INVENTING NEW MEDICINES

WITH TARGETED PROTEIN DEGRADATION

41st Annual J.P. Morgan Healthcare Conference | January 10th, 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 ~$560m of cash***, enabling expansion of clinical impact into areas with large clinical and commercial opportunities

*Unaudited, estimated cash at 12/31/22

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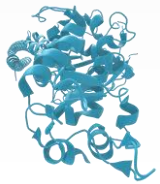
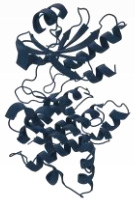
Kymera's Differentiated Approach to TPD

TARGET SELECTION

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





UD

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

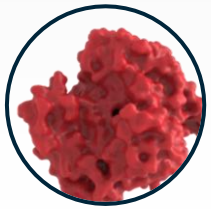
ID

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

Strong genetic validation within clinically validated pathway

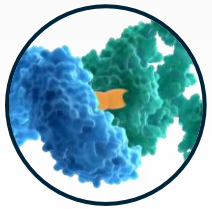
PLATFORM

Significantly **differentiated** investments



Tissue-selective E3 Ligases

- Enabling a whole new generation of clinical programs

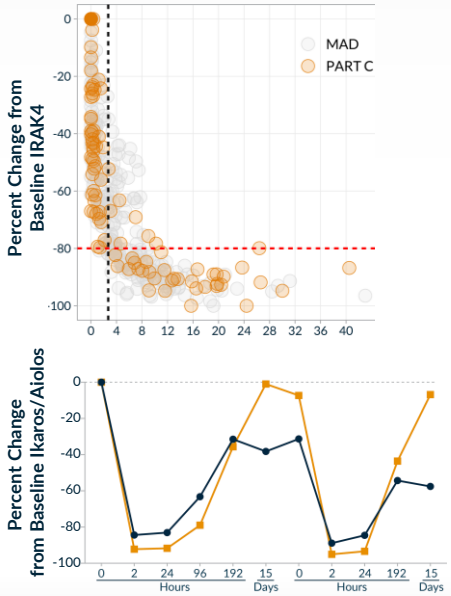


New Molecular Glue Approach

- 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)**

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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

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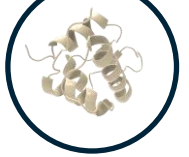
Building Franchises in Immunology and Oncology in Diseases with Large Unmet Needs and Commercial Opportunities

Immunology Franchises

DERM.	GI	RHEUM.	RESP.		
●	●	●	●		**IRAK4** KT-474
●	●	●	○	Scaffolding Kinase	**Undisc.**
●	●	○	●	Transcrip-tion 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

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Kymera's Commitment to Solving Meaningful Clinical Problems with TPD

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

Transcrip-tion Factor

STAT3

Novel Molecular Glue

Transcrip-tional Regulator

- Undrugged transcription factor with strong genetics validation

- Protein degradation only/best approach to deliver effective drug

MDM2
KT-253

STAT3
KT-333

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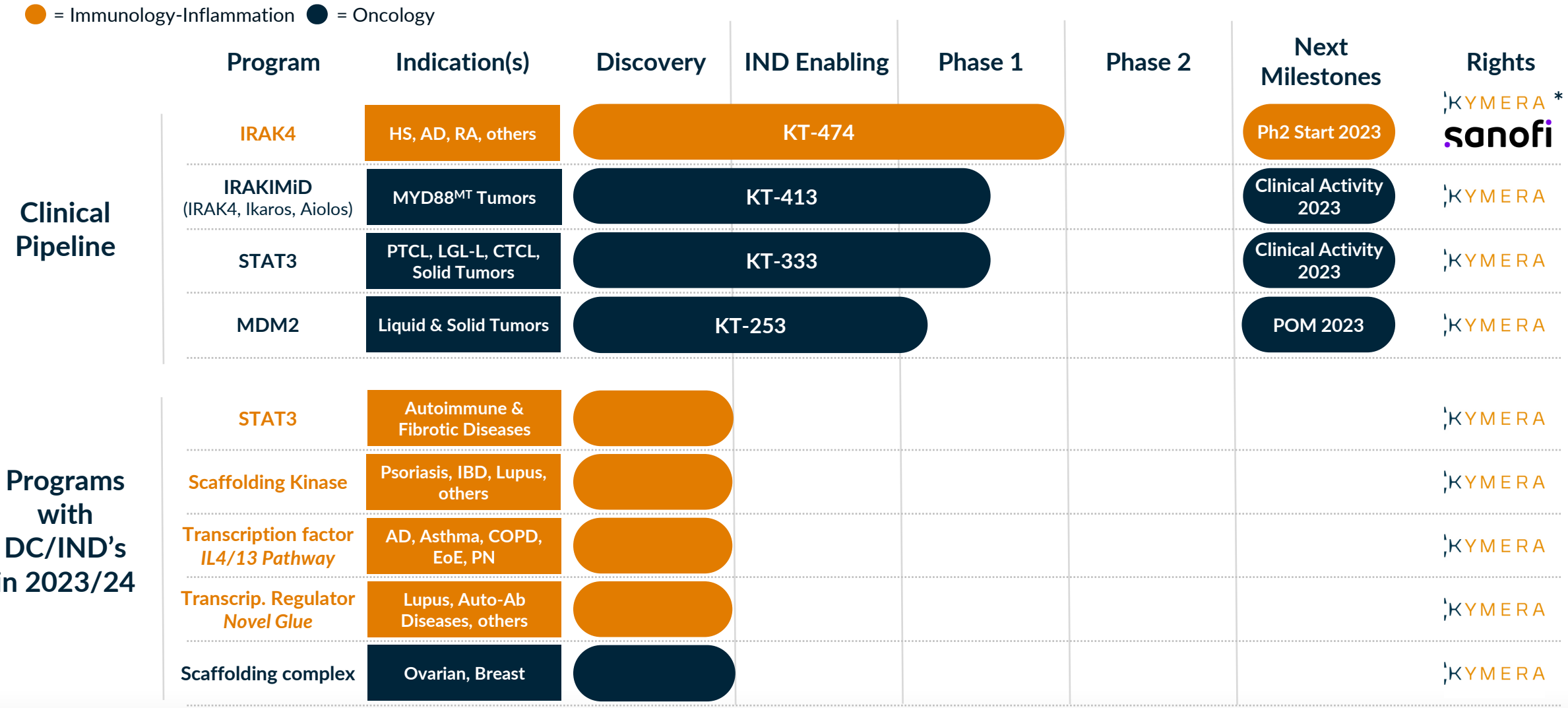
Kymera's Pipeline of Novel Protein Degraders



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

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Kymera's 2023 Milestones

- 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**

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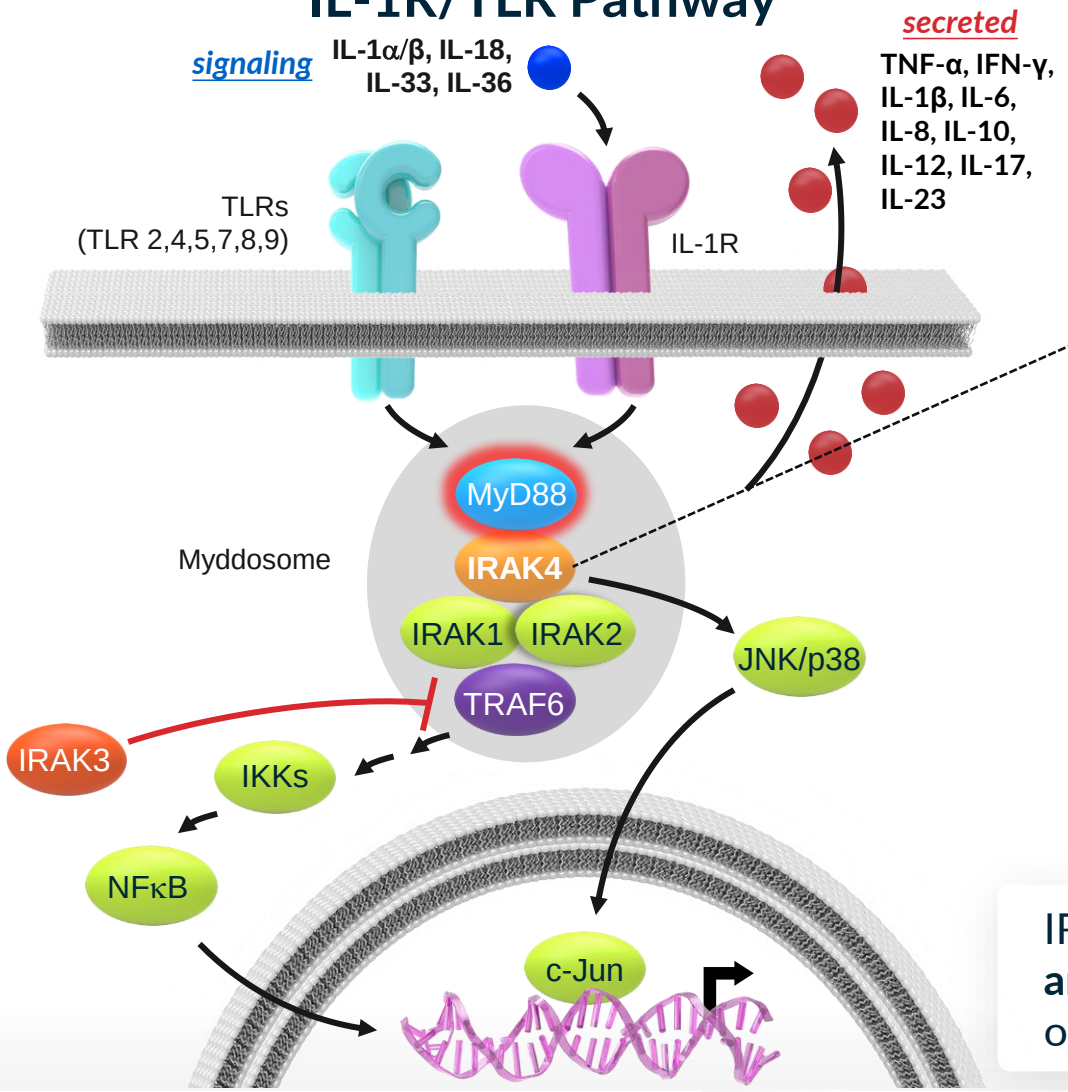
IRAK4

