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 HER2V659E 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. HER2V659E 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 adenocarcinoma. x 40; bar 50 µm.

Conclusions

- Somatic, coding HER2 point mutations occurred in 30% of canine pulmonary adenocarcinoma.
- HER2V659E is an activating mutation in canine pulmonary adenocarcinoma.
- Neratinib can block the activity of this transmembrane domain mutation.

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