Role of Clinical Studies for Pets with Naturally Occurring Tumors in Translational Cancer Research: *Mechanisms for Comparative Oncology Trials- Single Site Studies*

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Advantages of single site/limited site clinical trial enrollment

1. Significant commitment from primary PI so typically enthusiastic/rapid enrollment
2. Can respond to observations on clinical toxicities and/or observed responses with rapid changes in study protocol
3. Integrity of sample collection and analysis is maintained
4. Can flow from healthy to affected dog at same site; observe toxicities first hand prior to treating affected dogs

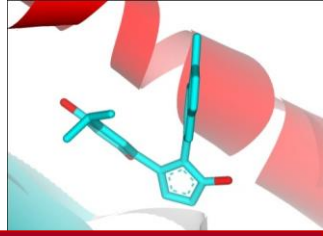
Drawbacks of single site/limited site clinical trials

1. **May not have representative population of patients**
   - **Purported geographic differences in disease biology**
   - **Over-represented breeds in specific geographic locations**
     - **Greyhounds with osteosarcoma at OSU**
2. **Competition for enrollment within single site**
   - **Multiple studies for lymphoma ongoing simultaneously**
3. **Rapid enrollment can occasionally result in toxicities that are overlooked or not noted until a larger sampling of patients are treated**
4. **Generally challenging to enroll large numbers of patients with a specific cancer in a timely manner**
   - **Osteosarcoma, transitional cell carcinoma**

EXAMPLES

1. Ganetespib (HSP90 inhibitor, Synta Pharmaceuticals) pre and post IND
2. KTN0158 (humanized KIT mAb, Kolltan Therapeutics) pre IND
3. LY5 (STAT3 inhibitor, OSU College of Pharmacy) pre IND
4. RV1001 (PI3K inhibitor, Rhizen Pharmaceuticals) post IND
5. KPT335/330 (XPO1 inhibitor, Karyopharm Therapeutics) pre and post IND

Evaluation of HSP90 inhibitor STA-1474 in dogs with cancer



- Ganetespib, (STA-9090, Synta Pharmaceuticals Corp.) is a novel small molecule inhibitor of HSP90 with significant in vitro and in vivo activity at low nM concentrations

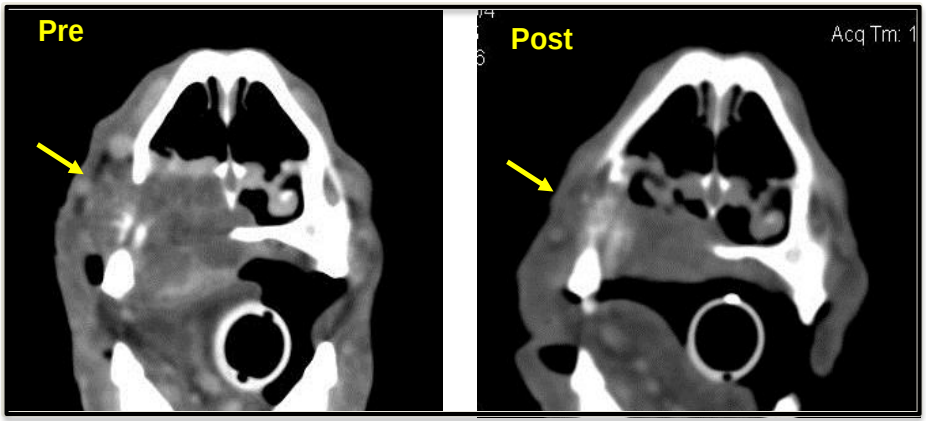
- STA-1474 is the highly soluble prodrug of ganetespib

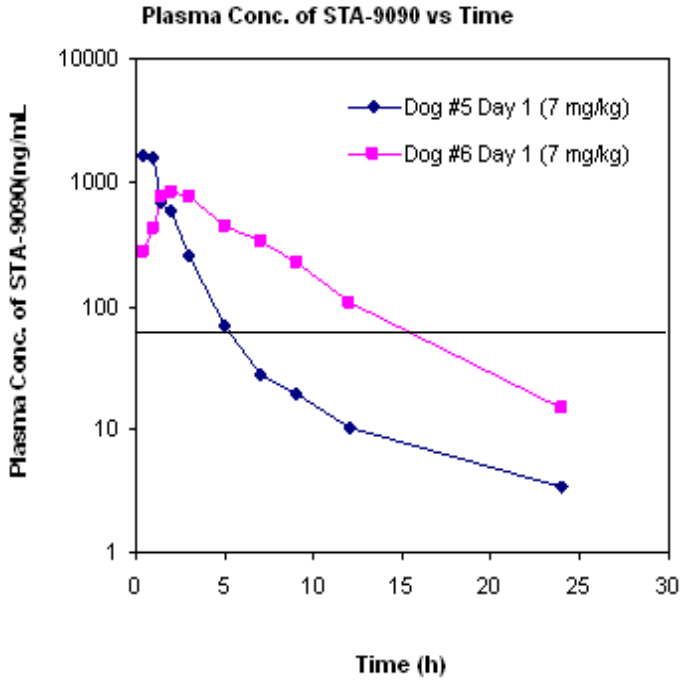
- Phase I study of STA-1474 was performed in dogs with cancer pre-IND submission:
  - Test 2 dosing regimens, full PK in all dogs
    - 1 hr once per week
    - 1 hr twice per week
  - Determine clinical toxicities
  - Establish surrogate biomarkers
  - Provide preliminary evidence of biologic activity

Evaluation of STA-1474 in dogs with cancer: Altered PK associated with objective response

- Only 1/12 dogs in the first treatment group (7-10.25 mg/kg over 1 hr once/wk) experienced an objective response to therapy
- This dog had a drug extravasation that markedly altered the PK of ganetespib