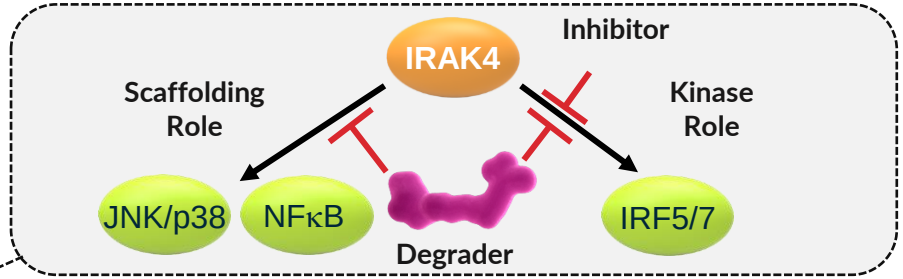
KYMERA

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

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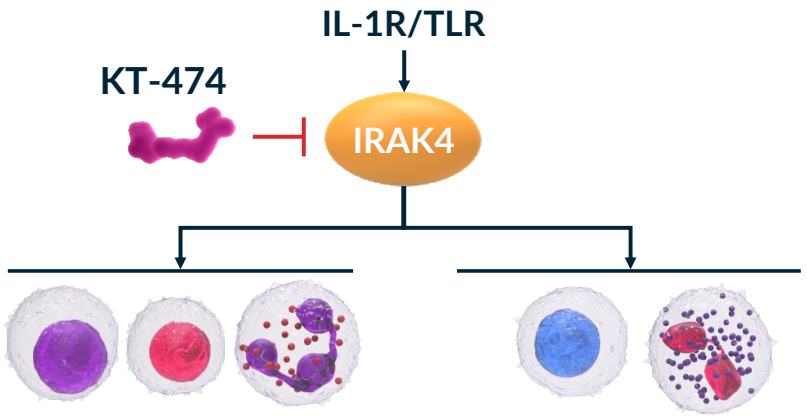
IRAK4 Degrader Best-in-class Potential in Immune-inflammation

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.

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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

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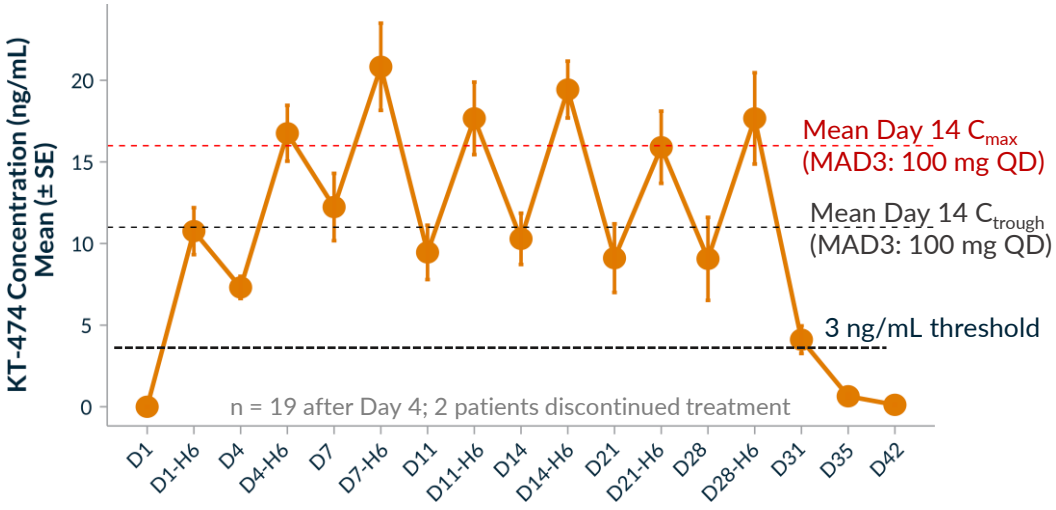
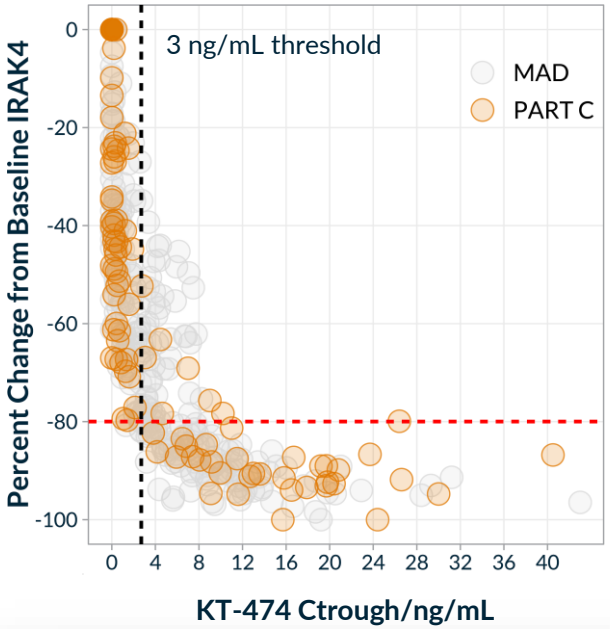
KT-474 Plasma PK and IRAK4 Degradation in HS and AD Patients Dosed for 28 Days is Comparable to HV

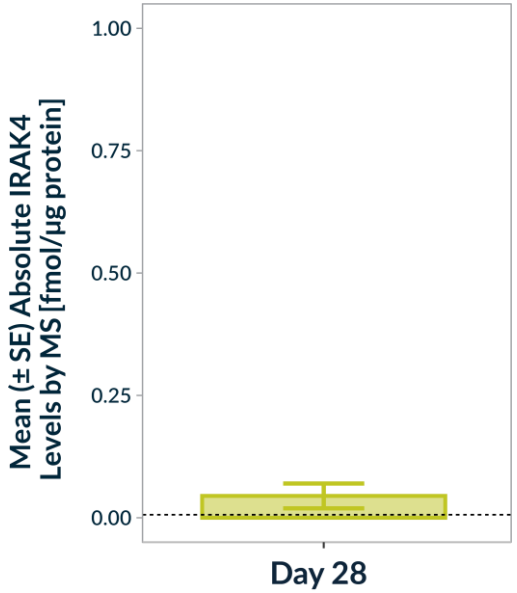
Part C KT-474 Plasma PK



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**

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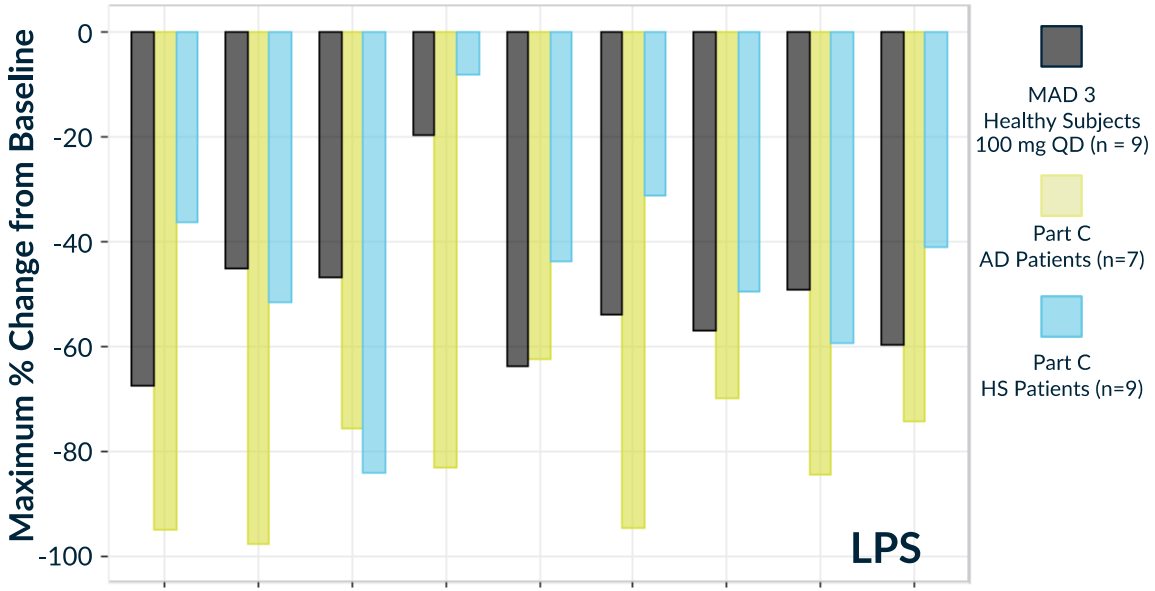
Profound Inhibition of Disease-Relevant Cytokines *Ex Vivo* and *In Vivo* in both HS and AD Patients

