OXFORD GLOBAL
Virtual Symposium: Targeted Protein Degradation & PROTAC
16 - 17 February 2021 | GMT (UTC+0)

Discovery of potent and selective STAT3 targeted protein degraders with excellent in vitro and in vivo ADME properties

February 2021

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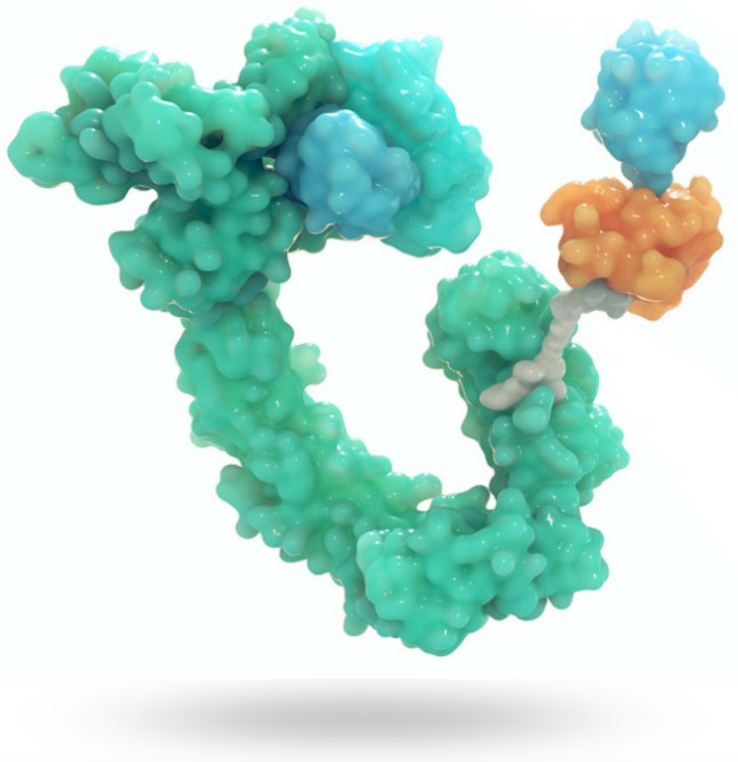
Kymera: A Leading Targeted Protein Degradation Company

Founded:	2016
NASDAQ:	KYMR
Employees:	~75
Cash balance at Q4'20*:	~$458M
Cash runway*:	2025

KYMERA



- Premier protein degrader discovery platform
- Key partnerships:

SANOFI VERTEX gsk

- Initial focus in immune-inflammation and oncology
- Expect **3 INDs** and clinical initiations by end of **2021**
- Dosing HV, I/I and cancer patients with first proof-of-biology in humans in **2021**

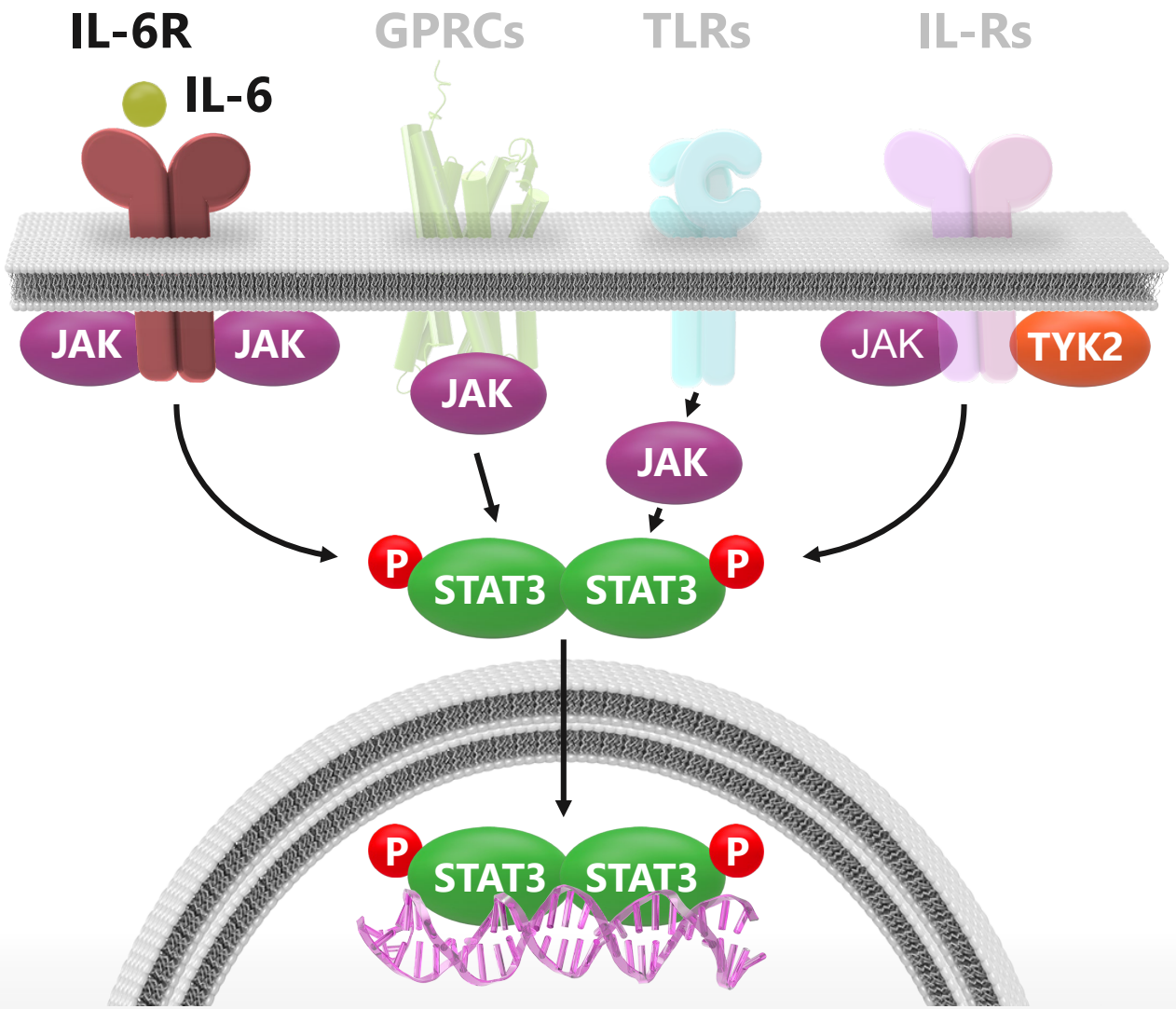
* Kymera expects that its cash, cash equivalents, and investments as of 12/31/2020, excluding any future potential milestones from collaborations, will enable the Company to fund its operational plans into 2025. This cash estimate is based on information currently available, and may differ from the actual cash balance to be included in the Company's audited financial statements