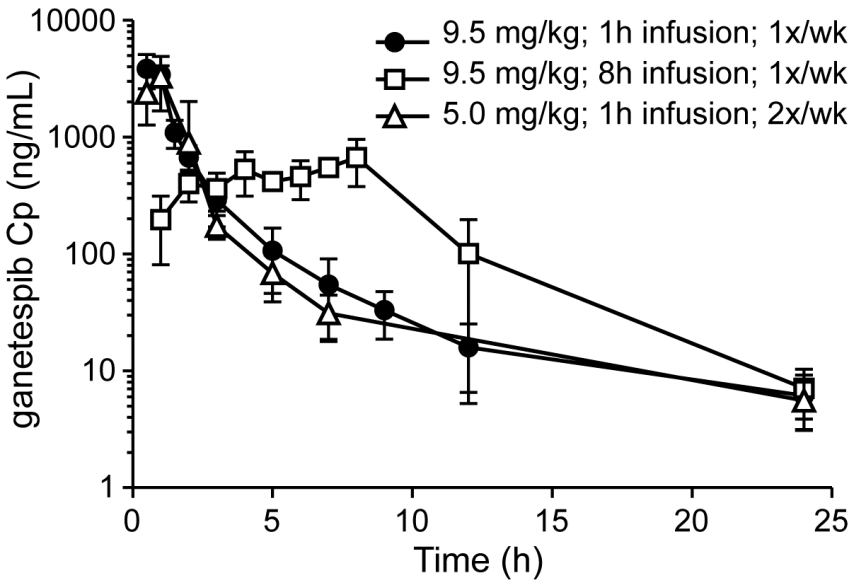
Oral Melanoma





London et al, PLoS 2011

STA-1474/ganetespib PK/PD



Regimen	Dose (mg/kg)	No. of dogs	Response to therapy
1 hr/wk	7.0 9.5 10.25	4 5 3	none 1 PR** none
8hr/wk	9.5	6	2 PR, 1 MR, 2 SD
1hr/2x wk	5.0	7	2 PR

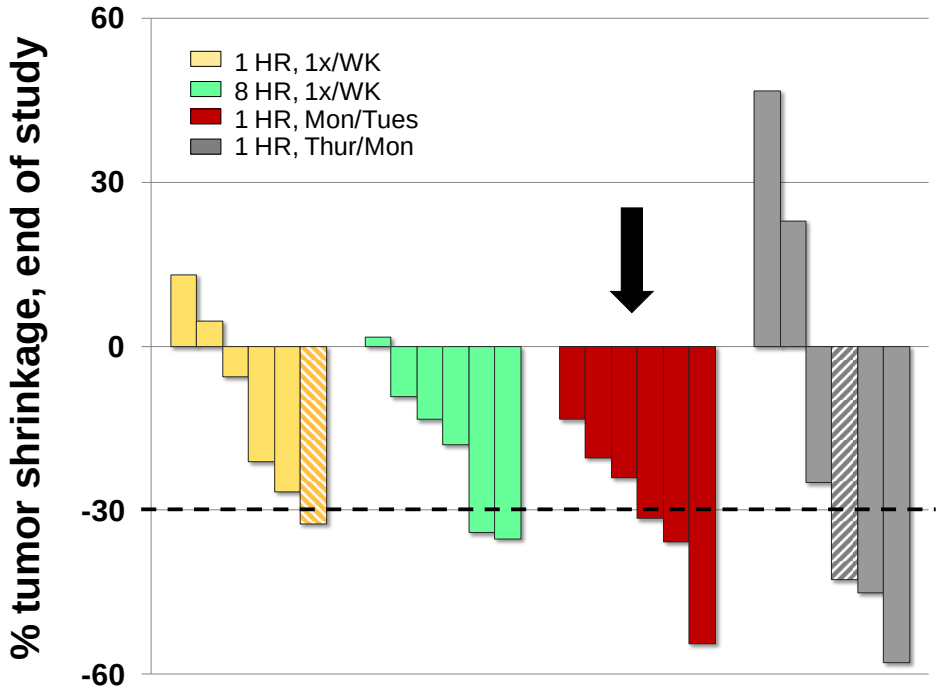
- **Objective responses to therapy were associated with sustained blood levels of ganetespib between 200-600 ng/ml for 8-10 hours**
- **Subsequent murine modeling confirmed that longer drug exposure was associated with more efficient inhibition of HSP90 activity in tumor cells**

London et al, PLoS, 2011

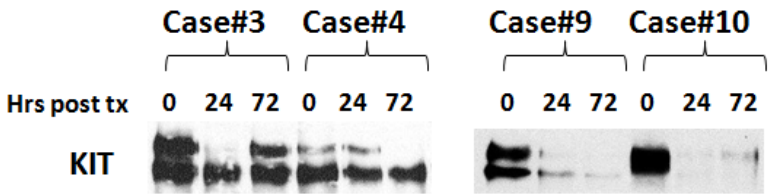
Identification of most effective ganetespib treatment regimen

- While STA-1474 is water soluble, ganetespib requires solvent that limits duration of infusion to 3 hrs duration
- Goal of second study was to identify a dosing regimen that most effectively recapitulates the 8 hr infusion protocol with respect to biologic activity and sustained downregulation of HSP90 client proteins: KIT target modulation in dog mast cell tumors
- Dogs with mast cell tumors received one of 4 dosing regimens with equivalent dose intensity across groups:
  - 6 mg/kg 1 hr once per week
  - 6 mg/kg 8 hr once per week
  - 3 mg/kg 1 hr twice per week: Mon/Tue
  - 3 mg/kg 1 hr twice per week: Thu/Mon
- Biopsies performed at 0, 24, and 72 hr post treatment for assessment of KIT phosphorylation and expression