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%

* 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

Demonstrating for the FIRST TIME Pathway Activation in both HS and AD

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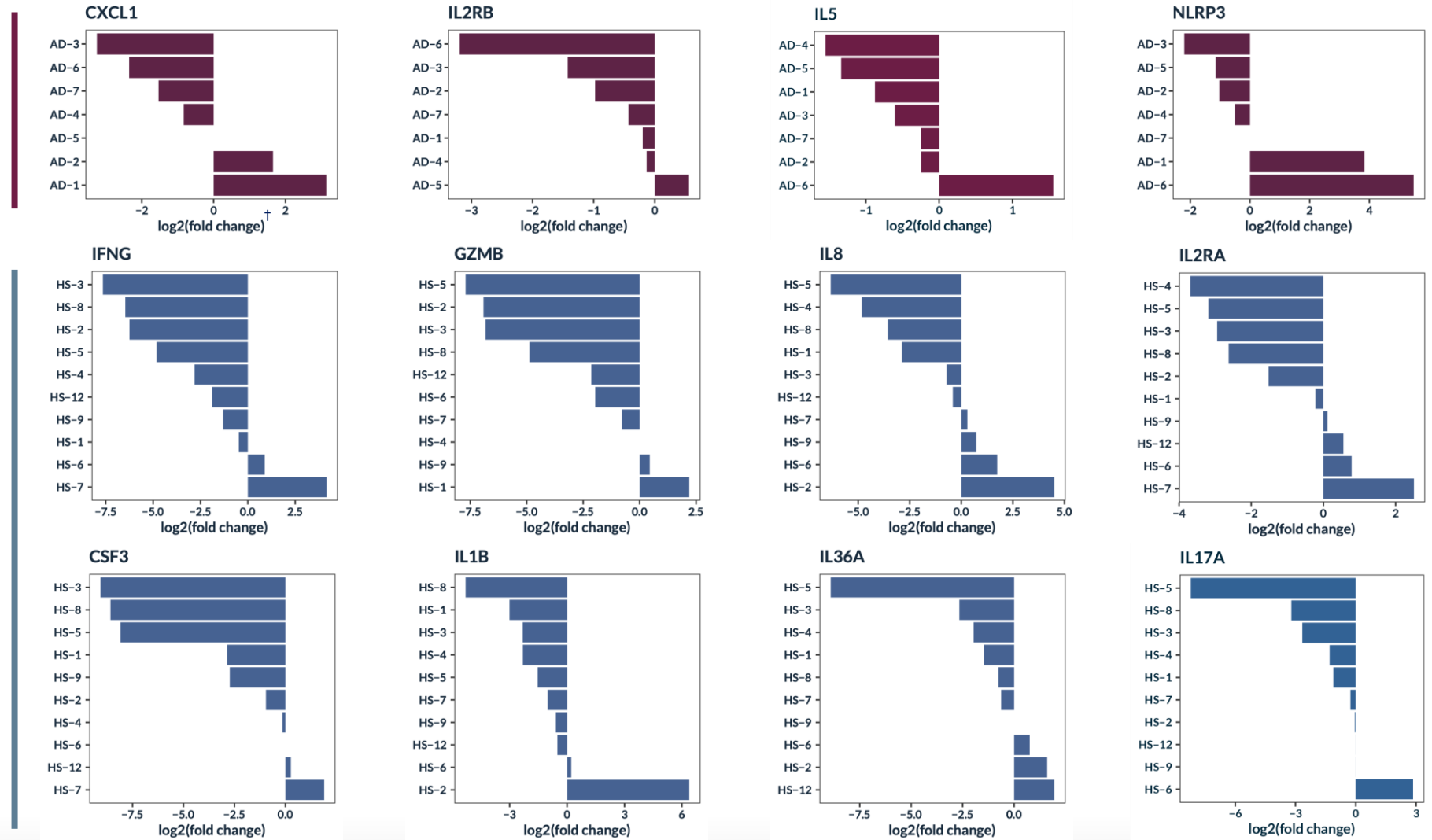
Disease-Relevant Genes Downregulated in Skin Lesions in ≥ 50% of Evaluable* AD (N=7) and HS (N=10) Patients at Day 28 (RNAseq)

- 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.

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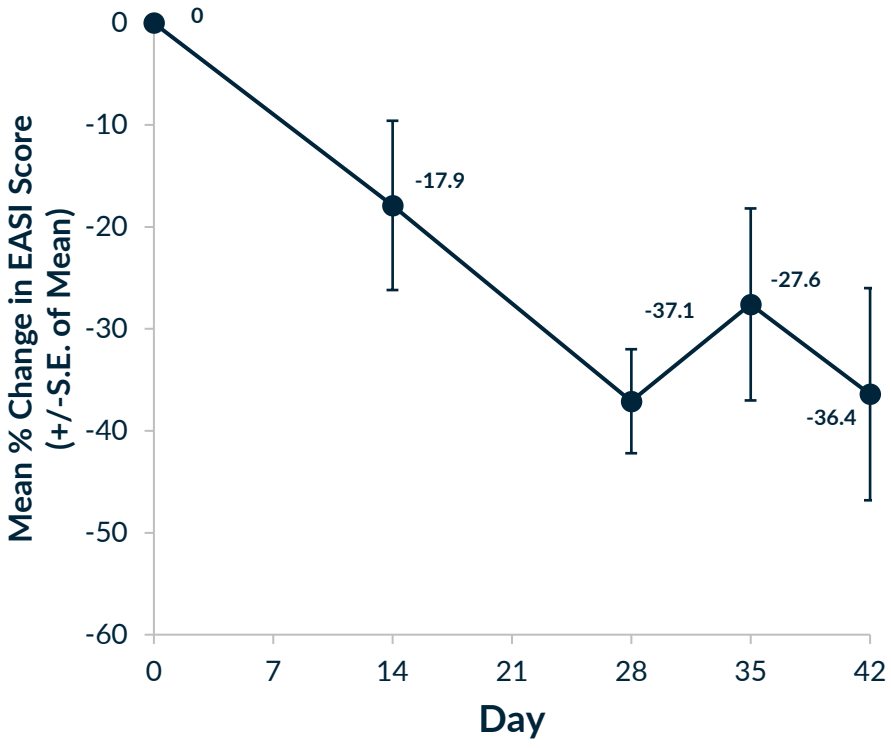
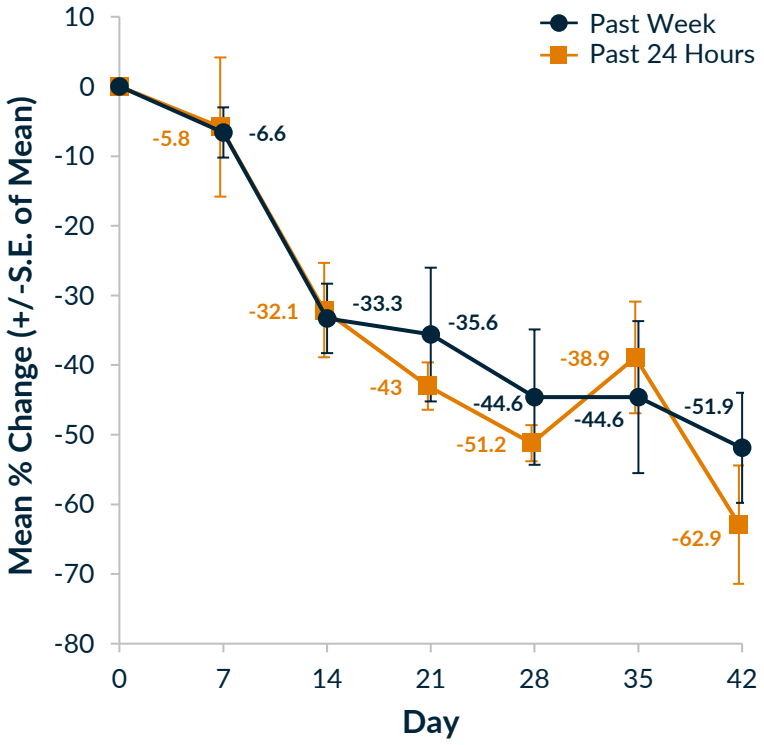
AD: Substantial Reduction in EASI Score and Pruritus

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



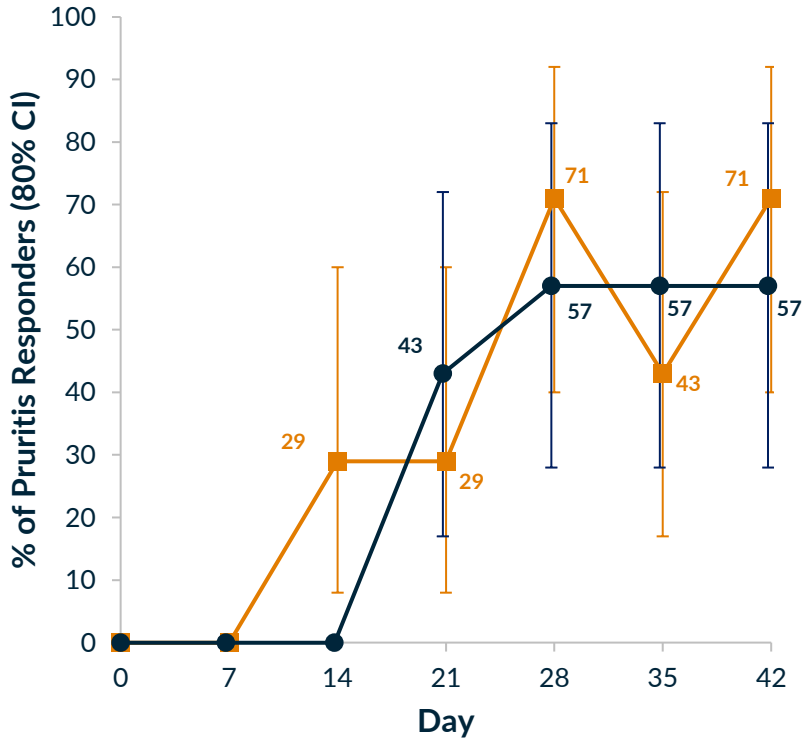
Mean reduction in EASI Score reached maximum at day 28 (-37%)

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



Mean reduction in Peak Pruritis reached maximum at day 42 (-63%)

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



Pruritus Responders reached maximum at day 28 (71%)