Outline

- STAT3 biology and the rationale of STAT3 degradation
- KTX-201 potently and selectively degrades STAT3
- In vitro and in vivo ADME profile of KTX-201
- KTX-201 efficacy and PK/PD in mouse xenograft models
- Summary and conclusions

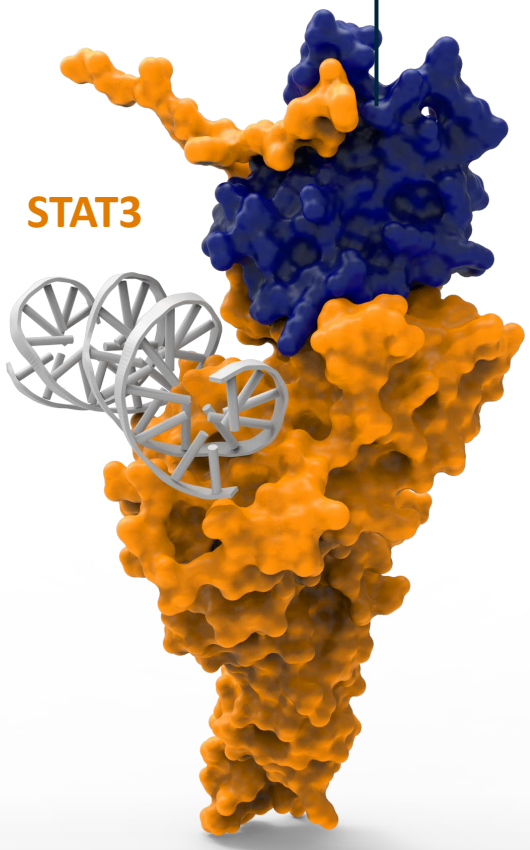
STAT3 Biology and Degrader Rationale

- STAT3 is a traditionally largely undrugged transcription factor activated through cytokine and growth factor receptors via JAKs and non-JAKs mediated mechanisms
- High degree of validation of JAK-STAT pathway in oncology and immuno-oncology supported also by numerous publications
- STAT3 plays a role in tumor biology, evasion of immune surveillance and inflammation/fibrosis
- No known drugs specifically affect STAT3 broadly across all relevant cell types
- First in class opportunity to address STAT3 driven pathology across large and diverse indications

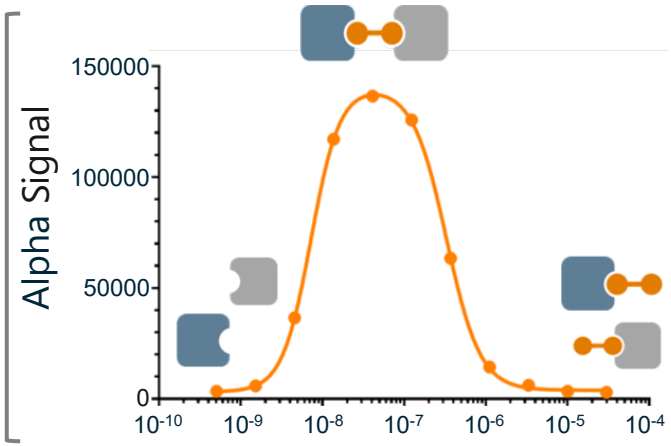


Specific and Potent STAT3 Degradation

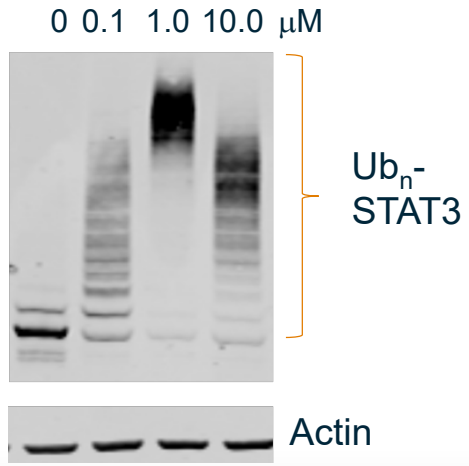
Kymera binders recruit STAT3 to E3 ligase and affect ubiquitination



