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Mechanisms of Anti-Tumor Activity of STAT3 Degraders in Lymphoma

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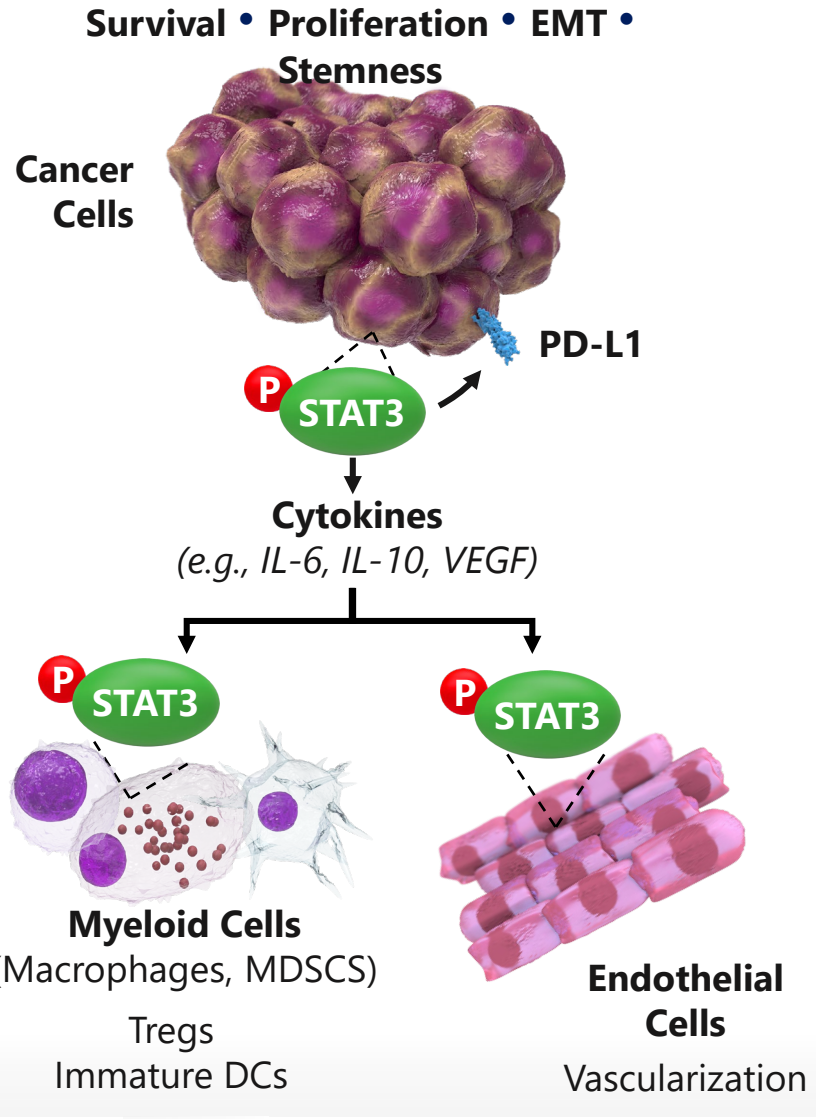
Disclosure