Waterfall plot of responses



Best change in response at end of study. Diagonal marks denote patients with PD at week 4 due to progression of non-target lesions



6mg/kg over 1hr
once per week

3mg/kg over 1hr
2 days in a row

Lessons from ganetespib studies

- Single site phase 1 study permitted rapid change in dosing regimen
- This resulted in identification of a drug exposure/response relationship
- A subsequent clinical trial involving 4 sites defined a PK/PD relationship in a relevant client protein of HSP90; this facilitated subsequent human clinical trials of ganetespib pre and post IND
- Importantly, while the second clinical trial initially involved 4 sites, only 2/4 enrolled cases; the primary site enrolled the majority (20/24) of the cases

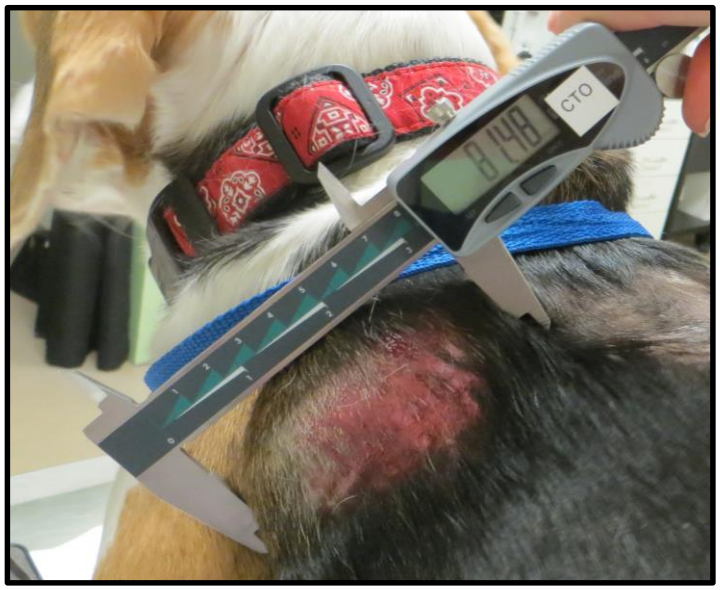
KTN0158: from healthy to affected dogs

- KTN0158 is a humanized monoclonal antibody that binds human and canine KIT, but not rodent KIT
- Preclinical studies performed at OSU in healthy dogs to assess the adverse event profile prior to subsequent phase 1 clinical trial in dogs with mast cell tumors to generate data for IND:
  - same PI for both studies facilitated transition from healthy to affected dogs
- Expected toxicities were observed in dogs with tumors, but additional adverse events were noted resulting in a protocol change

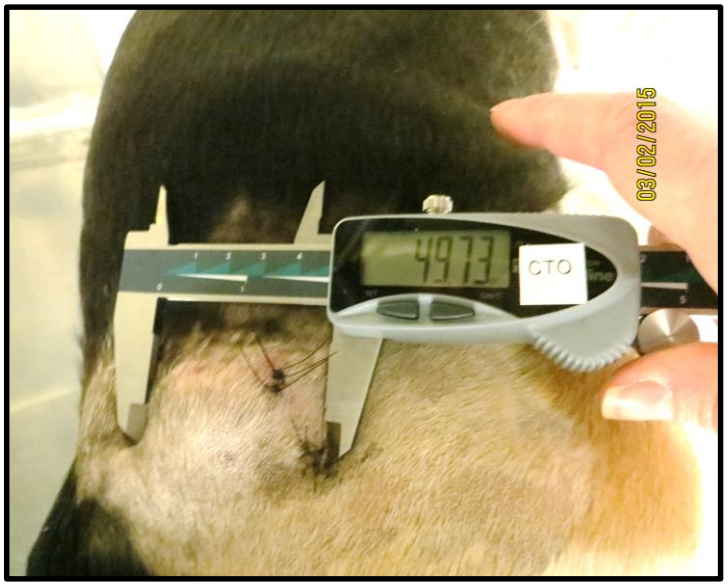
KTN0158: from healthy to affected dogs

- **Objective responses have been observed with a single KTN0158 treatment and there has been unexpected dose dependence**

