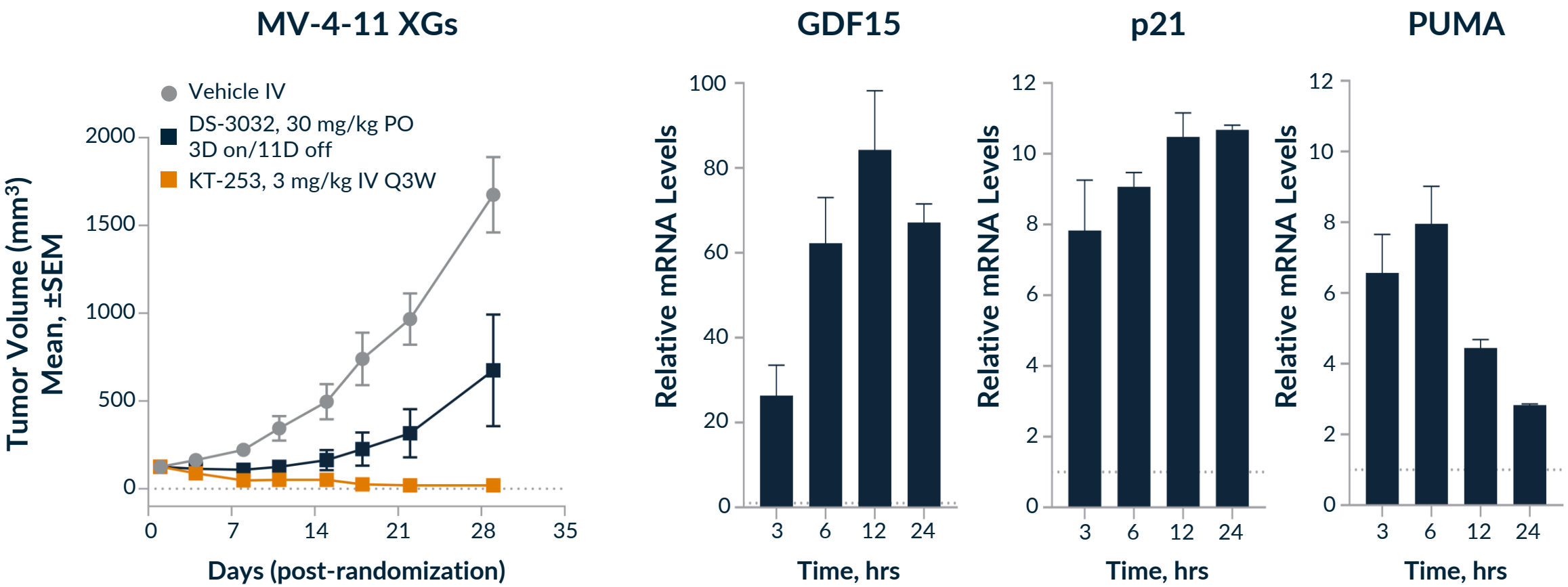


MDM2 Degradation (KT-253, 1 mg/kg) Leads to Fast Increase in p53, p21, and PUMA (Key Apoptotic Biomarker)



- Clinical equivalent doses of small molecule inhibitors have no significant *in vivo* impact in these xenograft models