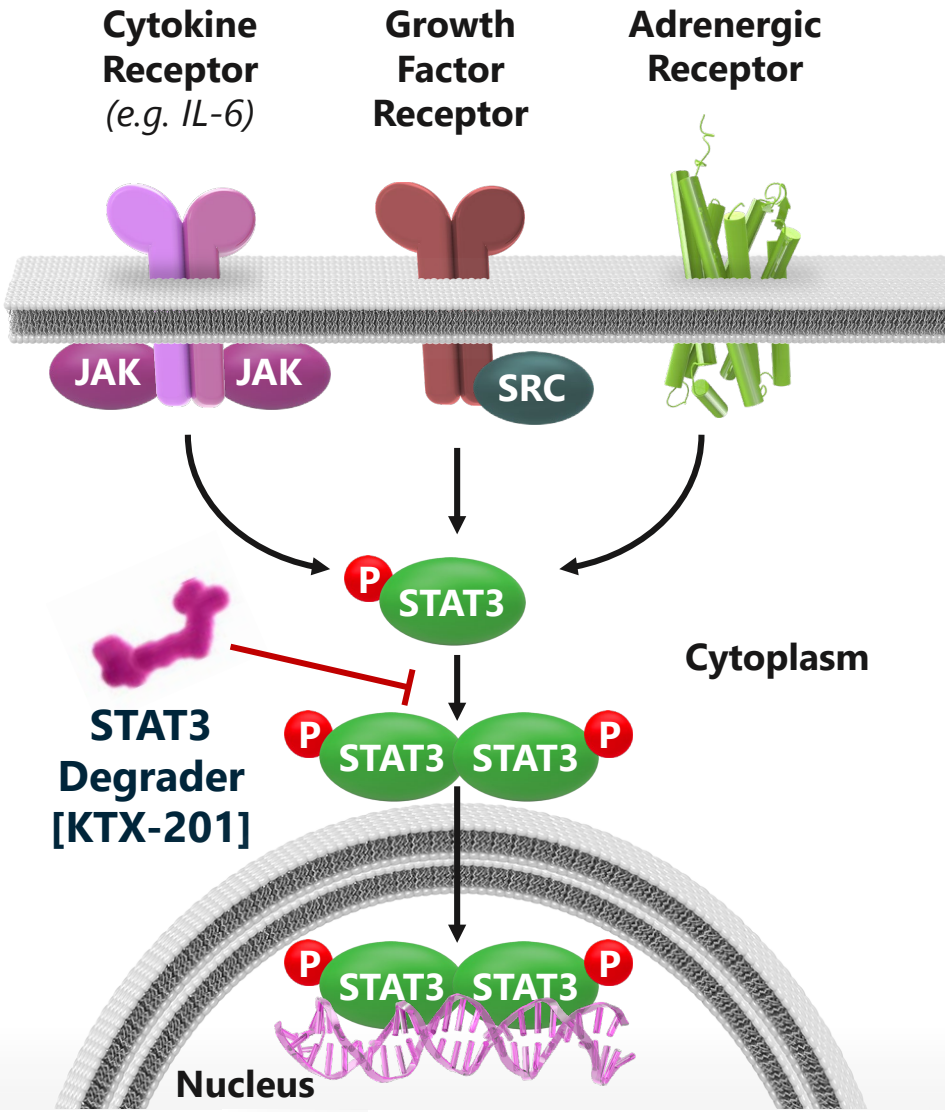
Rong, Sharma, Dey, Yang, Liu, Mayo, Yuan, Rusin, Shi, Li, Chutake, Karnik, McDonald, Zhu, Walker, Gollob, Chesworth, Mainolfi and De Savi are Kymera Therapeutics employees and equity owners.

Csibi and Ji are Kymera Therapeutics equity owners.

STAT3 Integrates Multiple Upstream Signaling Events to Regulate Tumor Cell-Intrinsic and -Extrinsic Functions

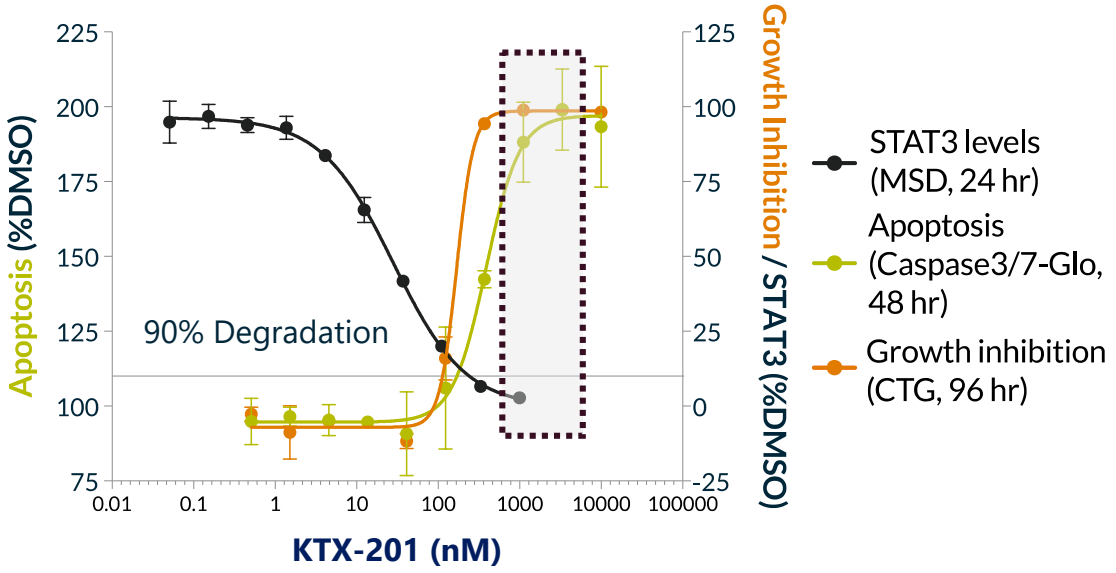
- Hyperactivation of STAT3 promotes tumor cell-intrinsic gene expression programs involved with survival, proliferation, stemness and metastasis of tumor cells.
- Additionally, STAT3 promotes the differentiation and activity of immunosuppressive cells in the tumor microenvironment.