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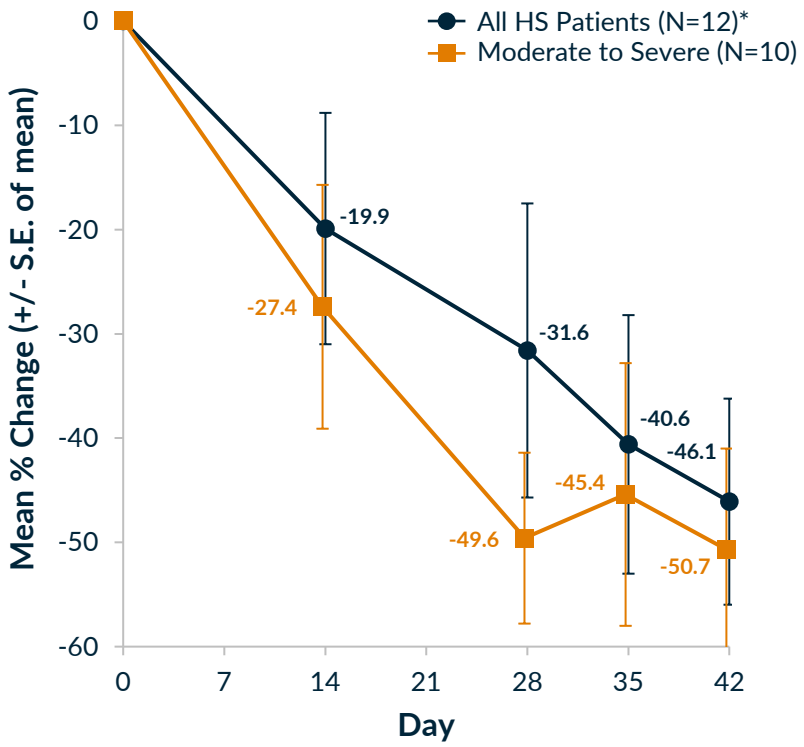
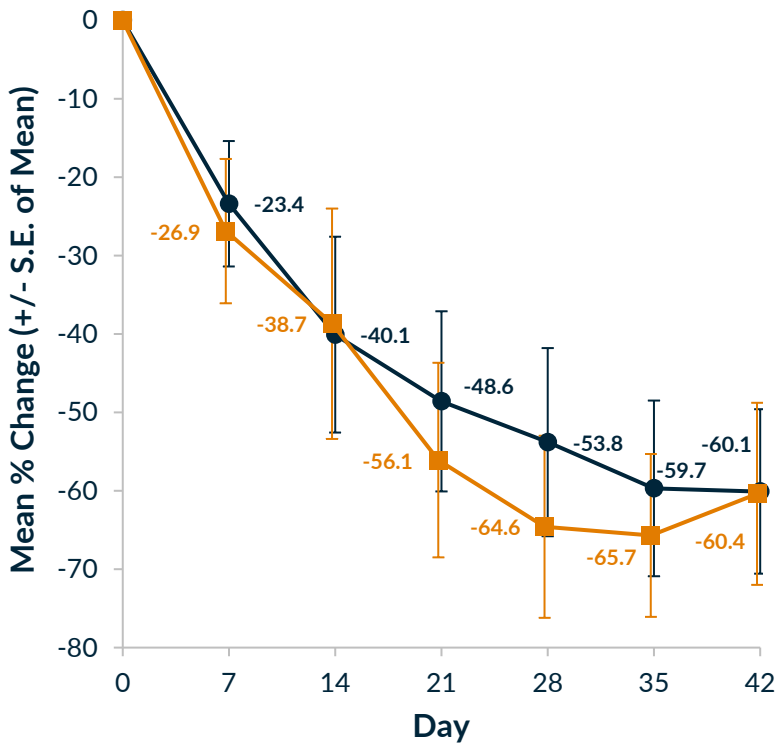
HS: Substantial Reductions in AN Count, Pain and Pruritis

Mean % Change in Total AN Count Over time



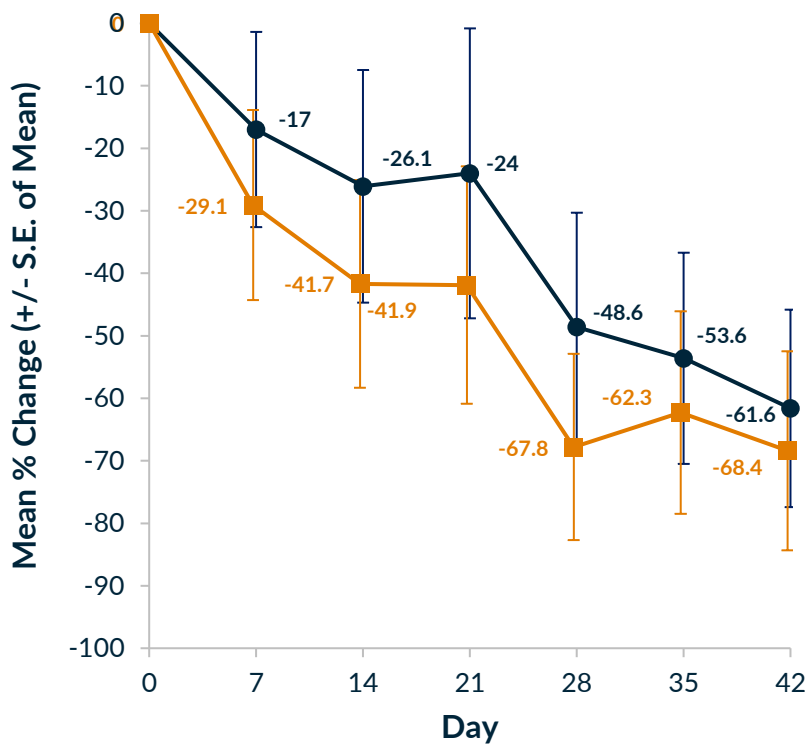
Mean reduction in AN Count reached maximum at day 42 (-51% in mod to severe)

Mean % Change in Average Pain Over Past Week



Mean reduction in Pain reached maximum at day 35 (-66% in mod to severe)

Mean % Change in Worst Pruritus Over Past Week



Mean reduction in Peak Pruritis reached maximum at day 28/42 (-68% in mod to severe)

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

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

AD Summary

- Mean **EASI score reduction of up to 37%** by day 28, with maximum reduction of up to 76%
- Mean **peak pruritus NRS reduction** of **51%** by day 28, and **63%** by day 42
- Peak pruritus **NRS Responder rate** of **57%** (past week) and **71%** (past 24 hours) at both day 28 and 42
- Investigator Global Assessment **(IGA) scores improved in 2 of 7 patients** and remained stable in the others

HS Summary

- In moderate/severe patients, mean total AN count was reduced **~50%**, with maximum reduction up to **100%**
- By D28, **42% of all patients and 50% of moderate/severe patients** had an AN count of 0, 1, or 2
- HiSCR50 response rate was **25-30%** by D28 and **42-50%** by D42
- HiSCR75 response rate was **8-10%** by D28 and **25-30%** by D42
- Pain NRS30 response in **50-60%** of patients; mean peak pruritis reduction of **49-68%** at D28 and **62-68%** at D42
- 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

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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

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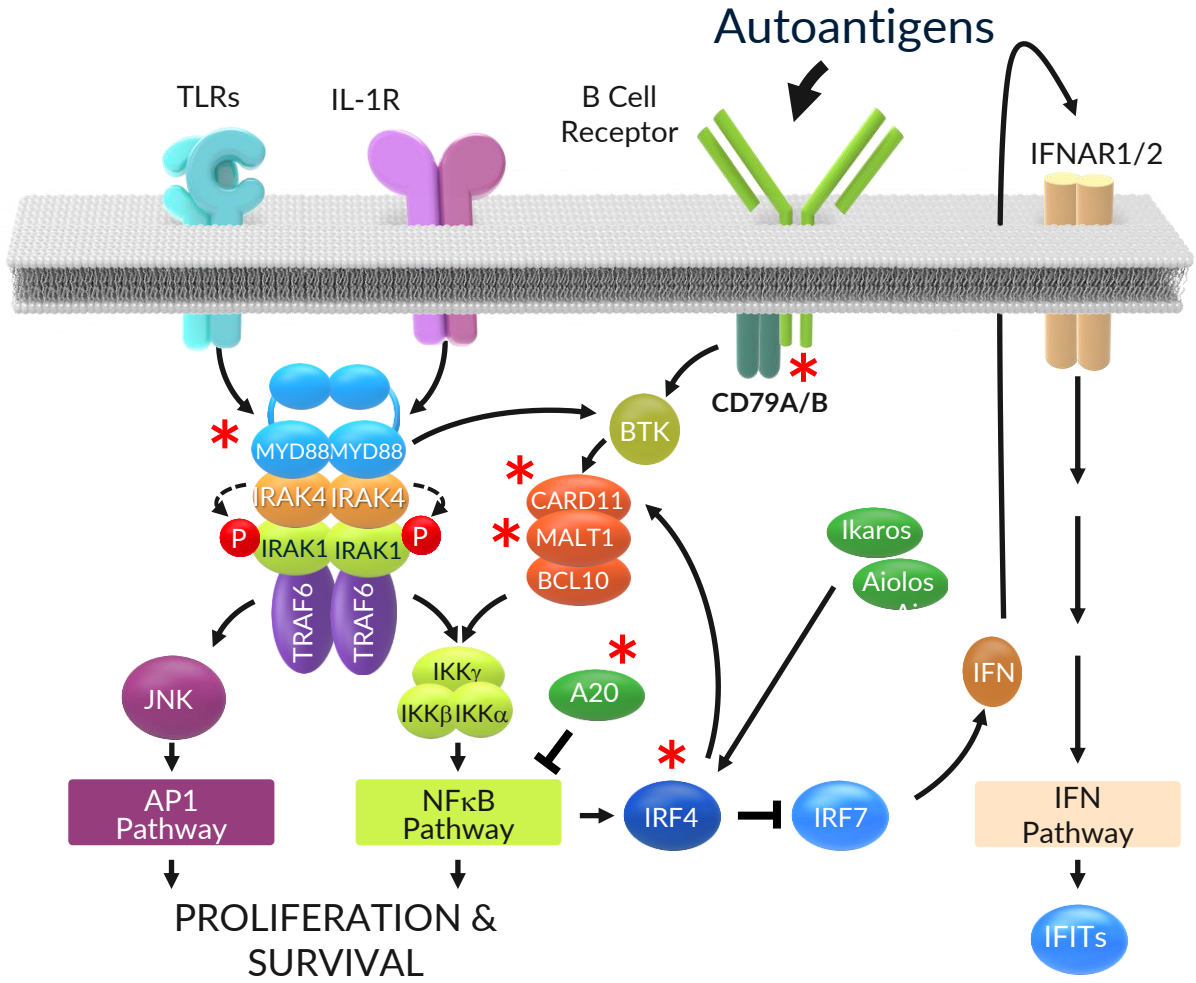
IRAKIMiD
KYMERA

