Introduction

• KRAS is the most commonly mutated oncogene in Non-Small Cell Lung Cancer (NSCLC).
• The majority of mutations are located at codon 12 followed by codons 13 and 61 (1,2).
• Newly developed KRAS-G12C and G12D inhibitors have highlighted the need to investigate the unique molecular and functional mechanisms of individual allelic subtypes.

Methods

• We developed a doxycycline inducible panel of isogenic cell lines (MEL-12: alveolar type II cells) expressing flag tagged KRAS.
• Cells were characterised in 3D using proliferation, viability, transformation and signalling assays.
• A panel of “RASless” mouse embryonic fibroblasts (MEFs) expressing KRAS WT, G12C, G12D and G13D were also evaluated.
• For clinical validation, we developed a Trans-Atlantic clinical database (RAS-PM).

Conclusions and future directions

• Our findings highlight molecular and functional differences across the panel of KRAS mutations evaluated demonstrating differences in proliferation, viability and signalling.
• These preclinical results indicate unique therapeutic vulnerabilities across allelic subgroups.
• RNA-sequencing and kinome profiling will allow us to further characterise these mutations in NSCLC.

References