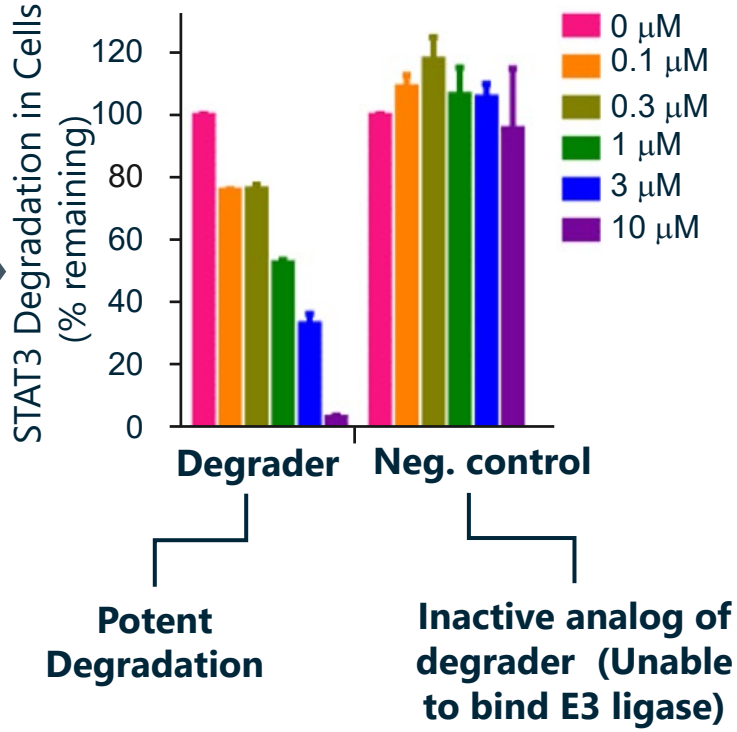
Efficient Ternary Complex Formation



Efficient Ubiquitination of Cellular STAT3



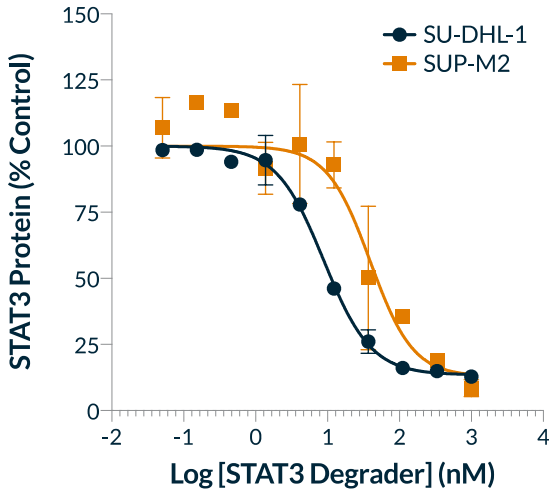
Potent, E3-Dependent Degradation



KTX-201 as a Tool Degrader Exhibited High Potency and Selectivity

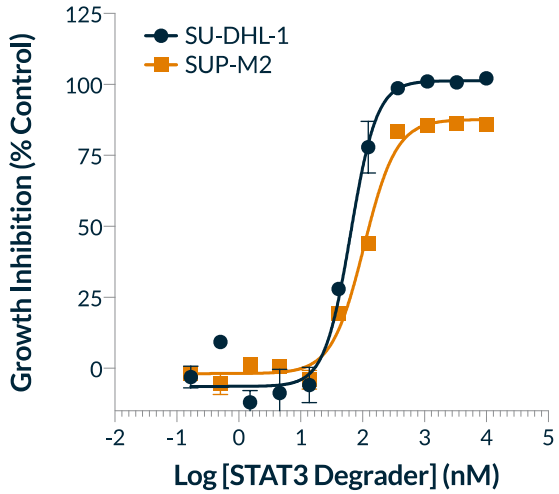
High Potency in SU-DHL-1 and SUP-M2 Cell Lines (ALK+ ALCL)

Degradation Potency



SU-DHL-1 24h DC_{50} 15 nM
SUP-M2 24h DC_{50} 86 nM

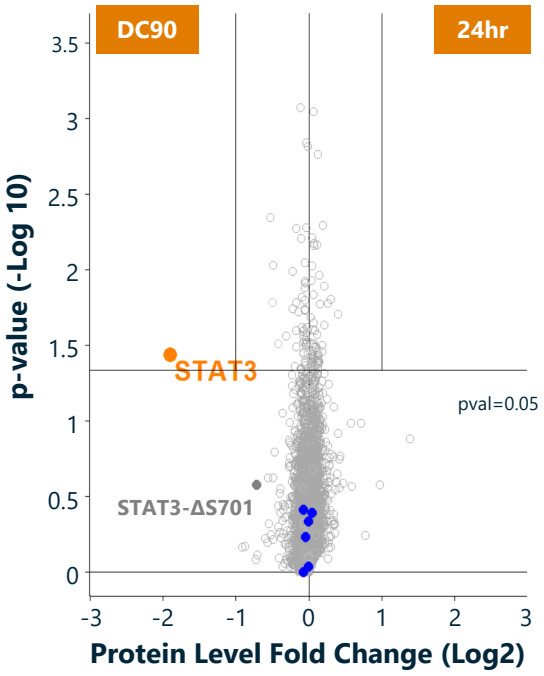
Growth Inhibition Potency



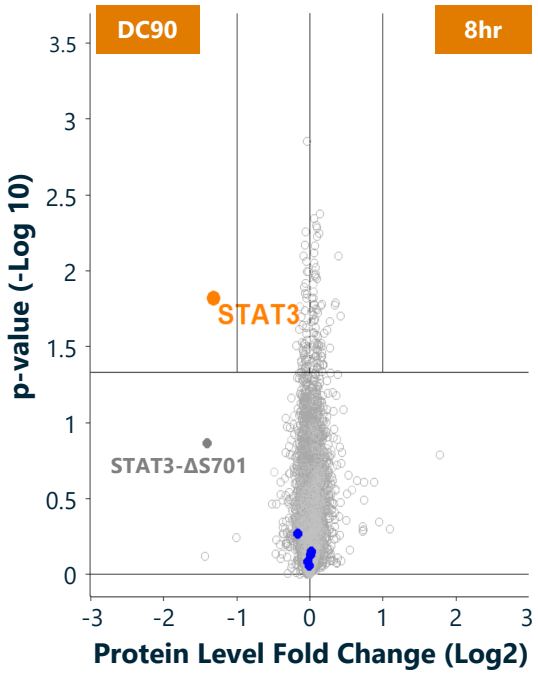
SU-DHL-1 IC_{50} 64 nM
SUP-M2 IC_{50} 105 nM