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

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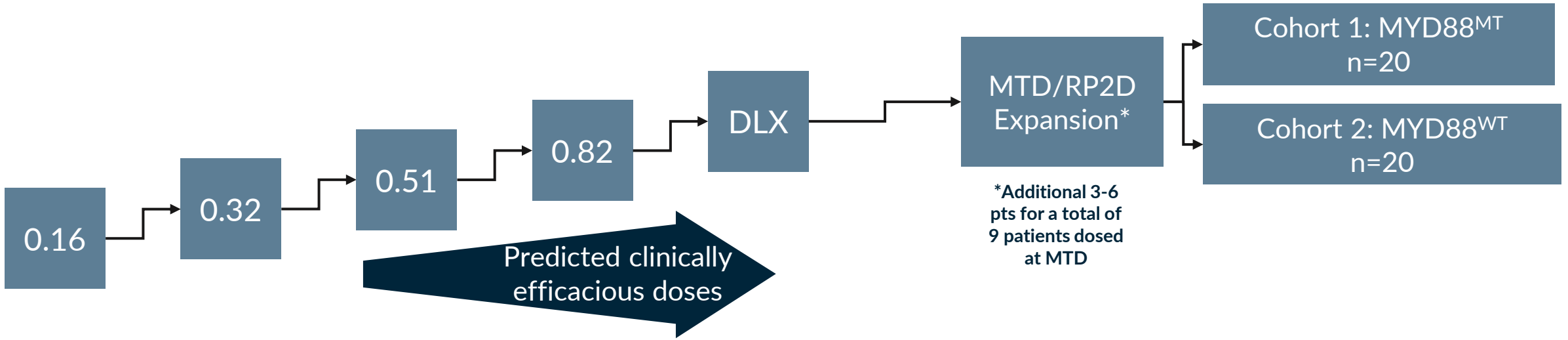
KT-413: Phase 1, Multicenter, Dose-Escalation and Expansion Trials to Evaluate KT-413 in Patients with R/R DLBCL

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

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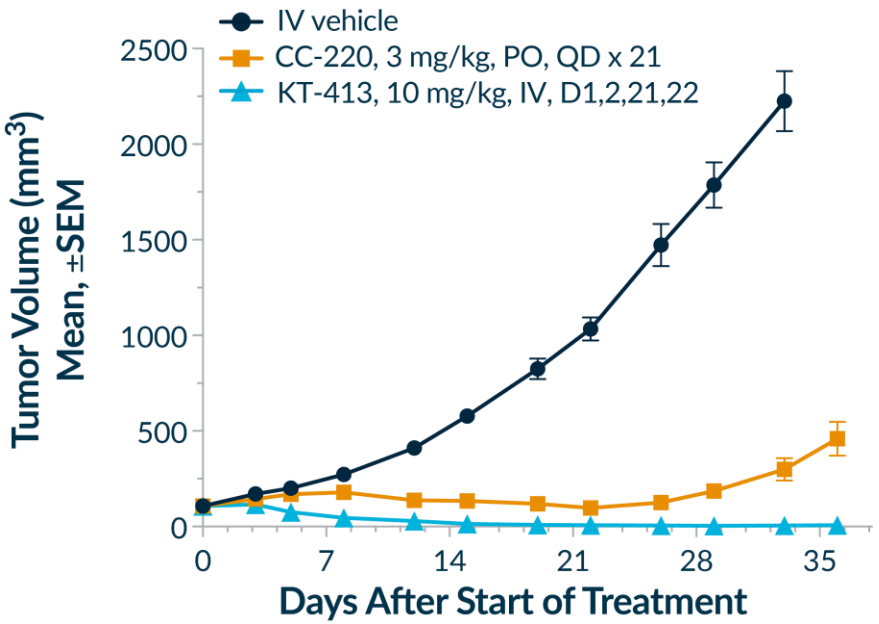
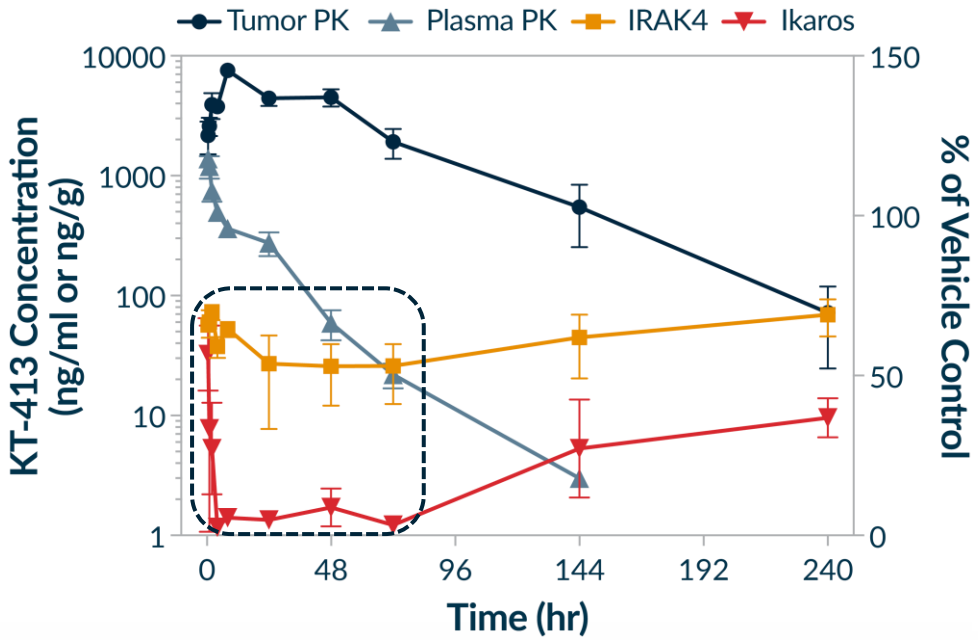
KT-413 Highly Active on Intermittent Dosing in Preclinical Models

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**

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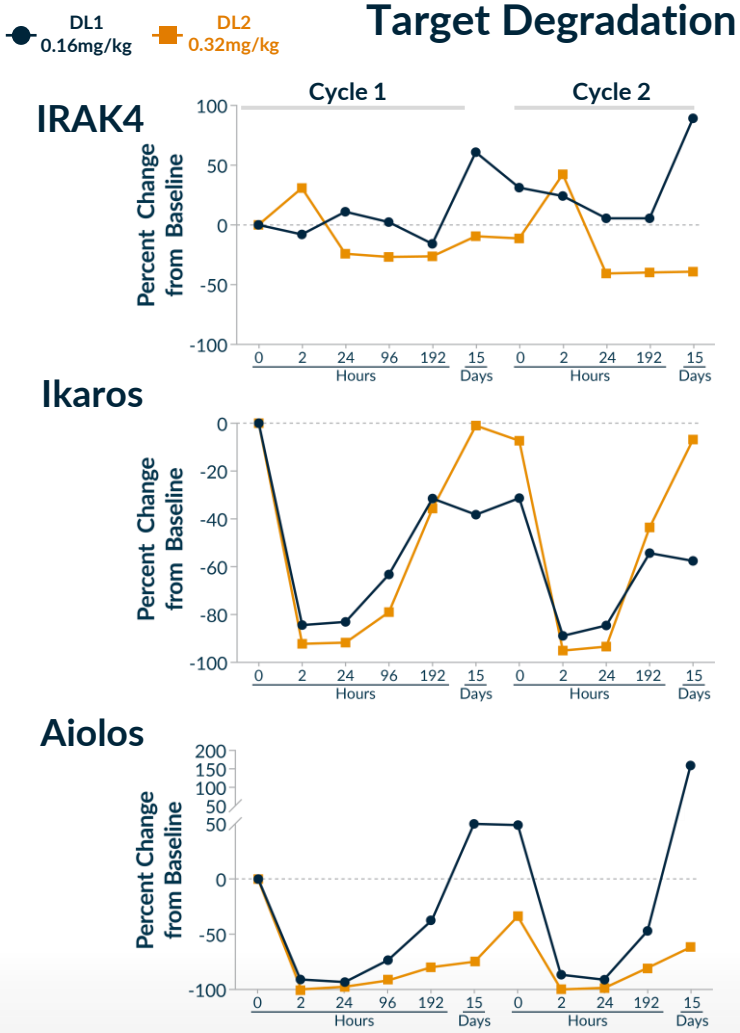
Degradation Profile of IRAK4, Ikaros and Aiolos in DL1/DL2 Consistent with Preclinical Models in Blood and Tumor

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%

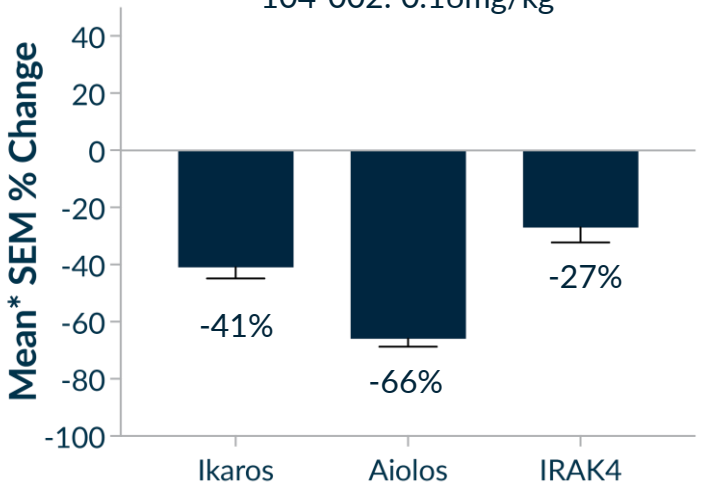
Dose Level	Cycle 1	Cycle 2
DL1	-84%	-88%
DL2	-92%	-95%

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

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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

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STAT3

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STAT3 Degraders In Oncology: KT-333

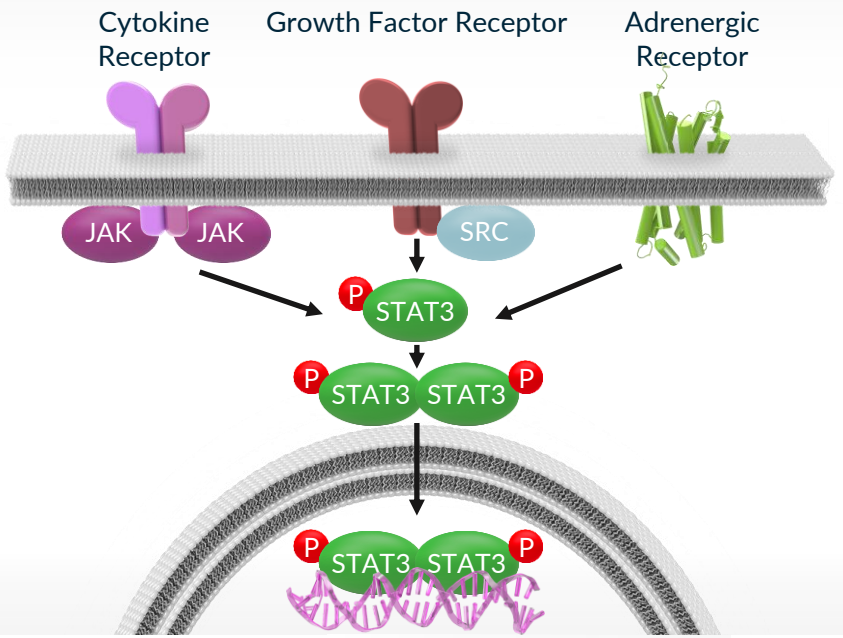
- High degree of validation of JAK-STAT pathway in oncology and immuno-oncology supported by >25k publications
- Traditionally undrugged target
- First-in-class opportunity to address STAT3 driven pathology across large and diverse indications