Pre-treatment



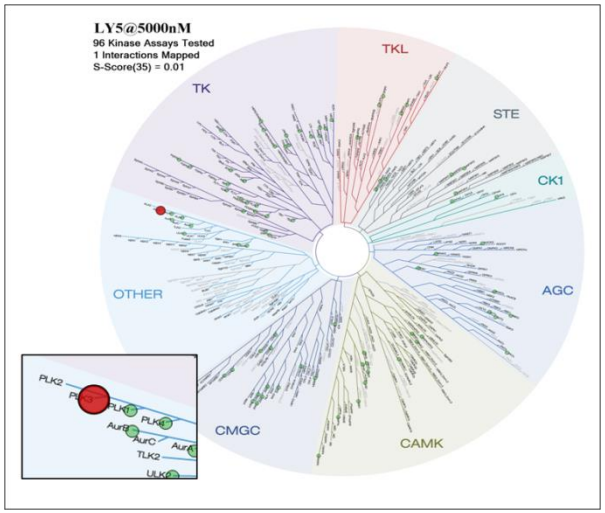
Post-treatment

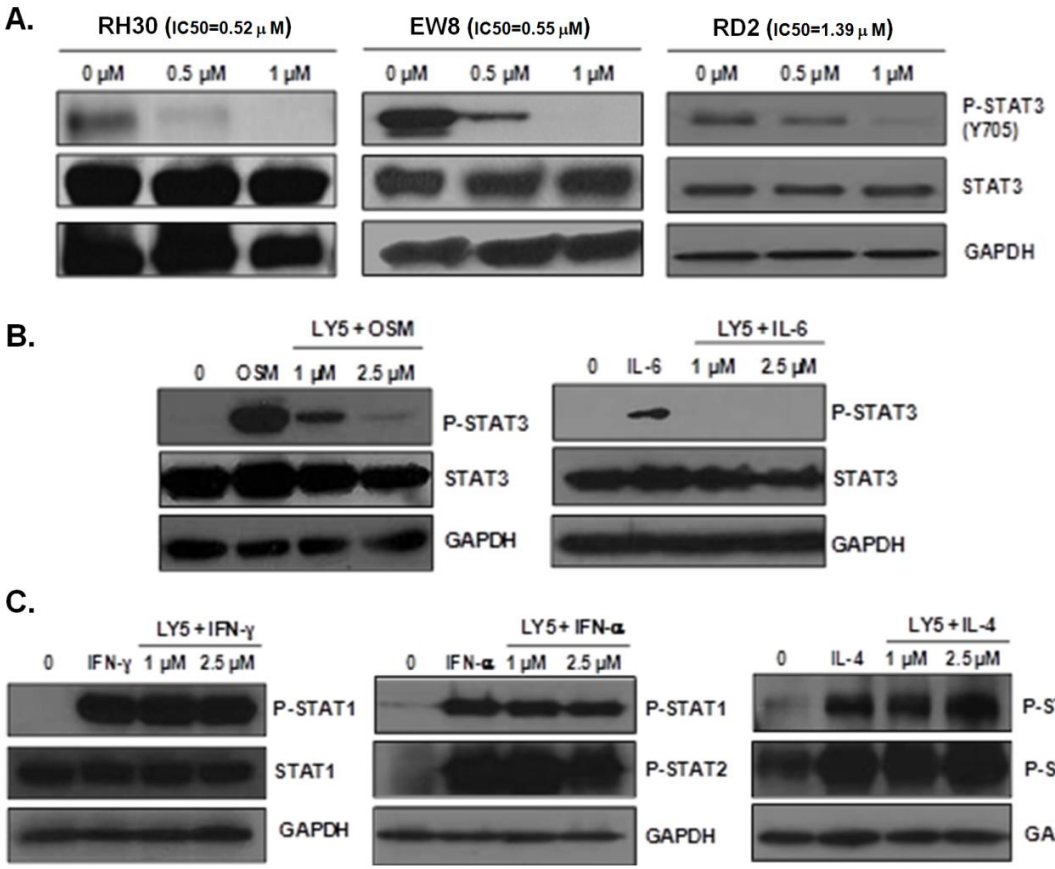


- **This study involved 2 sites (primary site OSU), and again, enrollment was skewed: only 1 of 12 cases was enrolled at the second site**