High Selectivity in huPBMCs and SUDHL-1 Cell

huPBMCs

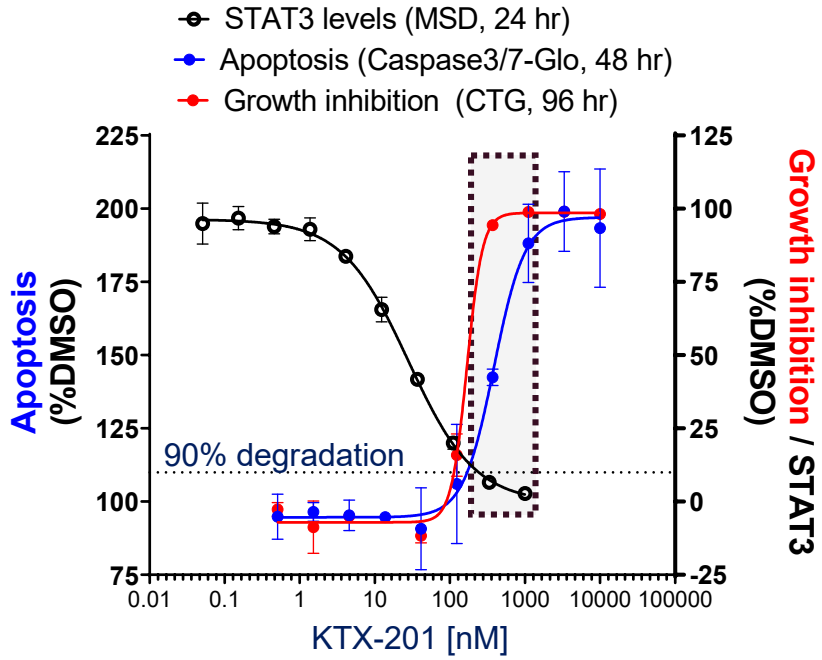


SU-DHL-1



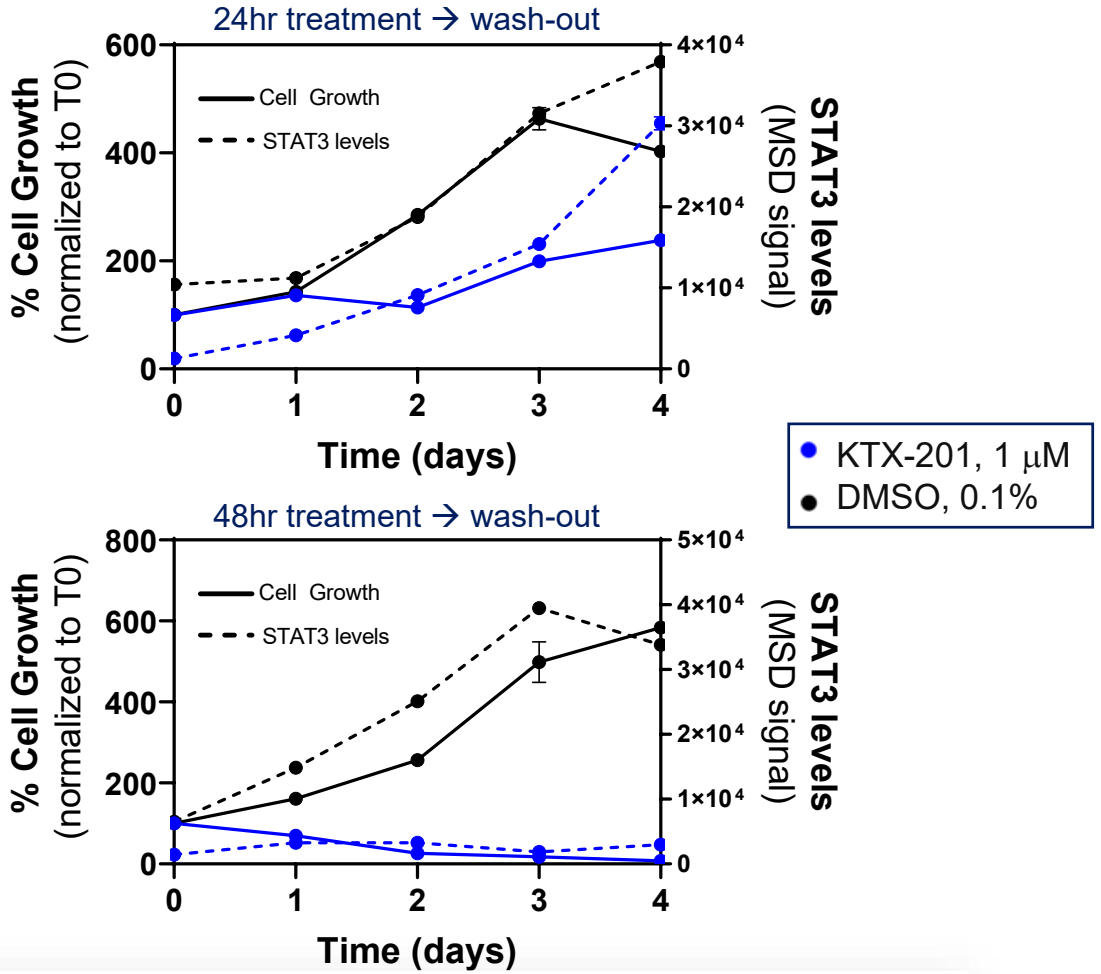
● STAT Family Members: **STAT1, STAT2, STAT4, STAT5A, STAT5B, STAT6**

Sustained and robust degradation of STAT3 with KTX-201 is necessary to induce SU-DHL-1 apoptosis and inhibit cell growth



Assay	SU-DHL-1
STAT3 levels, MSD DC_{90} (μM) at 24 hr	0.15
Apoptosis, Caspase3/7-Glo IC_{50} (μM) at 48hr	0.38
Growth inhibition, CTG IC_{50} (μM) at 96 hr	0.167

- A decrease of STAT3 by 90% is necessary to induce SU-DHL-1 apoptosis and inhibit cell growth



- Wash-out study demonstrates sustained degradation is required for SU-DHL-1 cells to commit to death

In vitro ADME properties of KTX-201 are suitable for IV dosing route-of-administration (RoA)