	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



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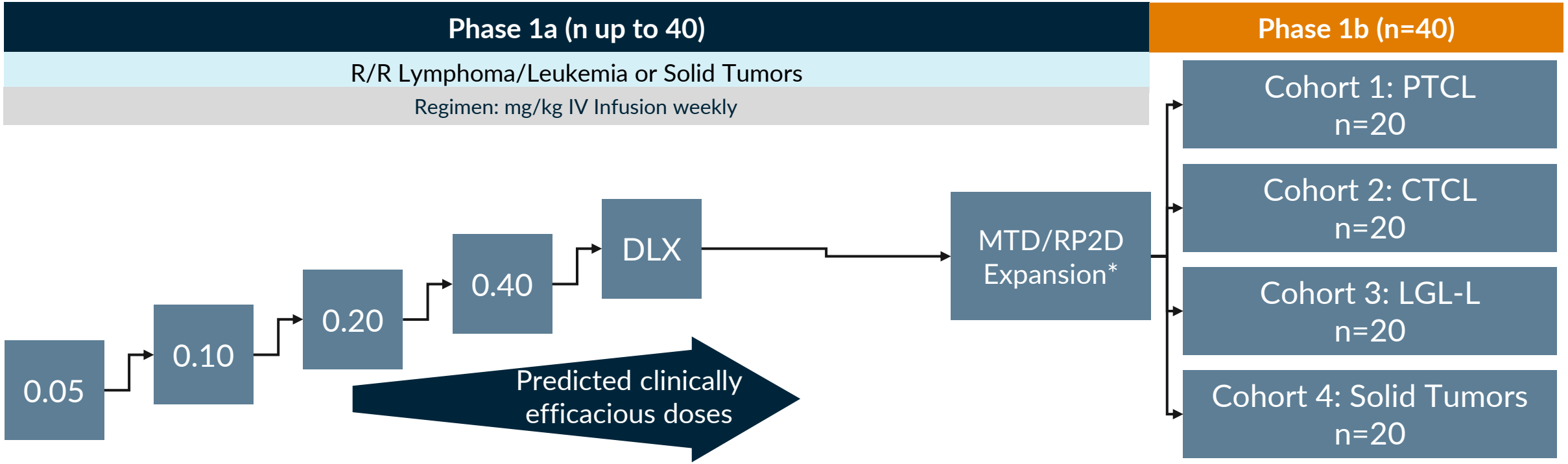
KT-333: Phase 1, Multicenter, Dose-Escalation and Expansion Trial to Evaluate KT-333 in Adult Patients with PTCL, CTCL, LGL-L, and Solid Tumors



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

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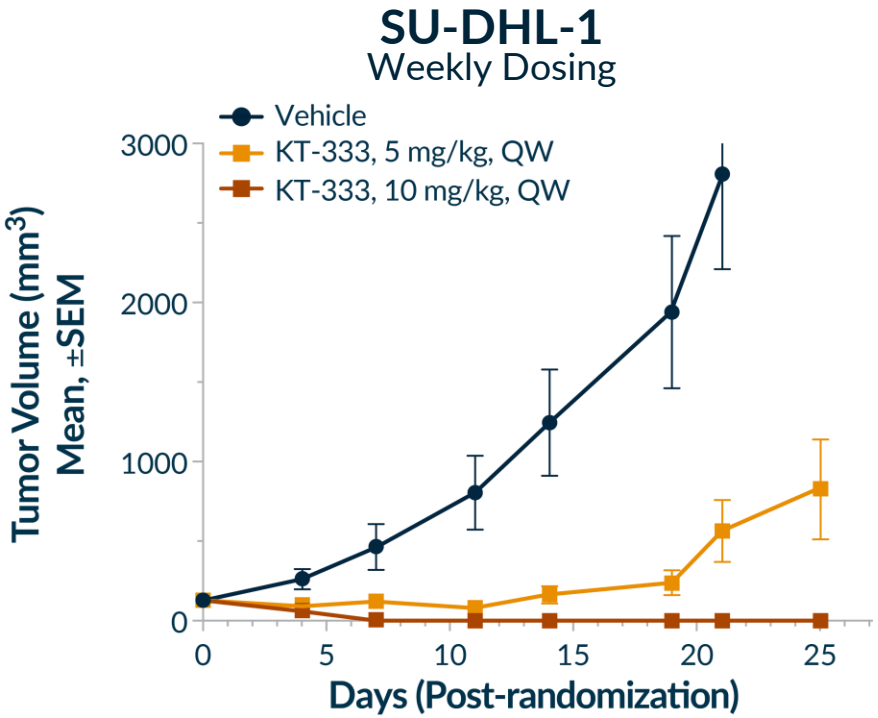
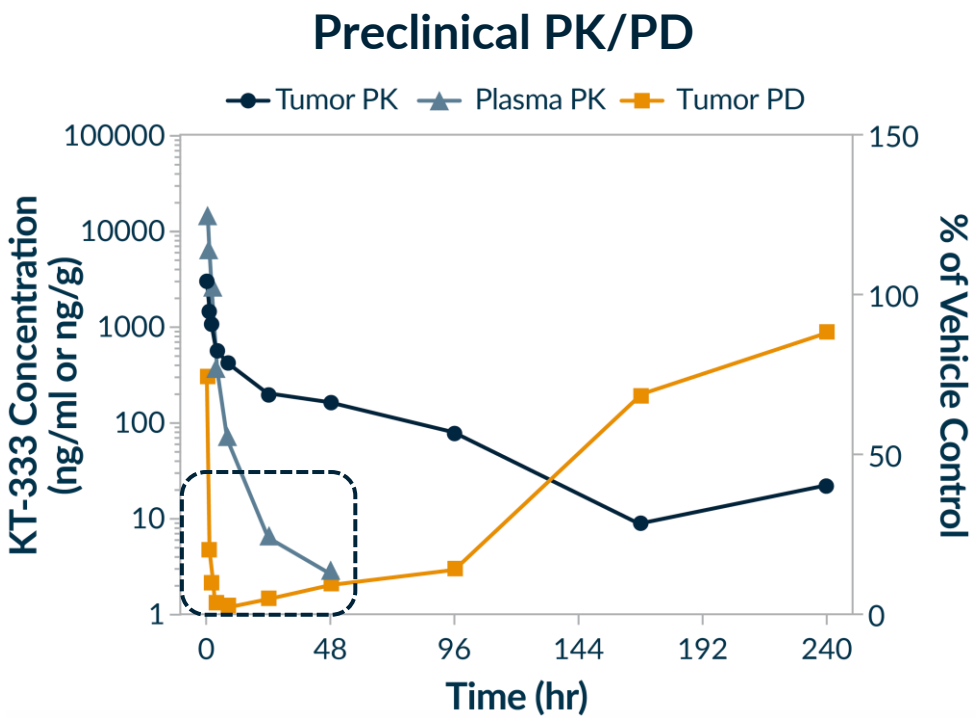
KT-333 Highly Active on Intermittent Dosing Regimens

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

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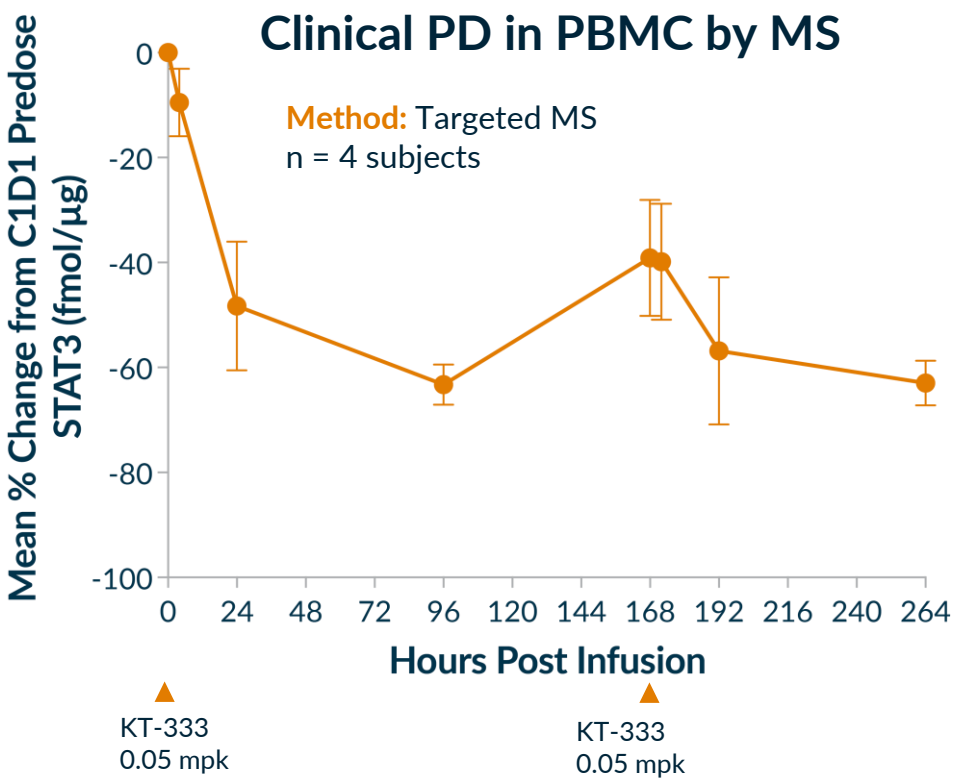
STAT3 Degradation in Blood at Dose Level 1 (DL1: 0.05 mpk) Consistent with Prediction from Preclinical Modeling



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

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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
- 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