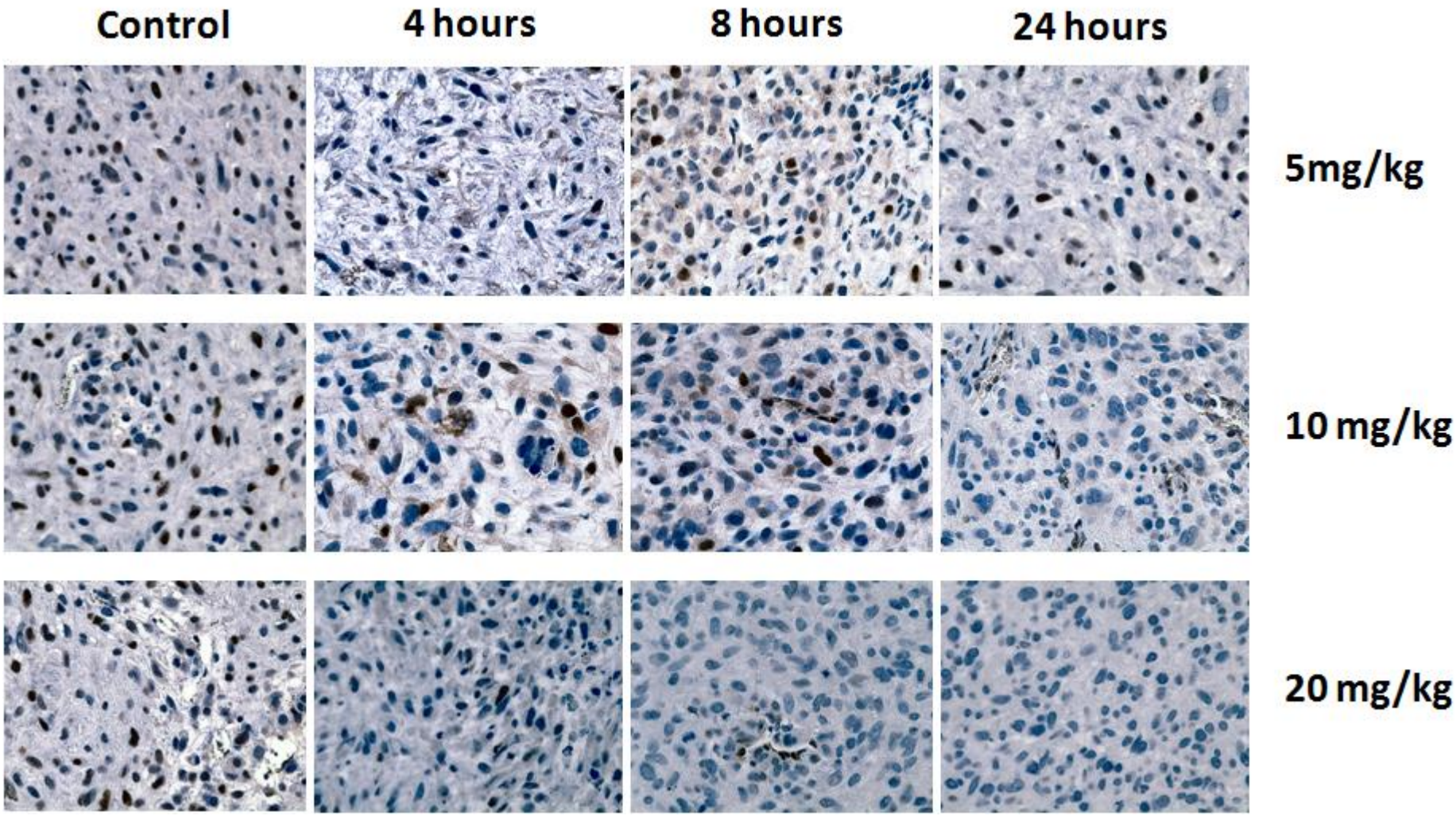
LY5: from healthy to affected dogs

- **LY5 is an allosteric small molecule inhibitor of STAT3 developed at the College of Pharmacy at OSU**





LY5 inhibits STAT3 phosphorylation in human OSA tumor xenografts



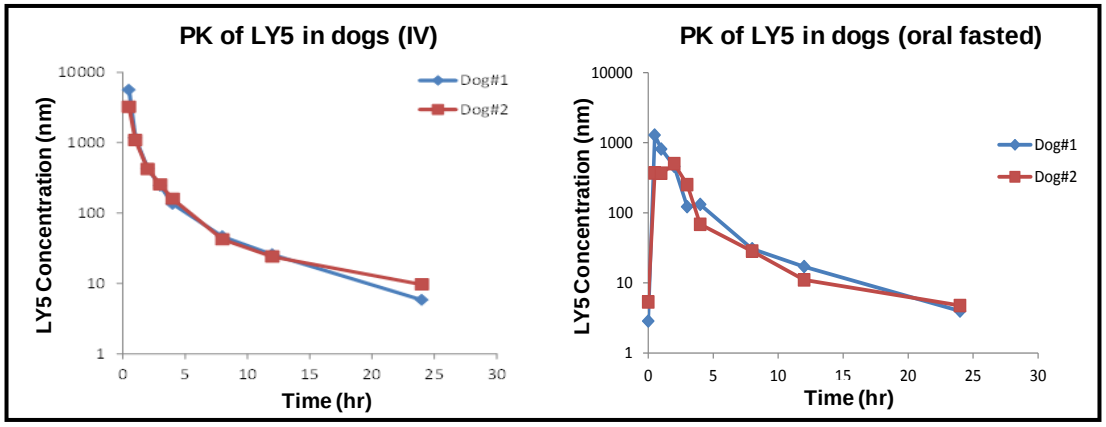
LY5 exhibits good oral bioavailability in dogs

Mouse

PK parameters	IV	IP	PO
Tmax (hr)	0.08	0.08	0.5
Cmax (ng/mL)	547	179	168
AUCall (ng/mL*hr)	374	236	257.9
AUC inf_obs (ng/mL*hr)	376	333	295
F%	100	88.6	78.6

Dog

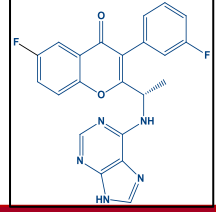
	Dog#1		Dog#2	
Animal ID/Route	IV	PO w/ fast	IV	PO w/ fast
Dosage (mg/kg)	0.97	0.9	0.97	0.9
Cmax (nM)	5586	1284	3222	499.7
AUC_{obs} (nM*hr)	5096	2438	3917	1611
F_{obs}%	100	51.56	100	44.33



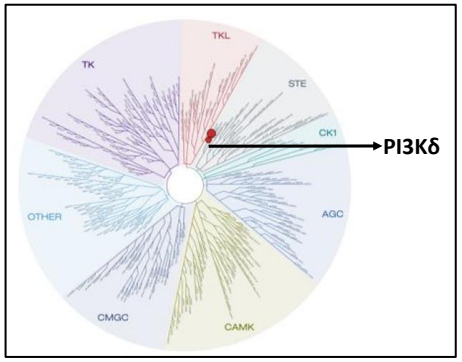
LY5: from healthy to affected dogs

- LY5 has demonstrated activity in mouse models of cancer
- LY5 has good oral bioavailability in dogs
- Future clinical trials in both normal dogs and dogs with cancer/OSA are planned to define:
  - MTD
  - PK/PD relationships
  - Biologic activity
  - Adverse event profile
  - Dosing/regimen
- Single site mouse, healthy dog, and affected dog studies will facilitate drug development and will impact the expected submission of IND