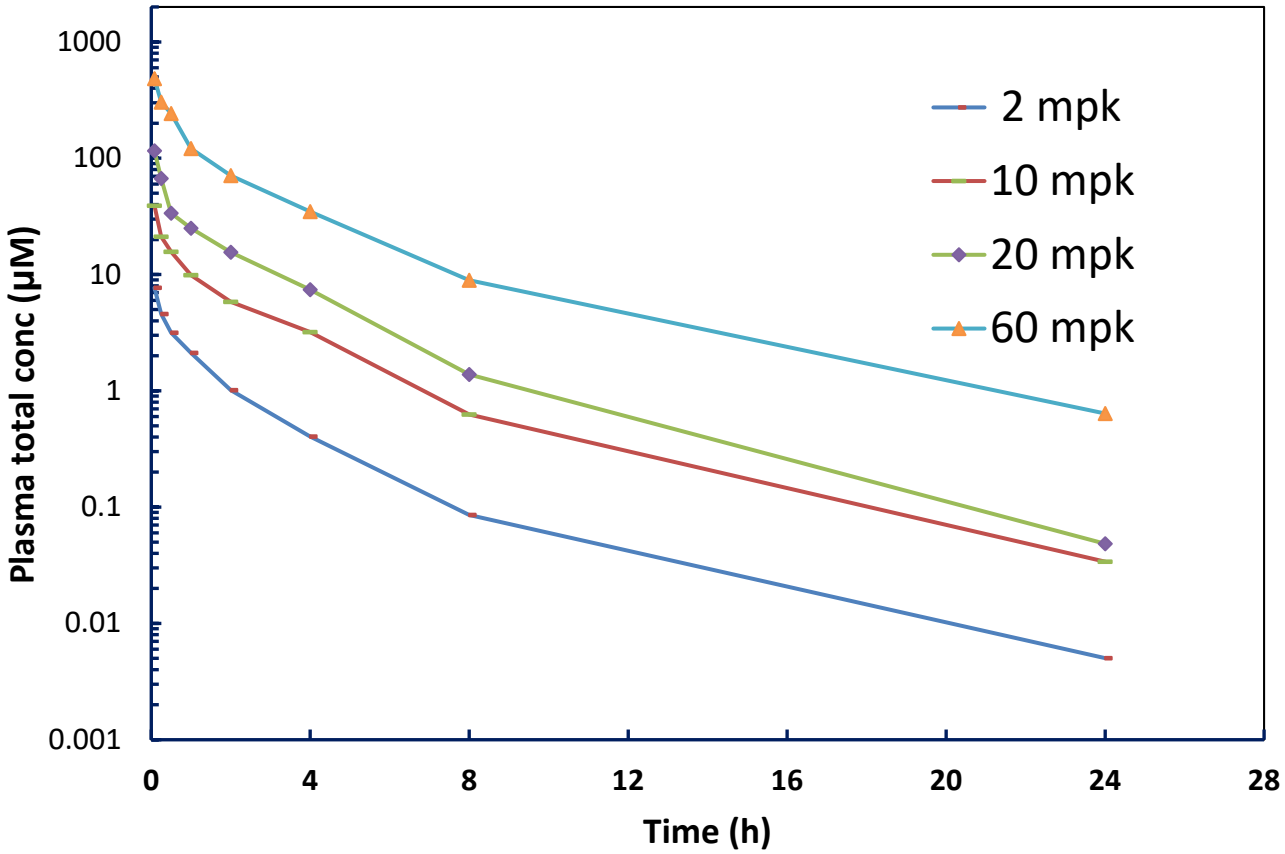
Physical and DMPK properties	KTX-201
cLogD	-1.3
Solubility in PBS pH 7.4	>28 mg/mL
PPB (hu / mouse / rat / dog / Mk)	95.8% / 99.3% / 99.1% / 97.1% / 97.3%
HLM / RLM / DLM / MkLM hepatic extraction ratio	0.2 / <0.04 / 0.27 / <0.05
Hu hepatocytes hepatic extraction ratio	0.03
CYP3A4 / 2C9 / 2C19 / 2D6 inh. IC_{50}	All > 50 μM
CYP3A4 TDI	No IC_{50} shift with pre-incubation
PXR activation	Negative at 10 μM

KTX-201 has low clearance in preclinical species and dose proportional exposure via IV dosing

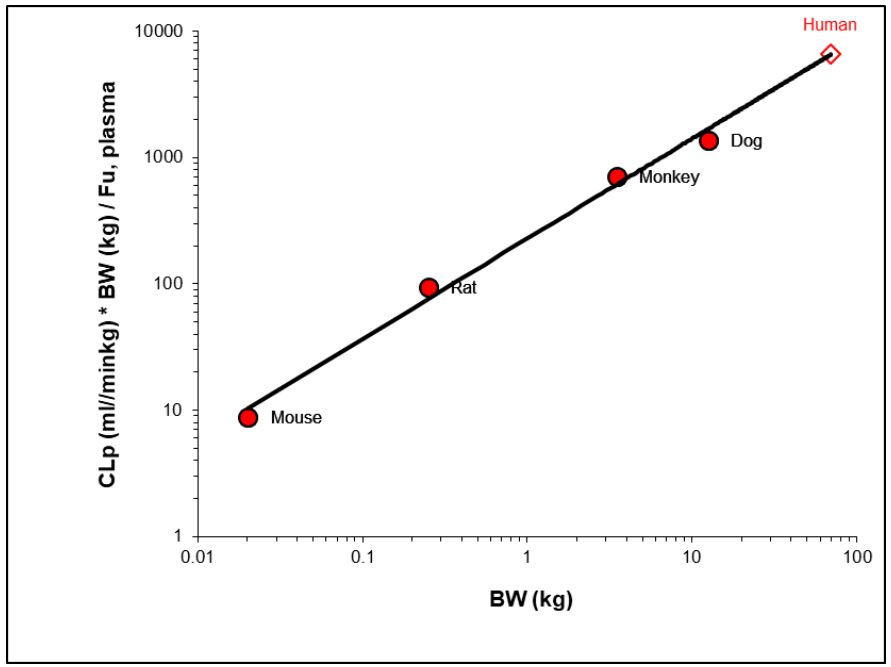
Similar PK profile across preclinical species for KTX-201

In vivo DMPK properties	Mouse	Rat	Dog	Monkey
Cl (mL/min/kg)	**2.4**	**3.3**	**3.2**	**5.5**
Vdss (L/kg)	**0.4**	**0.4**	**0.7**	**0.7**
$t_{1/2}$ (h)	**4.1**	**3.3**	**9.2**	**5.6**