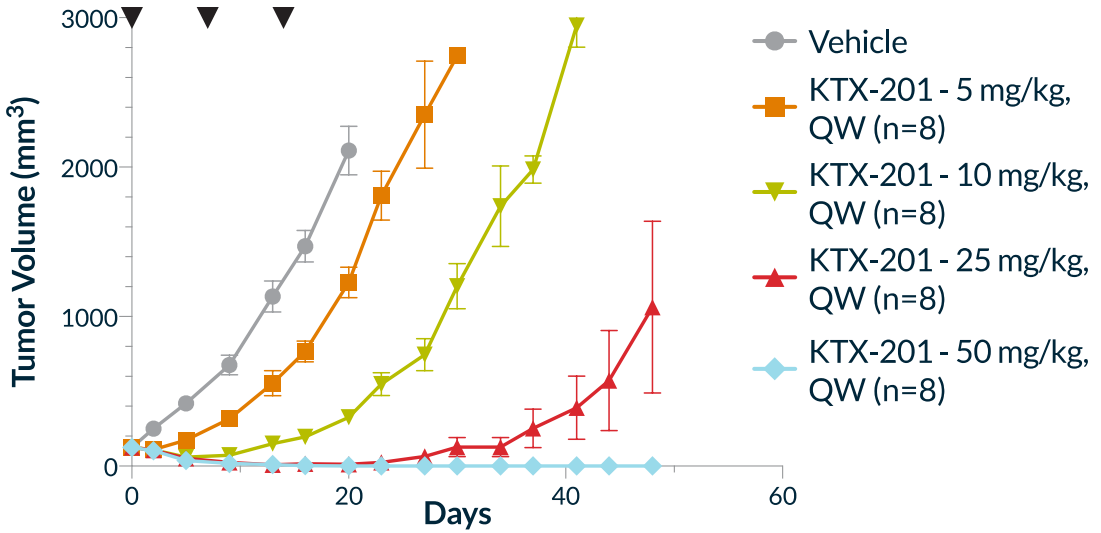
Tumor Cell-Intrinsic Effect: Efficacy *In Vitro* and *In Vivo*

In Vitro Degradation and Growth Inhibition



- >90% STAT3 degradation led to induction of apoptosis and growth inhibition in ALK+ALCL SU-DHL-1 cells

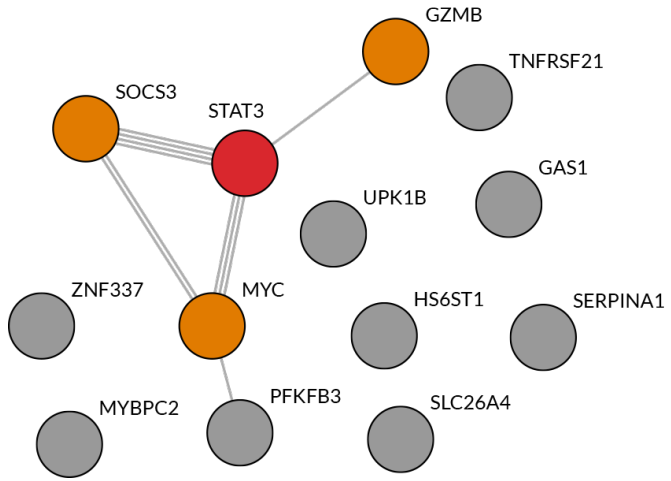
Anti-Tumor Activity with Weekly Dosing Regimen



- KTX-201 showed significant TGI in SU-DHL-1 XG mouse with weekly dosing regimen
  - At 50 mpk, all animals showed complete tumor regression, with no regrowth 30 days after cessation of dosing

