**INTRODUCTION AND OBJECTIVES**

**Background**

Lung cancer remains the deadliest malignancy worldwide. Inhibitor of differentiation-1 gene (ID1), is a dominant negative transcription factor that regulates the ID gene family, since it associates with other members of class I and class II Ids, directly blocking the transcription by sequestration. ID1 is marked in the regulation of proliferation, invasion, migration, metastasis, angiogenesis and immune response.

Previously, we have found that Id1 expression inversely correlates with the mRNA expression levels of several markers related to immune response. Suppression of Id1 promotes PD-L1 expression on the tumor cell surface irrespective of KRAS status. Furthermore, we reported the efficacy of a combined blockade of PD-1 and MEK in a lung cancer mouse model, through infiltration of CDD-1 T cells.

**Objectives**

- Evaluate the effect of trametinib in the pharmacological downregulation of ID1 in different KRAS-mutant LUAD
- Investigate the proximal and functional role of ID1 in the acquired resistance to trametinib and sensitizing KRAS-driven LUAD tumors to anti-PD-1/PD-L1

**MATERIAL AND METHODS**

**In vitro**

- **Trametinib effect on Id1 levels in vivo**
- **Trametinib and anti-PD-1 synergy**

**In vivo**

- **Trametinib mustard LUAD cells**
- **Anti-tumor effect in KRAS-mutant tumors**

**RESULTS AND DISCUSSION**

**I. Trametinib reduced Id1 expression in vitro and in vivo, through proteasome activation**

- **Trametinib reduces Id1 levels in vitro and in vivo in KRAS-mutant LUAD cells, through post-transcriptional downregulation of Id1** protein via proteasome. Additionally, both trametinib and MEK downregulation impairs lung cancer tumor growth.

**II. Id1 is associated with the trametinib acquired resistance in KRAS-mutant LUAD cells**

- **Trametinib sensitizes KRAS-mutant LUAD tumors to anti-PD-1 immunotherapy, via Id1 downregulation**

**CONCLUSIONS**

- **Graphical summary**

- **This study supports the potential role of trametinib as a novel therapeutic strategy to pharmacologically downregulate ID1 levels in KRAS-mutant LUAD tumors.**
- **We demonstrate the role of Id1 as a novel target to restore the sensitivity to MEK inhibitors.**
- **We provide here praxical evidence on how trametinib sensitizes KRAS-driven lung tumors to anti-PD-1/PD-L1 axis-based therapies.**

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**2324P: Trametinib PLUS Anti-PD-1 Immunotherapy Impairs Tumor Growth and Increases Survival of Lung Cancer through Id1 Downregulation**

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