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MDM2

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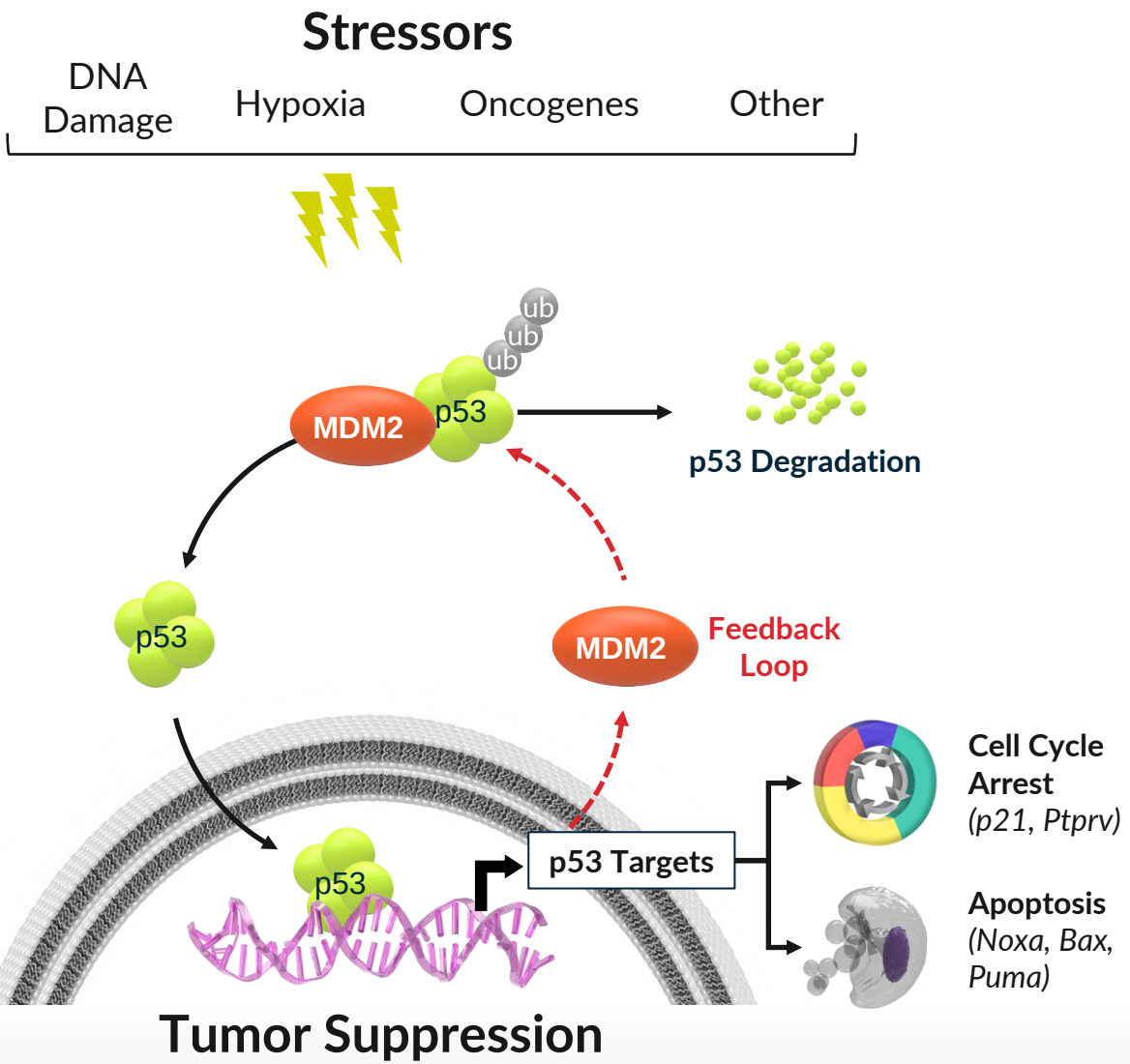
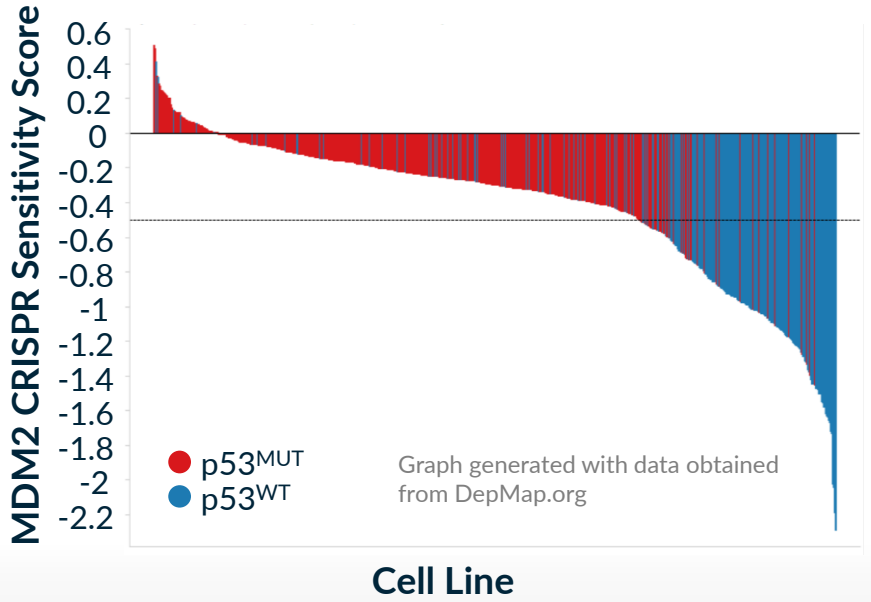
MDM2 is the E3 Ligase that Modulates P53, the Largest Tumor Suppressor



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

Dependency of p53^{WT} cells on MDM2



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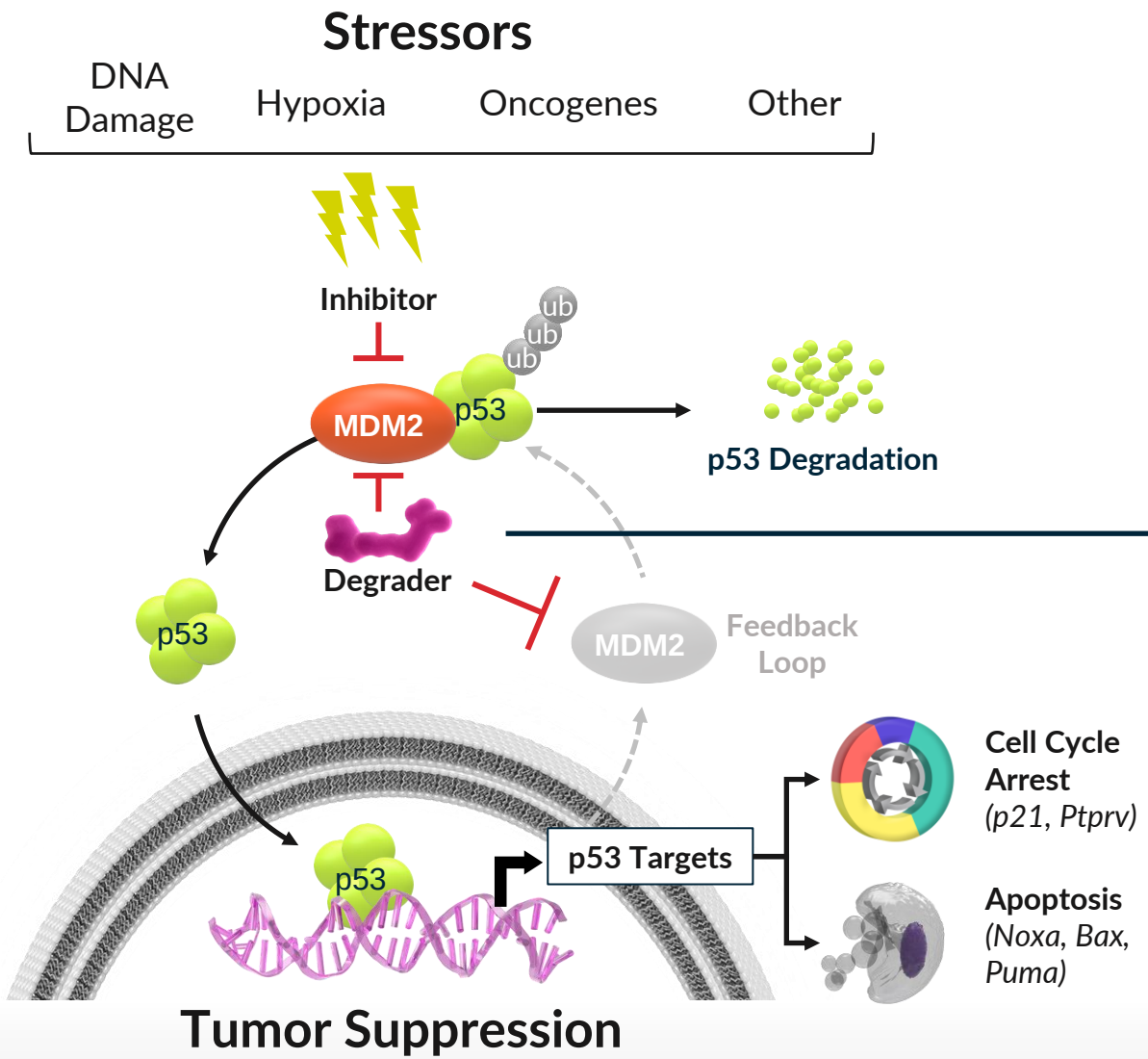
MDM2 Degradation, Not Inhibition, Efficiently Restores p53



Clinical Validation

- **MDM2 small molecule inhibitors** of MDM2/p53 interaction **show activity in the clinic**..
- **...but they induce MDM2 feedback loop** resulting in limited impact on pathway

Degrader Advantage

- **MDM2 degraders**, by removing the protein, **can overcome the p53-dependent feedback loop that upregulates MDM2**
- MDM2 degrader can induce an acute apoptotic response in tumor cells, **increasing efficacy and therapeutic index vs a small molecule inhibitor**