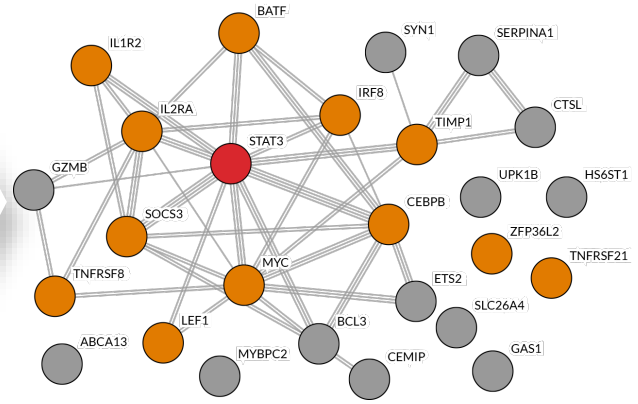
Proteomic Analysis Shows Time-Dependent Changes in STAT3 Targets and Associated Pathways in SUDHL-1 Cells

STAT3 Degradation (16 Hr)



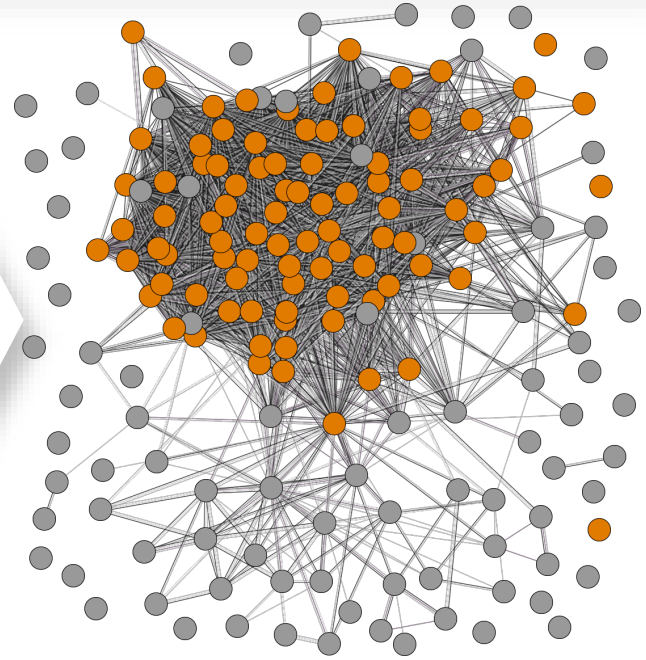
- Downregulation of STAT3-mediated proximal signaling: SOCS3, MYC, Granzyme B

Expansion (24 Hr)



- Expansion of downregulation to proteins involved in response to cytokine stimulus *(15 of 953)*