RV1001 Phase 1 clinical trial

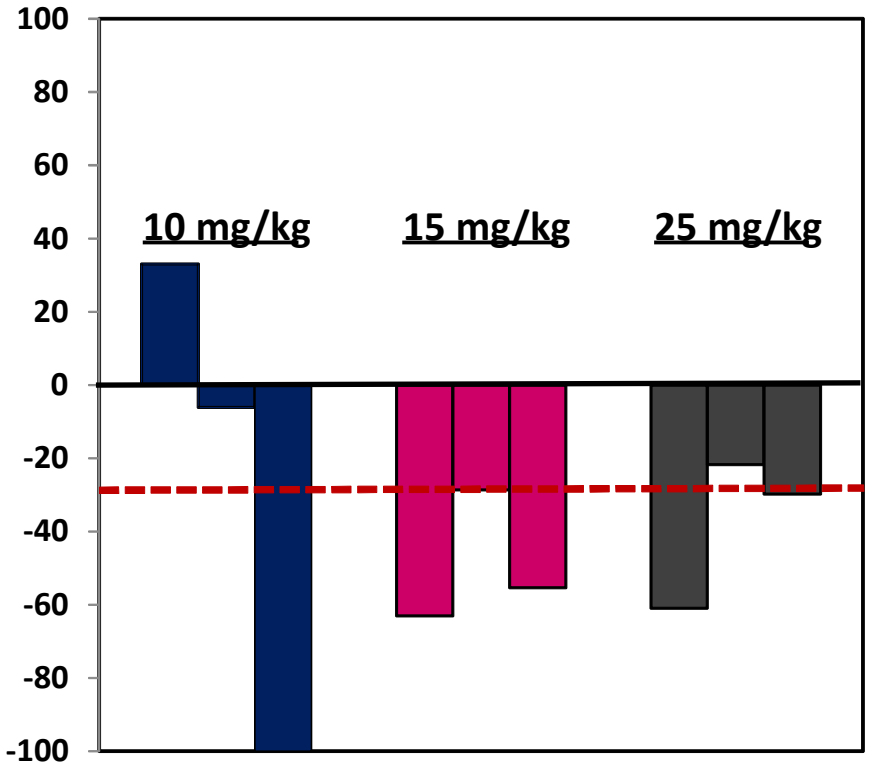


- RV-1001 is an orally bioavailable inhibitor of PI3K family members
- It has a strong binding affinity towards PI3Kδ, binds Val-882
- Highly selective in a 451-kinase panel
  (1 µM, Kinome Scan, USA)



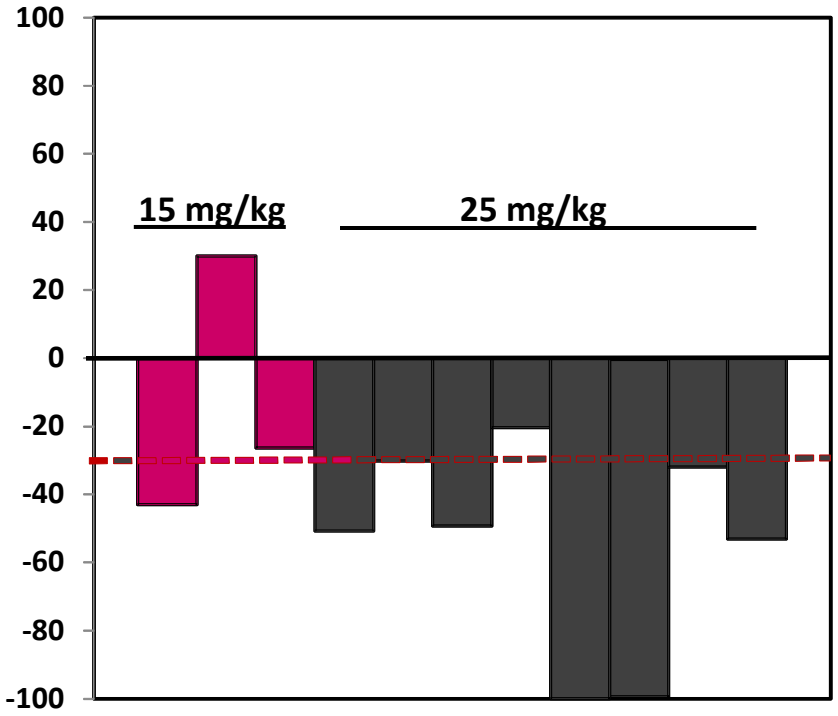
- Phase 1 clinical trial performed in dogs with newly diagnosed and relapsed T or B cell lymphoma:
  - oral dosing once per day, starting at 10 mg/kg

Response to therapy: Daily dosing



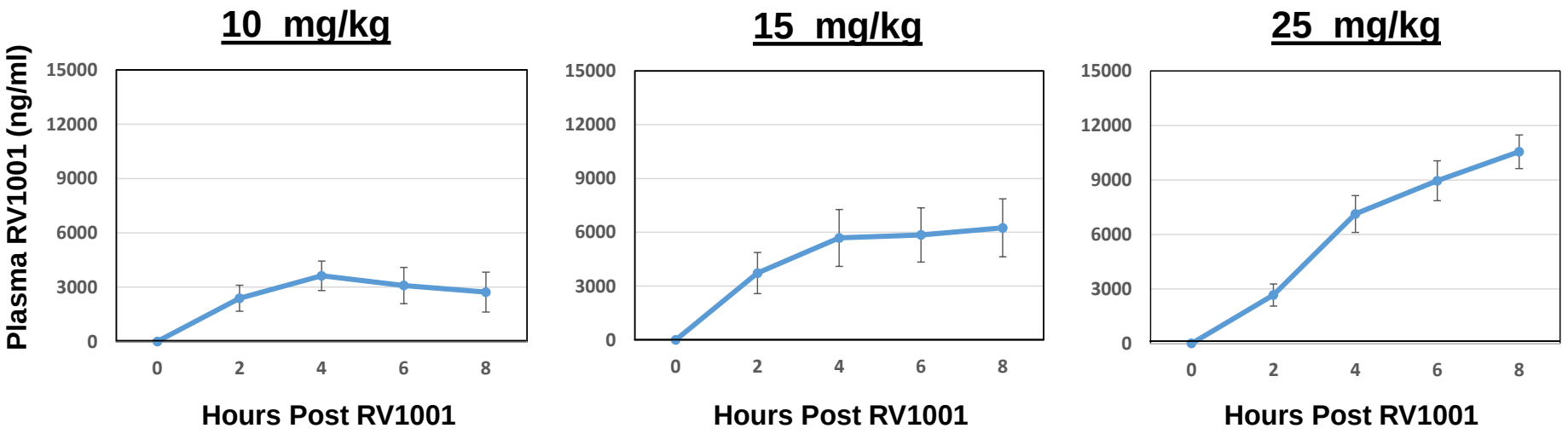
- Enrollment was rapid, with all cohorts having patients enrolled within 4 weeks
- Grade 3 and 4 hepatotoxicity was noted in all dosing groups typically after 1-3 weeks of drug administration
- Interim PK demonstrated association of hepatotoxicity with high trough blood levels of drug (20-30 µM)

