**INTRODUCTION**

ICIs are monoclonal antibodies that neutralise inhibitory CTLA-4 and PD-1 signalling pathways and thus boosting cytotoxic T-cell antitumor activity.

- ICIs have already transformed clinical guidelines for NSCLC, renal cell carcinoma, metastatic melanoma, hepatocellular carcinoma
- At least 50% of treated patients develop immune-related adverse events with NO risk factors/mecanisms known to date
- PD-L1 expression, BMI, and lncRNA are associated with ICI efficacy, albeit with NO established mechanisms

**Datasets of interest:**

- GSE79691 (metastatic melanoma) and GSE67501 (renal cell carcinoma)
- Treatment with Nivolumab
- RNA was obtained from FFPE samples
- Mir-27B (p=0.02) and mir-miR-let7D (p=0.003) were significantly higher among non-responders
- SMD was 4.57 (Mir-27B) and 3.9 (miR-let7D) higher among non-responders
- Low study heterogeneity scores: I²=22.67% and T²=0.36

Does ncRNA affect the response rate to immune-checkpoint inhibitors?

**RESULTS**

**Control datasets:**

- GSE99898 (metastatic melanoma) and GSE74174 (renal cell carcinoma)
- Treatment with kinase inhibitors
- RNA was obtained from FFPE samples
- Expression of mir-27B (p=0.928) and mir-let7D (p=0.41) was not significantly different among responders and non-responders

Mechanisms (DAVID online tool):

- Both miRNAs may regulate pro-cachexia cytokines (IL-1, IL-6, TNF-α) and PI3K/Akt and NF-kB signalling pathways

- Said cytokines may stimulate FcR-mediated clearance of immunoglobulins
- Cachexia itself may promote the destruction of circulating proteins, particularly ICIs

**CONCLUSIONS**

- Mir-27B and mir-let7D are significantly higher among non-responders to ICI therapy, supporting their possible predictive role
- There is NO difference in expression of said miRNAs among responders and non-responders treated with non-ICI therapeutic regimens
- Both miRNAs can interfere with different signalling pathways (PI3K/Akt, NF-kB) and regulate cachexia

**PERSPECTIVES**

**Fast facts:**

- Risk factors of immune-checkpoint inhibitors mediated liver, endocrine, and gastrointestinal toxicity

**ICEMELT study**

Design: Multicenter prospective cohort study

Location: Sydney, New South Wales, Australia

Results: Preliminary results are anticipated by March 2022

Research aims:

- To identify ncRNAs significantly associated with ICIs
- To achieve pathways/mechanisms of such association
- To establish therapeutic targets interfering with found mechanisms, thus enhancing clinical outcomes of cancer immunotherapy

Abbreviations: ICIs - immune-checkpoint inhibitors; FDA - Food and Drug Administration; n-cRNa - non-coding RNA; miR - miRNA; IncRNA - long non-coding RNA; SMD - standardized mean difference; BMI - body mass index; tRNa - transfer RNA; ceRNA - ceRNA; miR-let7D - microRNA-let-7D; FFPE - formalin-fixed paraffin-embedded

NO CONFLICTS OF INTEREST TO DECLARE