KT-253 Achieves Tumor Regression in MV-4-11 (AML) Xenograft Model

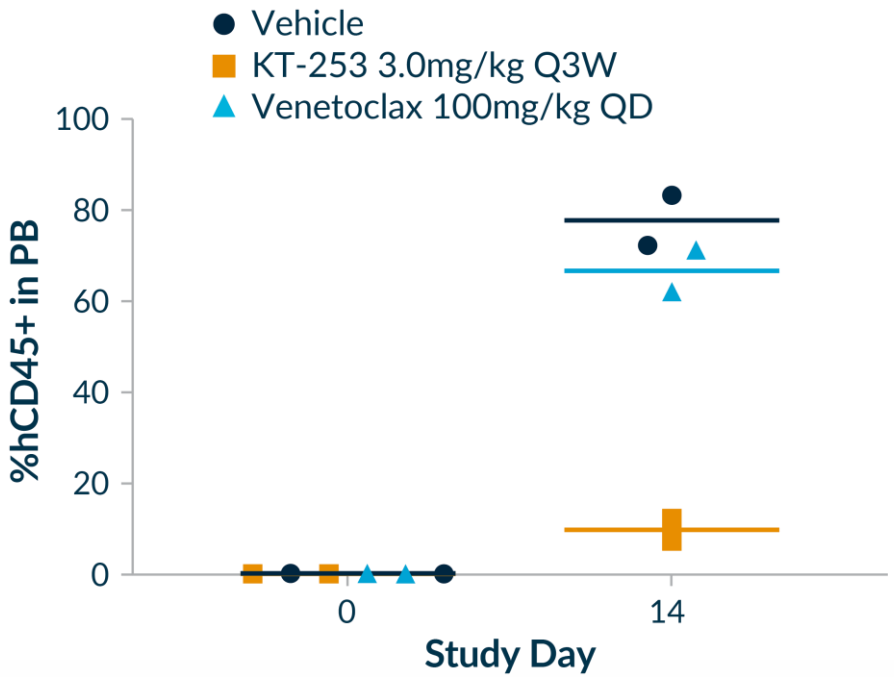


- KT-253 achieves sustained tumor regression in MV-4-11 xenograft model
- MDM2 degradation (KT-253, 3 mg/kg) leads to rapid upregulation of p53 downstream targets

Strong Single Agent and Combinatorial Activity in Venetoclax Resistant AML Models

Whole Blood

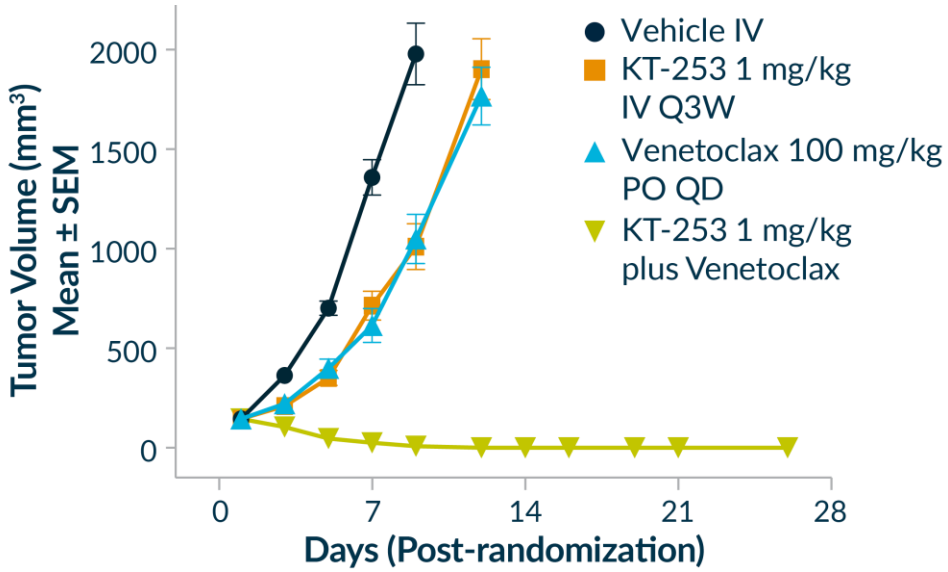
DFAM-68555 Day 14



DFAM-6855 Characteristics:

- M5a (monoblastic); Mutations: FLT3, MLL3
- KT-253 3 mg/kg Q3W dosing significantly reduces hCD45+ cells in Peripheral Blood

MOLM-13 AML XGs



- Single dose of KT-253 in combination with daily dosing of Venetoclax achieves sustained tumor regression in MOLM-13 xenograft model