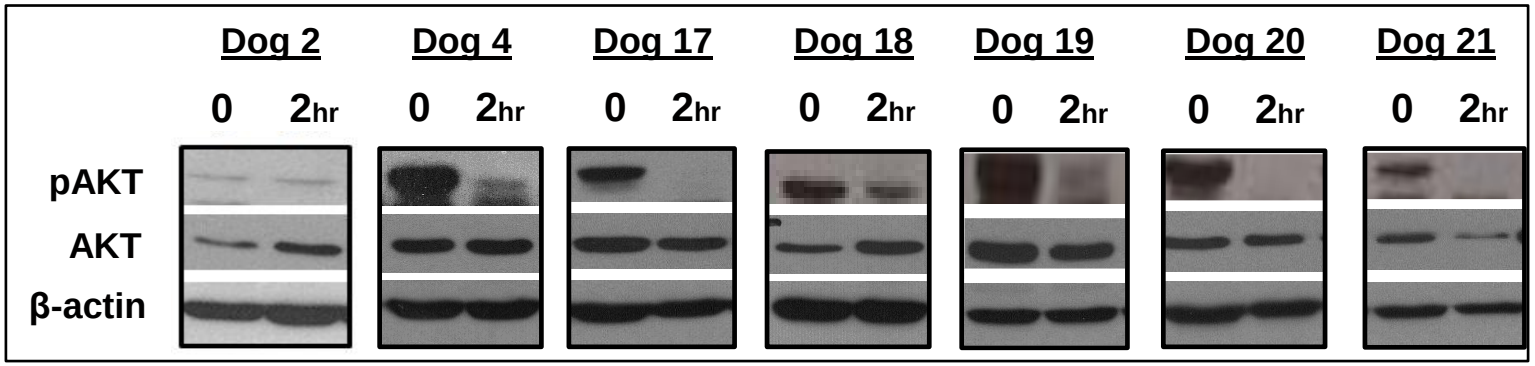
Response to therapy: M-F dosing



- The M-F dosing regimen was well tolerated by nearly all dogs; hepatotoxicity occurred in only two patients
- Response to therapy was noted at both 15 and 25 mg/kg dose levels