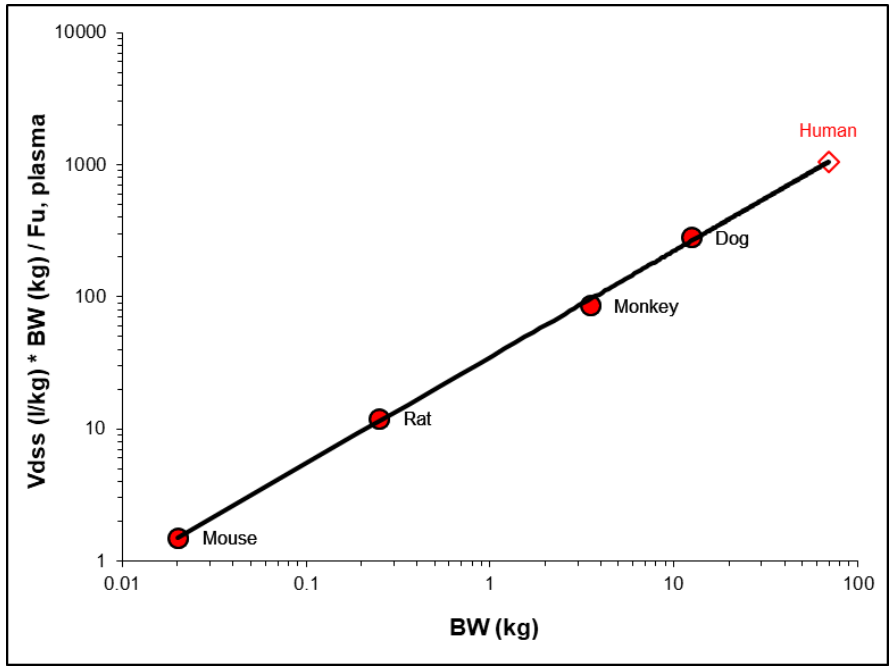
Linear IV PK in rat for KTX-201



KTX-201 is predicted to have low plasma clearance and low volume of distribution in human



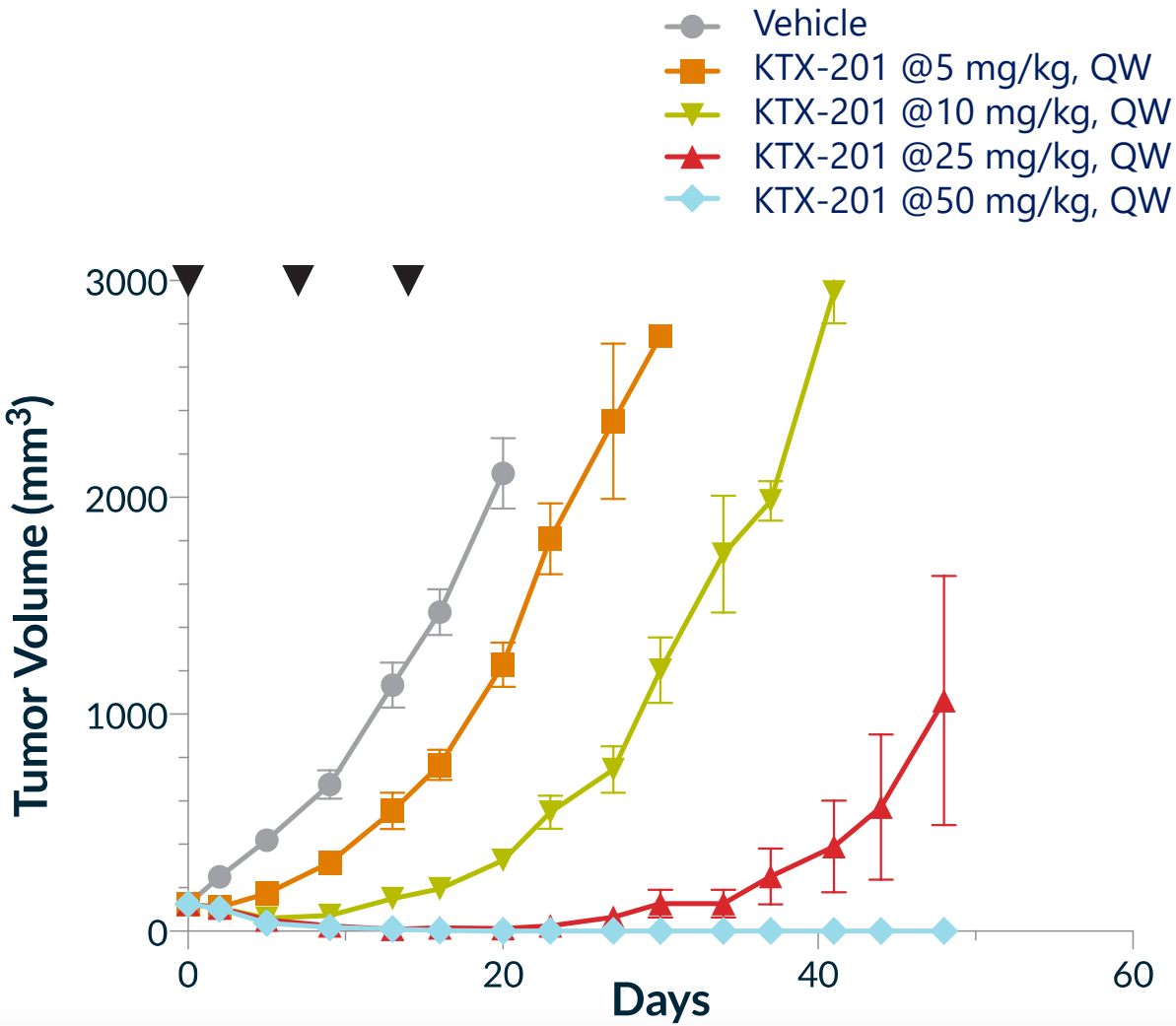
Projected human plasma Clearance: 4 mL/min/kg



Projected human steady state Volume of distribution: 0.6 L/kg

KTX-201 showed significant anti-tumor activity *in vivo* with weekly dosing regimen

- KTX-201 in SUDHL-1 XG Mouse
  - IV bolus at 5 to 50 mg/kg
  - Weekly dosing
  - Treatment on D1, D8, D15
- KTX-201 showed significant anti-tumor activity
- The treatments were well tolerated, with no significant body weight loss
- Three doses sufficient to drive durable complete responses