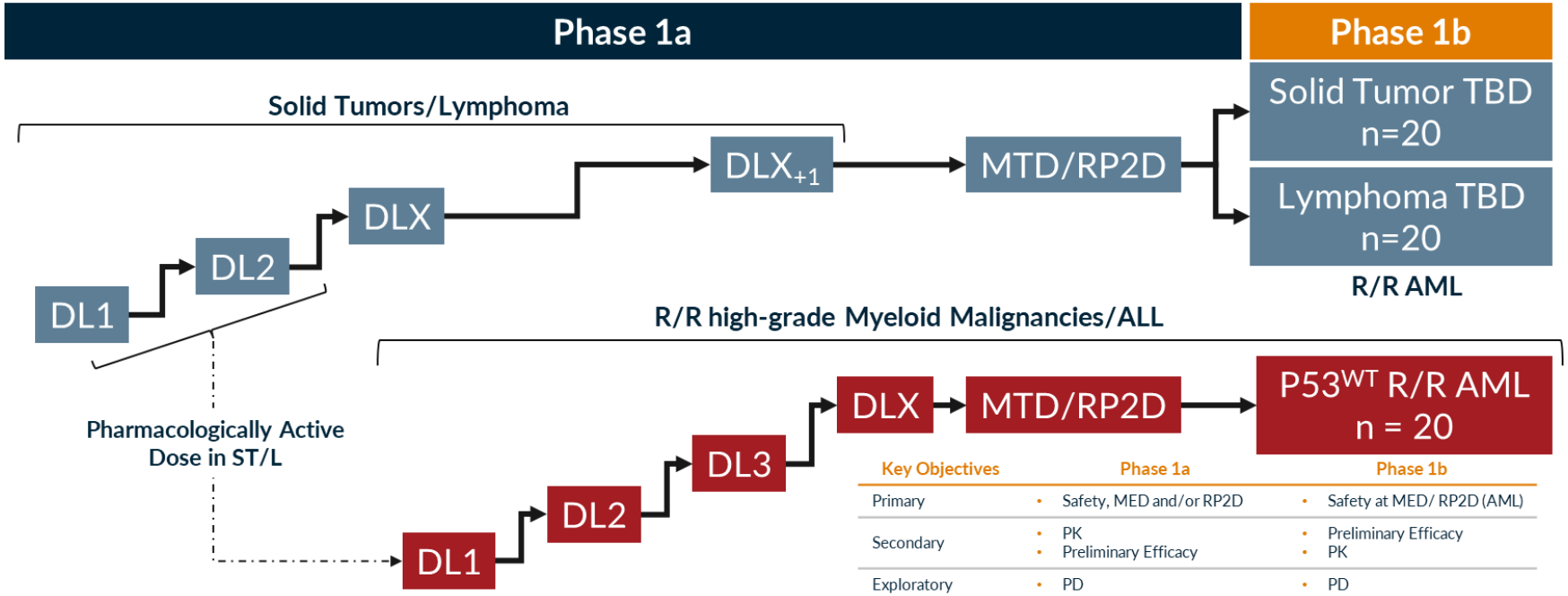
KT-253: Phase 1, Multicenter, Dose-Escalation and Expansion Trial to Evaluate KT-333 in Adult Patients with Liquid and Solid Tumors

Hematological Malignancies

- **AML** identified as initial indication based on strong pre-clinical KT-253 activity
- Developed **patient stratification strategy** to target subsets of leukemias most sensitive to KT-253 as mono- and combination therapy
- Preclinical data also support potential development in other heme indications, such as ALL and P53WT **lymphomas**

Solid Tumors

- Preclinical studies have identified several solid **tumor types sensitive to KT-253**



Phase 1a

- Initiate dose escalation in **solid tumor/lymphoma (ST/L)**
- Initiate dose escalation in **AML** once pharmacologically active dose identified in ST/L

Phase 1b

- Initiate expansion **in R/R AML**
- Initiate expansions in select solid tumors and lymphomas based on data from 1a and ongoing preclinical efforts

First MDM2 Degrader, KT-253, in Clinic

- KT-253, unlike small molecule inhibitors, **overcomes the feedback loop** which up-regulates MDM2 production and in doing so more effectively stabilizes the tumor suppressor p53
- KT-253 inhibits tumor cell growth with **picomolar potency** and is more **than 200-fold more potent** than clinically active MDM2 small molecule inhibitors
- Broad franchise opportunities available for this mechanism (>50% tumors are p53 WT), Kymera is focused on indications with **specific sensitivity to degrader mechanism**, through a biomarker strategy
- Opportunity to translate clinically, as for IRAK4, superiority of degrader over SMI
- **First patient dosed April 2023**
- **POM data expected in 2023**

First-in-class Opportunity to Address p53 WT Tumors Across a Variety of Tumor Types

- First degrader against a **clinically proven but inadequately drugged target, MDM2**
- Profound **single agent activity** in preclinical liquid and solid tumor models
- Clinical development strategy includes accelerated registration path in p53 WT tumors with high **sensitivity to degrader mechanism such as AML, lymphomas, and other solid tumors**

Kymera Well-Positioned for Continued Success

- Kymera is executing on its mission to build a **fully-integrated, global biotech** company as a **recognized leader in TPD**
- Our industry-leading **R&D productivity** has produced **4 clinical programs** and a **deep and innovative pipeline** of valuable, high-impact programs
- We have demonstrated **PK, PD and safety** in Phase 1 trials that **validate our platform, molecule design and target selection** capabilities and strategies
- We are **well-capitalized** with an **experienced team** that is highly focused
- We are only at the beginning of our journey, as Kymera's **knowledge, experience and drive** positions us to **maximize the untapped potential** of TPD in areas with large clinical and commercial opportunities

Thank You

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