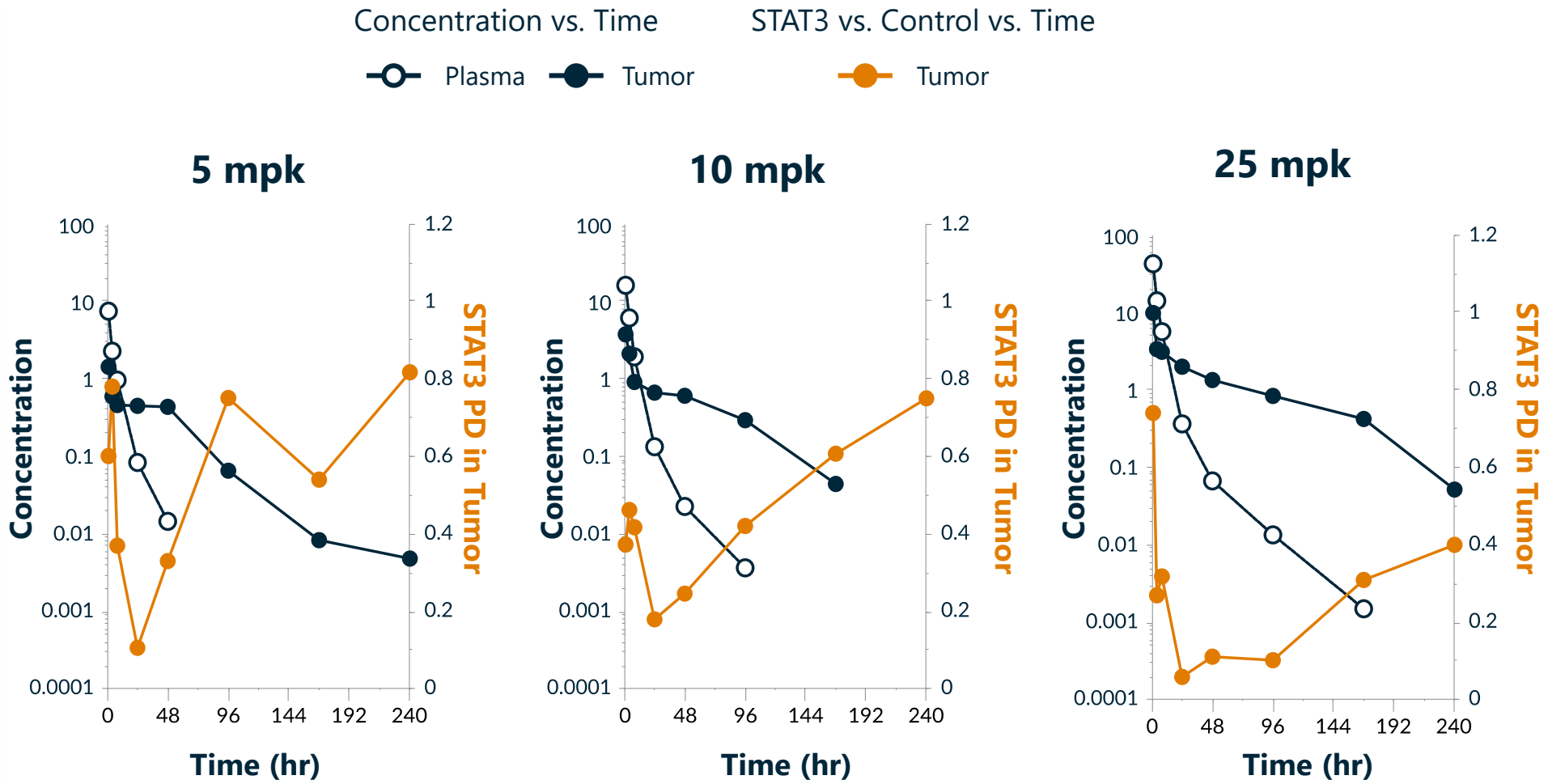
G1 Cell Cycle Arrest (48 Hr)



- Stark decrease in cell cycle-related proteins *(92 of 1263)*

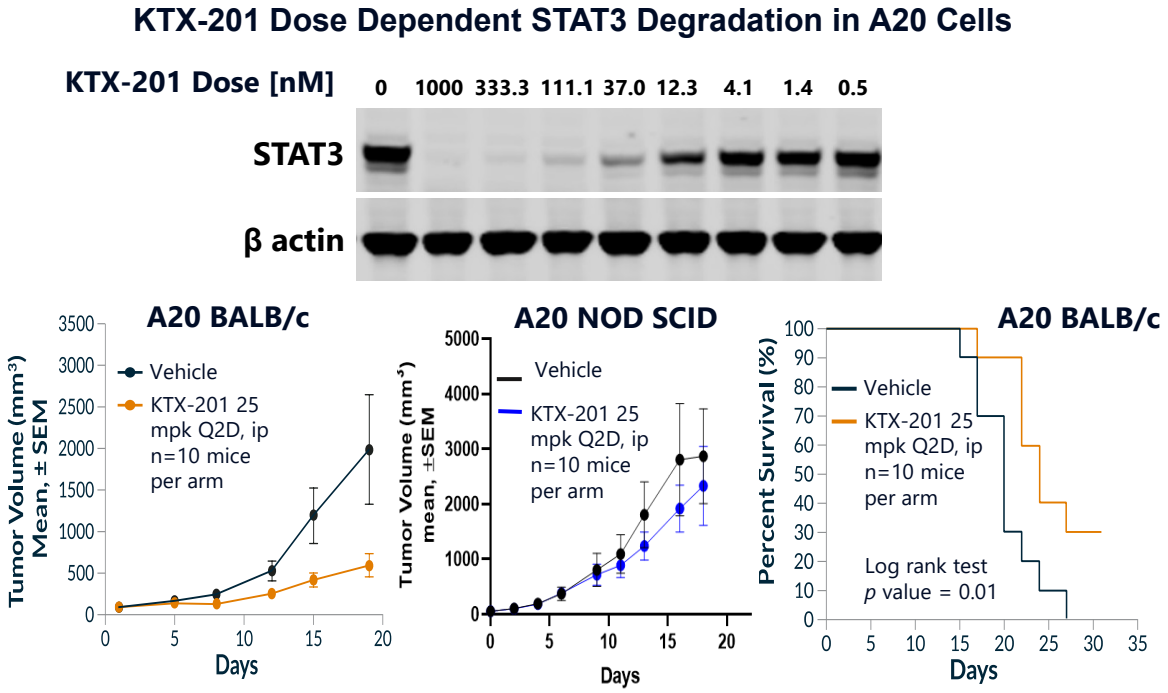
Exposure/STAT3 Degradation in Tumor Indicated Relationship Between PD Coverage And Efficacy