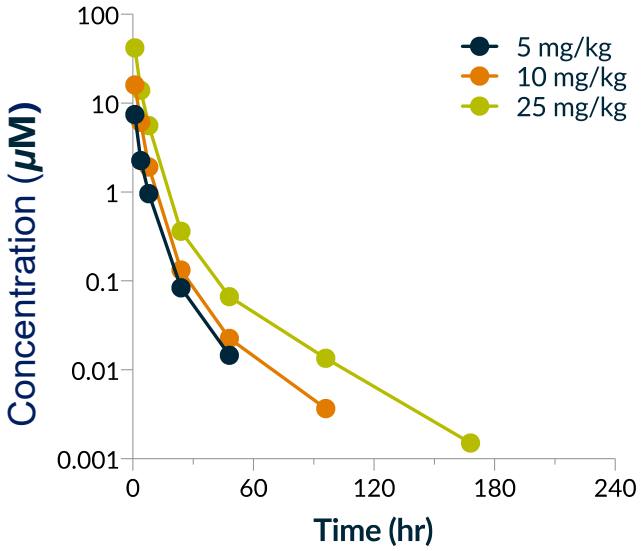


KTX-201 exhibited prolonged half-life in tumor

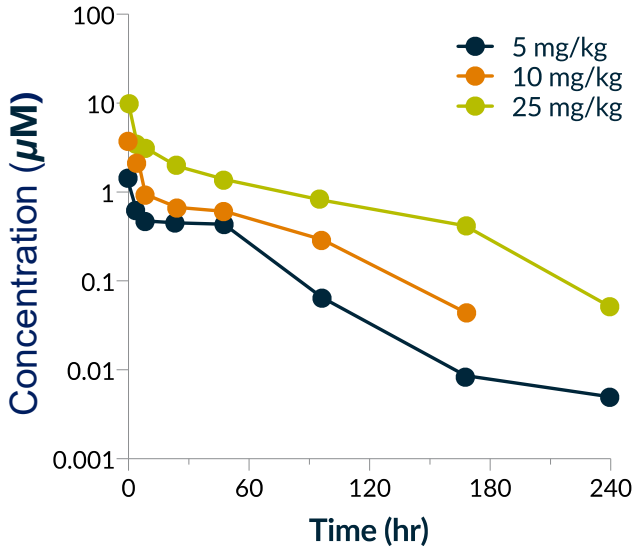
PK in Plasma and Tumor

- Plasma and tumor exposure increase as increase of dose
- $T_{½}$ in tumor > plasma
- Tumor/Plasma AUC ratio *Kp* ~1; consistent across 5 mpk to 25 mpk dose range

KTX-201 Plasma PK Profiles



KTX-201 Tumor PK Profiles

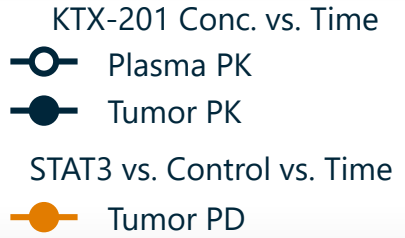


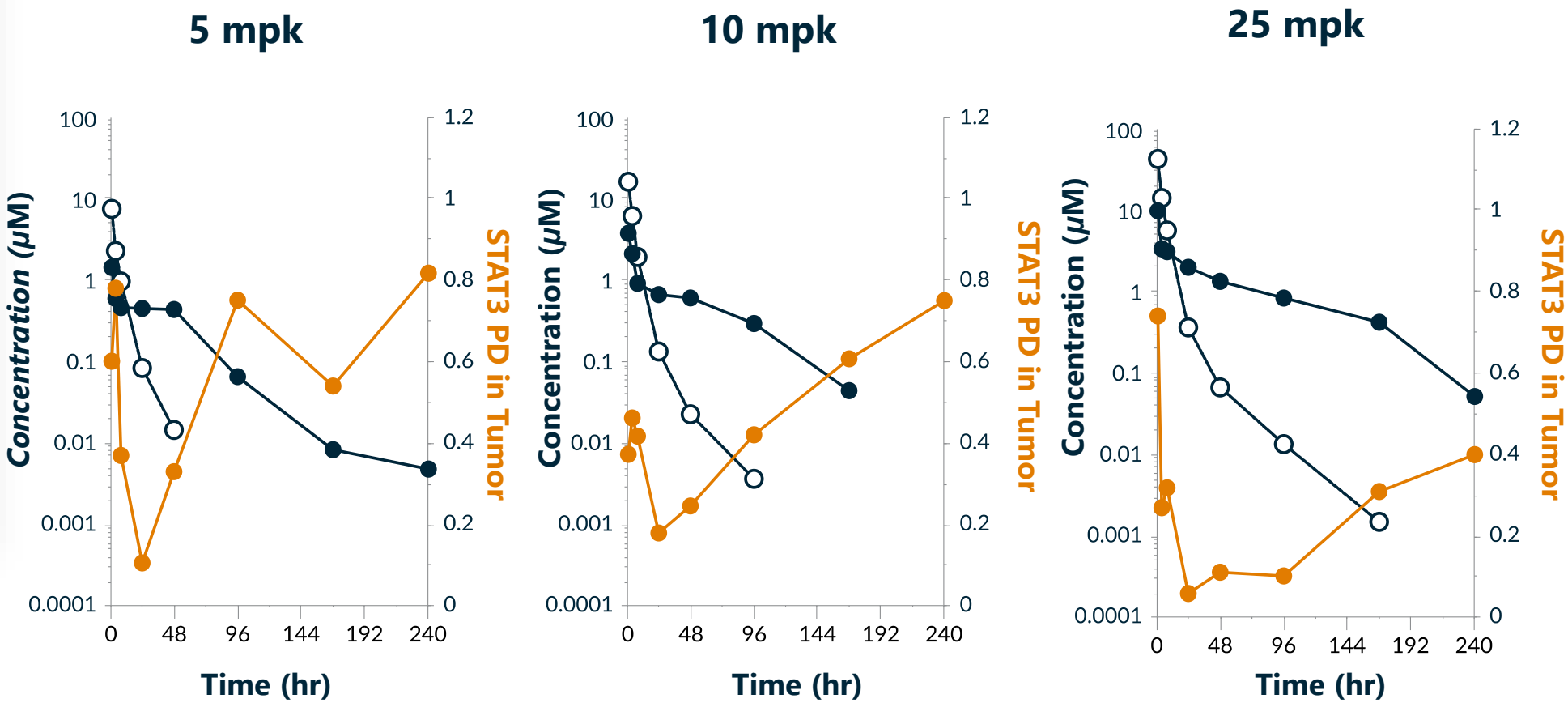
KTX-201		5 mpk		10 mpk		25 mpk	
PK Parameters	Unit	Plasma	**Tumor**	Plasma	**Tumor**	Plasma	Tumor
$T_{1/2}$	hr	6.8	**24**	16	**31**	16	**36**
AUC_{last}	μM*h	40	**36**	87	**78**	229	**231**