Pharmacokinetics and pharmacodynamics of RV1001 in dogs with NHL



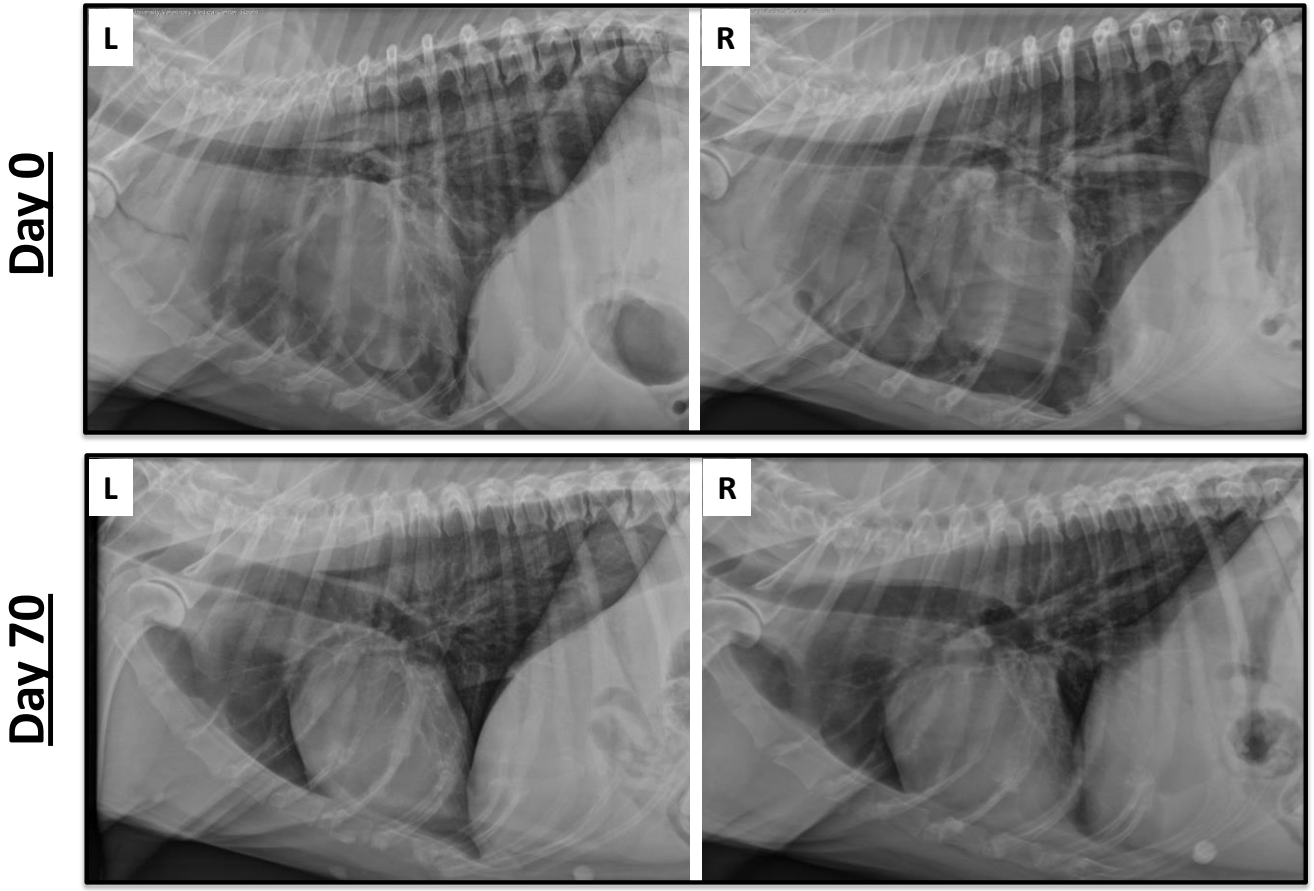


Lessons learned from RV1001 clinical trial

- The rapid enrollment resulted in the occurrence of hepatotoxicity in all dosing groups
- However, a drug exposure/toxicity relationship was identified resulting in a change in dosing regimen that markedly reduced the toxicity while maintaining response to therapy
- Two sites were used for this study and again, the primary site (OSU) enrolled the majority of the cases (17/21)
  - no naive lymphoma cases were enrolled at the second site
  - lack of enthusiasm for not using standard of care treatment up front

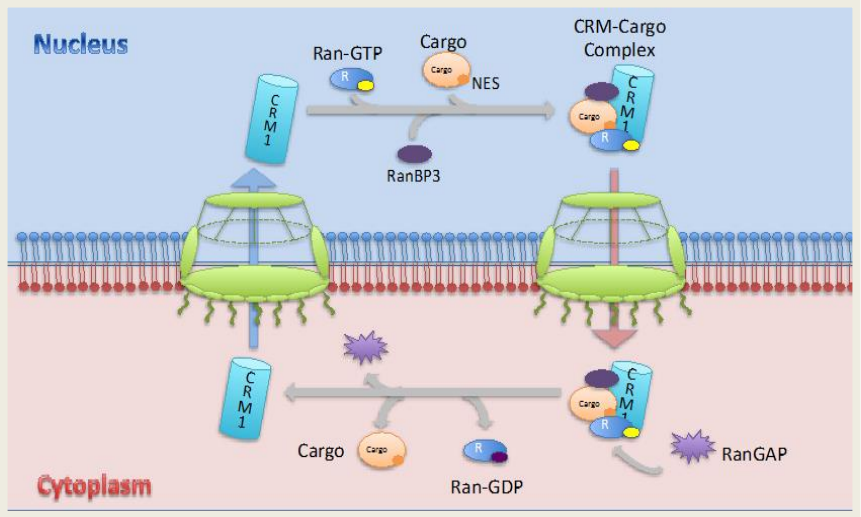
Lessons learned from RV1001 clinical trial

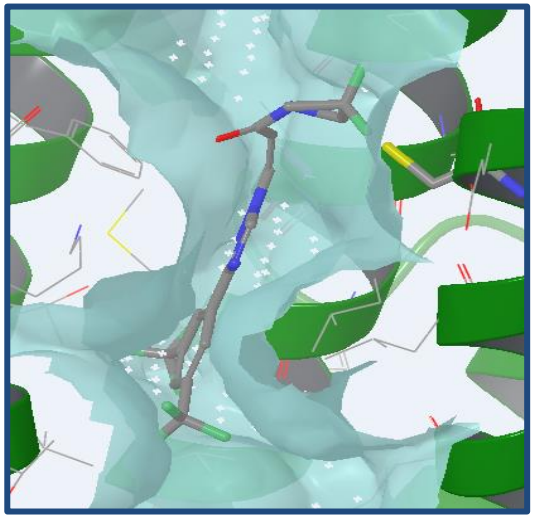
- Planned exceptional responder WGS to identify correlates of response, particularly in T cell lymphoma patients



Evaluation of KPT-335, a novel XPO1 inhibitor, in dogs with lymphoma

- Cancer cells must inactivate their Tumor Suppressor Proteins (TSPs) in order to perpetuate the neoplastic phenotype
- Most TSPs function in the nucleus; nuclear export functionally extinguishes their tumor suppressing activity and XPO1 is the ***exclusive*** nuclear exporter of most TSPs
- XPO1 blockade with KPT330/KPT335 leads to nuclear retention/activation of ***multiple*** TSPs resulting in apoptosis of tumor cells while normal cells undergo cell cycle arrest





Lessons learned from phase 1 and 2 studies with KPT-335

- Clinical trials of KPT-335 were performed in dogs with lymphoma in support of the compound moving forward in people (KPT-330) to assist with identification of adverse event profile and dose/regimen
- The phase 1 study performed at 3 sites initially used MTh dosing schedule but a small number of dogs (n=8) received MWF dosing which was thought to be well tolerated
- The phase 2 study in dogs started with the MWF dosing, that, when expanded to a larger cohort was found to be poorly tolerated, resulting in a regimen change (MTh) during the study
- Subsequent work in people with KPT-330 used canine data to set drug regimen and supportive care protocols to address toxicities

Summary

- **Single site clinical trials in dogs with spontaneous cancer often have several advantages including:**
  - **High commitment from PI resulting in rapid enrollment**
  - **Ability to be flexible in protocol alteration when clinical observations dictate study changes**
- **However, they sometimes introduce biases that can potentially affect study outcomes:**
  - **Inadequate representation of breeds**
  - **Underrepresentation of particular adverse events**
- **For phase 1 single site clinical trials to be effective, support from an organized and well-staffed clinical trials unit is essential**
  - **Manage patient workflow and ensure IACUC and GCP compliance**
  - **Support tissue and blood sampling, which can be quite involved**
  - **Interface with sponsors to provide timely updates/enact protocol changes**

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