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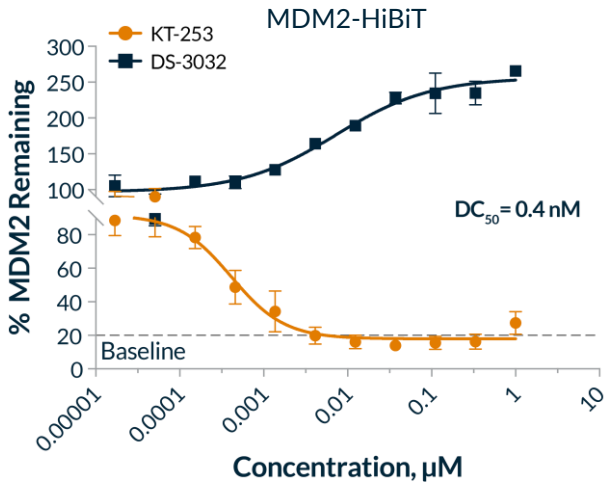
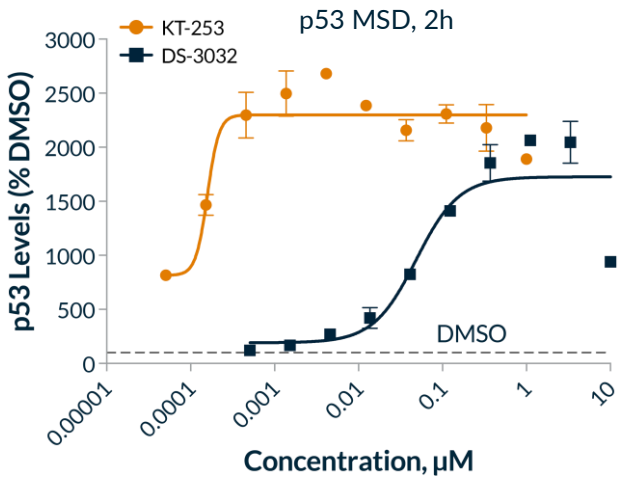
Kymera's MDM2 Degrader Development Candidate, KT-253 is Superior to MDM2/p53 Small Molecule Inhibitors

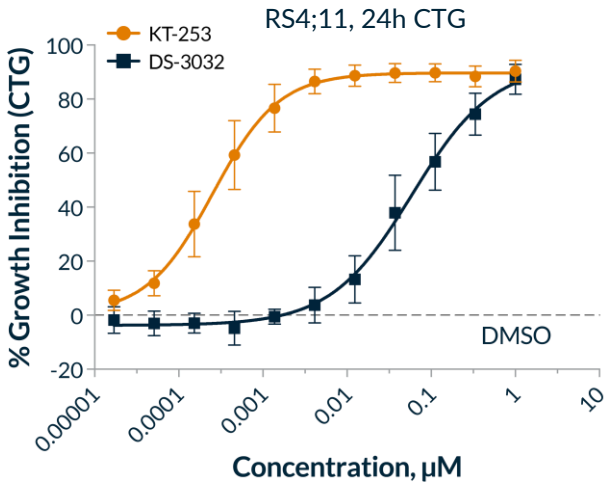
KT-253 is a potent MDM2 degrader



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

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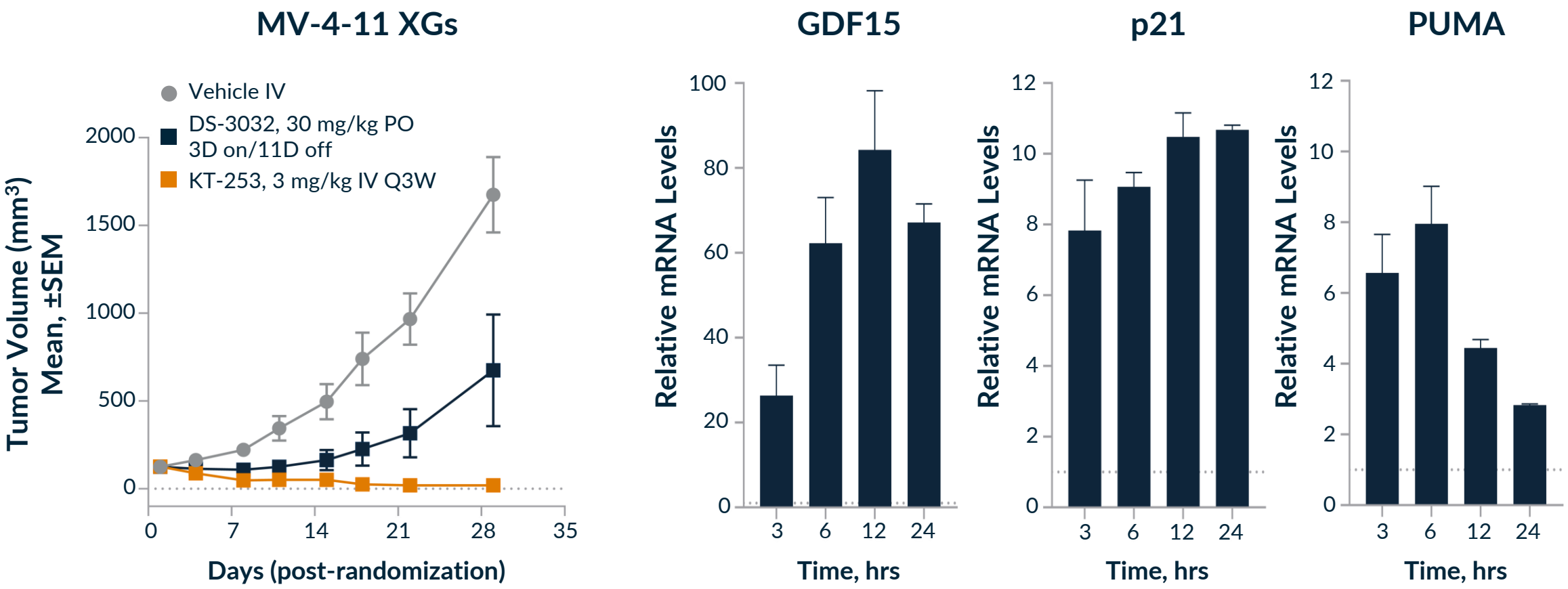
KT-253 Achieves Tumor Regression in MV-4-11 (AML) Xenograft Model



- 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

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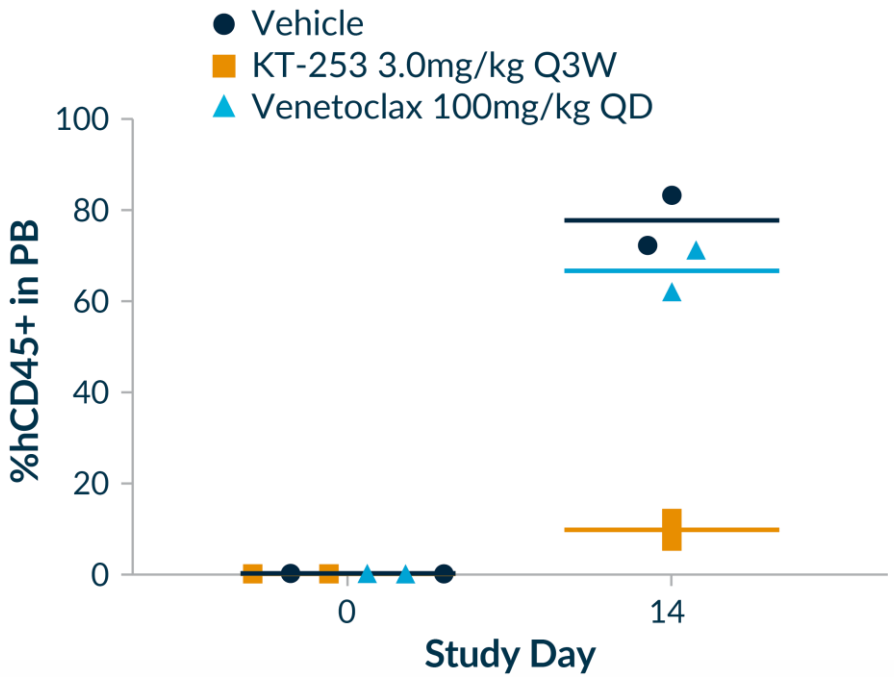
Strong Single Agent and Combinatorial Activity in Venetoclax Resistant AML Models

Whole Blood

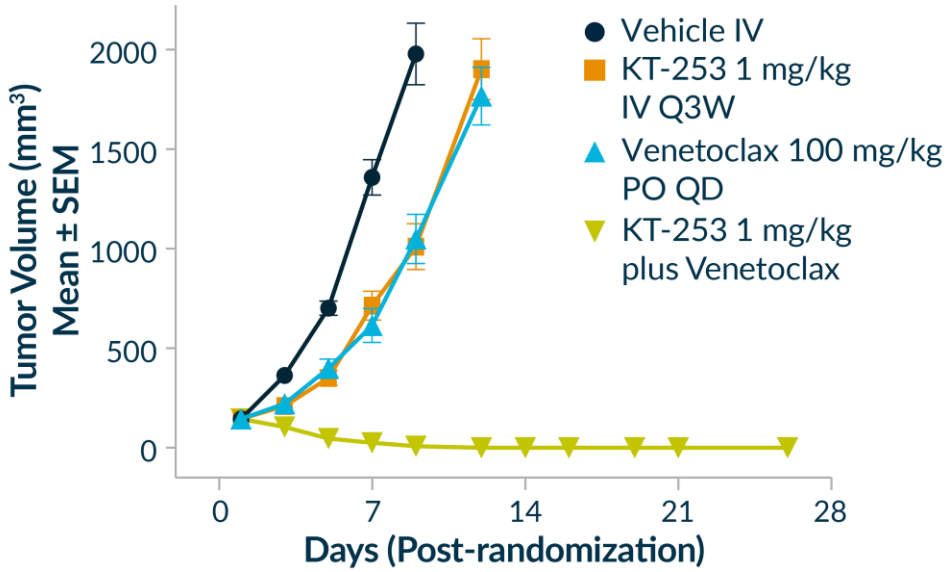
DFAM-68555 Day 14



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

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KT-253 Clinical Development Strategy

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 TP53WT **lymphomas**

Solid Tumors

- Preclinical efforts have identified and **prioritized indications** for monotherapy development and are focused on **patient stratification strategy** for selection of highly sensitive subset of patients

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First MDM2 Degrader, KT-253, in Clinic

- KT-253, unlike small molecule inhibitors, **blocks 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 (p53 WT is present in >50% tumors), 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
- **FIH in Q1 2023 with POM data 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**

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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

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Thank You

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