STAT3 degradation in tumor was exposure-dependent

KTX-201 dose-dependent PD

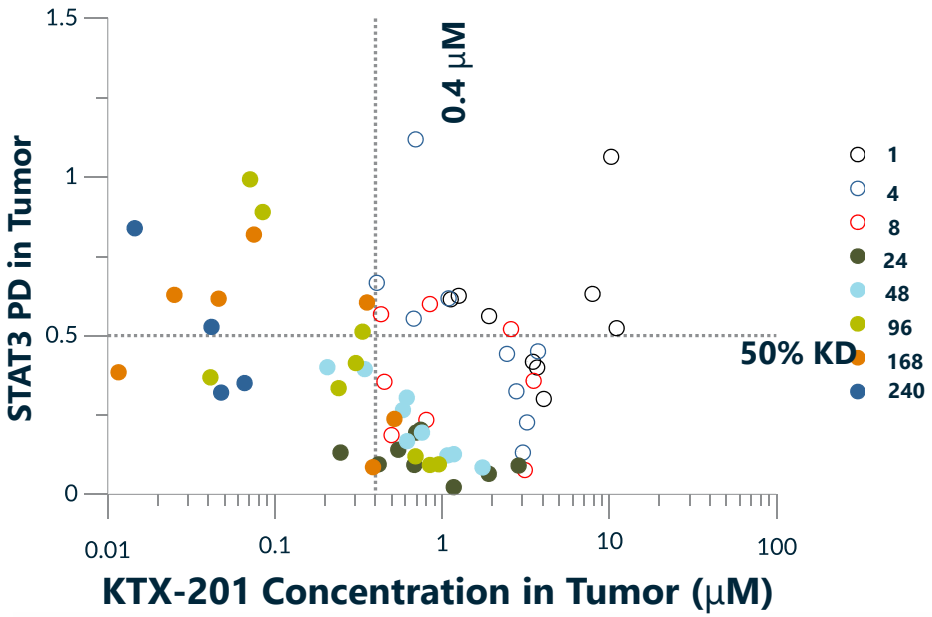
- Maximal STAT3 degradation occurred at 24 hr post dose for all doses
- Maximal degradation is >90% at 25 mpk
- Prolonged degradation in tumor is partially due to longer drug $t_{1/2}$ in tumor
- $T_{½}$ of STAT3 return to baseline is dose-dependent → higher dose/higher exposure/ prolonged degradation

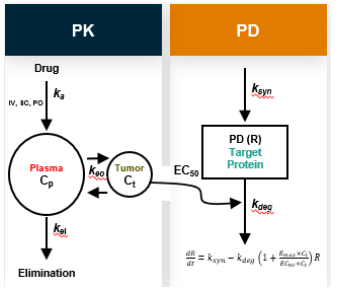




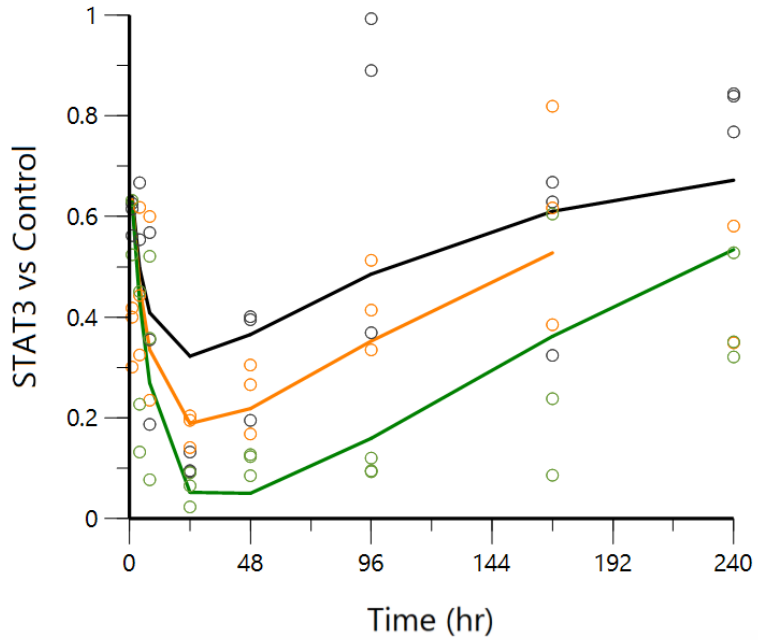
Important *in vivo* parameters can be derived from PK/PD modelling to enable human dose projections

KTX-201 Exposure-response in SU-DHL-1





KTX-201 PK/PD model in SU-DHL-1



5, 10, 25 mg/kg
Solid lines (simulation)
Open circles (observed)

- Hysteresis observed
- >0.4 uM $[KTX\text{-}201]_{tumor}$ leads to >50% STAT3 degradation
- *in vivo tumor* DC_{50} is expected to be 0.46 µM (using *in vitro* DC_{50} with PPB correction)

*10% FBS fu = 0.15; SUDHL-1 fu,t = 0.0049

PK/PD Parameters	Description	Estimate	CV
k_{deg}	Degradation Rate	0.0356 hr^{-1} ($t_{½}$ 19 hr)	17%
E_{max}	*In vivo* max. effect	14	16%
EC_{50}	*In vivo* potency	2.5 µM	16%

Summary and conclusions

- **Kymera has developed potent and highly selective STAT3 degraders which are active in models of heme malignancies.**
- **Preclinical ADME characterization showed excellent in vitro and in vivo ADME profile for KTX-201; low human plasma clearance is predicted using allometric scaling.**
- **Sustained STAT3 degradation of 90% or greater leads to apoptosis induction and cancer cell death within 48 hr *in vitro* and *in vivo.***
- **PK/PD modeling is a useful tool to understand STAT3 degradation and efficacy relationships and also allows projection of STAT3 degradation profiles in human.**

Acknowledgement

The Kymera Team