- KTX-201 exhibited prolonged half-life in tumor → prolonged STAT3 degradation in tumor
- $T_{½}$ of STAT3 return to baseline is dose-dependent
- Time over 90% STAT3 degradation in tumor is associated with anti-tumor activity
- Consistent with the result from *in vitro* washout experiment, partial coverage (ie 48 h to 96 h) of dosing interval is sufficient for efficacy

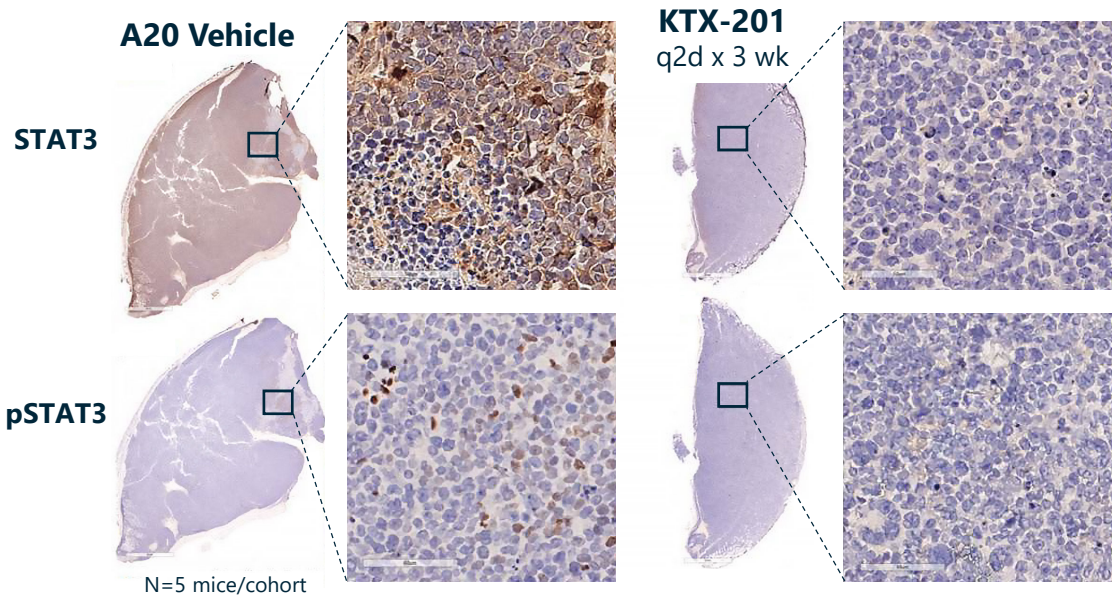


Anti-Tumor Activity of KTX-201 via Immune Directed Mechanisms

STAT3 degradation and anti-tumor activity of KTX-201 monotherapy in A20 lymphoma model



- *In vitro*, STAT3 degradation has no impact on A20 cell proliferation
- However, *in vivo*, KTX-201 monotherapy has anti-tumor response in A20 lymphoma-bearing mice extending survival
- Anti-tumor activity of KTX-201 was diminished in A20 SCID mice



- IHC analyses of A20 tumors show degradation of STAT3 and loss of pSTAT3 following KTX-201 treatment in tumor cells and cells in the TME

Conclusions

Tumor-Cell Intrinsic Effect

- **MOA:** Time course proteomic analysis of ALK+ALCL SU-DHL-1 cells treated with KTX-201 shows that STAT3 degradation promotes early changes in known STAT3-regulated proteins, key signaling nodes involved with proliferation and cytokine stimulation, followed by profound changes in apoptotic proteins.
- **PK/PD:** *In vivo* PK/PD analysis reveals that time over 90% STAT3 degradation in tumor is associated with anti-tumor activity. Consistent with the result from *in vitro* washout experiment, partial coverage (ie 48 hr – 96 hr) of dosing interval is sufficient for efficacy.

Immune-Directed Mechanism

- STAT3 degradation and anti-tumor activity of KTX-201 as monotherapy in A20 lymphoma model suggests underlying immune-directed mechanisms.

THANK YOU