Identification of frequent HER2 activating mutations in canine pulmonary adenocarcinoma

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INTRODUCTION

- Naturally occurring primary canine lung cancers are aggressive malignancies that are increasingly common in pet dogs.
- Canine disease course and biology resembles human lung cancer in never-smokers (NS) which causes 26,000 deaths annually.
- In the US, 85% of NS lung cancers are *EGFR* wild-type and commonly have a low mutation burden limiting benefits provided by small molecule inhibitors and immunotherapy.
- Neratinib is a pan-HER tyrosine kinase inhibitor that has been reported to inhibit preclinical cancer models with HER2 mutations.
- A need exists for improved biologic understanding and development of new models to fuel translational research in NS lung cancer.

OBJECTIVES

- Describe the genetic underpinnings of primary canine lung cancers and define translational relevance to human NS lung cancer.
- Determine the sensitivity of canine pulmonary adenocarcinoma cell lines to neratinib.

METHODS

- Multi-platform next generation sequencing was performed on 77-treatment-naïve cases of canine lung cancer with companion normal lung tissue and 11 cell lines.
  - Whole Exome Sequencing (n=5)
  - Custom Canine Cancer Targeted Amplicon Panel (n=83)
- Droplet digital PCR to detect *HER2*^{V659E} mutation in canine plasma.
- CellTiter-Glo® cell viability assay for drug dose-response studies.

RESULTS

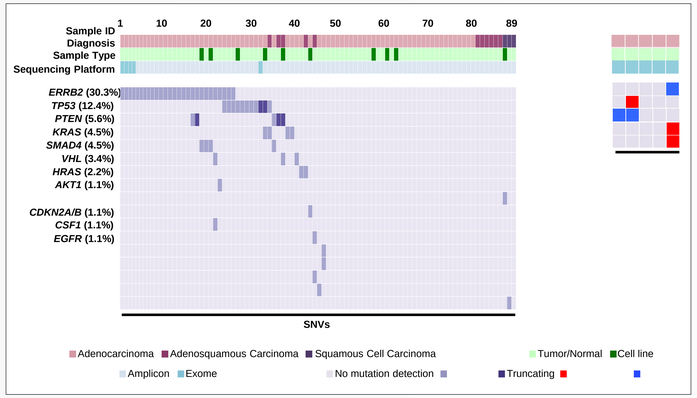

Figure 1. The genomic landscape of primary canine lung cancers.

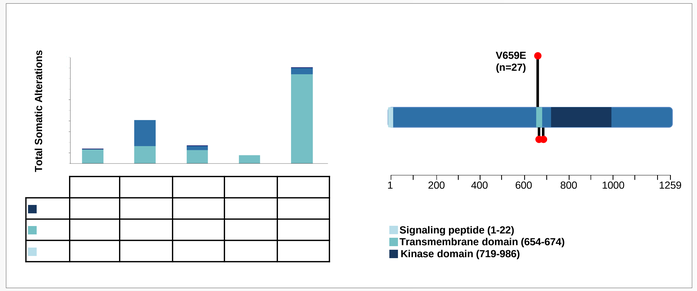

Figure 2. Somatic mutation burden (SNVs, CNVs and SVs) identified by exome sequencing and distribution of somatic *HER2* mutations within the HER2 protein identified in primary canine lung cancers.

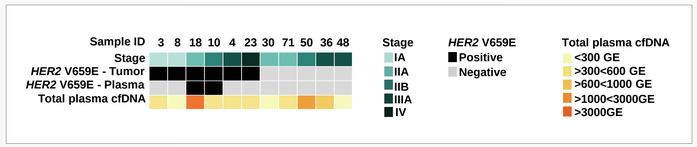

Figure 3. Detection of *HER2* hotspot mutations in plasma from 11 canine primary lung cancer cases.

Figure 4. *HER2*^{V659E} constitutively activates downstream HER2 signaling.

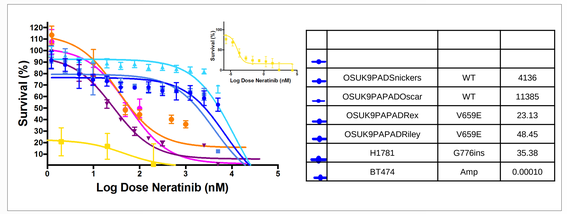

Figure 5. Neratinib drug-dose response studies in primary canine lung cancer and human breast and lung cancer lines.

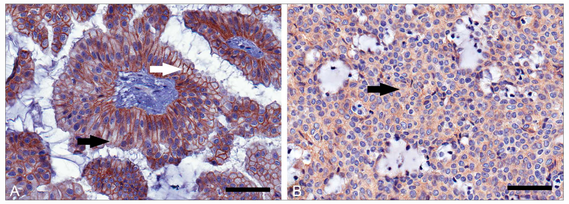

Figure 6. Membranous (A) and cytoplasmic (B) HER2 cellular immunolocalization in primary canine papillary adenocarcinomas. x 40; bar 50 µm.

- Somatic, coding *HER2* point mutations occurred in 30% of canine pulmonary adenocarcinoma.
- *HER2*^{V659E} is an activating mutation in canine pulmonary adenocarcinoma.
- Neratinib can block the activity of this transmembrane domain mutation.

CONCLUSIONS

- Primary canine lung cancers bear a low mutation burden and mimic those seen in human lung cancers.
- Somatic activating *HER2* mutations, including *HER2*^{V659E} transmembrane domain mutation, is frequently (30%) observed in canines with pulmonary adenocarcinoma and can be readily detected in both tumor and blood samples.
- Data offer immediate diagnostic and therapeutic opportunities for dogs with primary lung cancer.
- Clinical trials to evaluate neratinib in dogs with HER2 mutant lung cancer are warranted.

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