177 EXPLORING THE RELATIONSHIP BETWEEN TUMOUR HETEROGENEITY AND RESPONSE TO IMMUNOTHERAPY IN MALIGNANT PLEURAL MESOTHELIOMA

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Background Malignant pleural mesothelioma (MPM) is a rare and aggressive cancer with low survival probability. Using a combination of immune-checkpoint inhibitors (ICIs) Ipilimumab (IPI) + Nivolumab (NIVO) as a first line treatment for unresectable MPM, the CheckMate 743 trial reported higher overall survival. However, there was high occurrence of immune-related adverse events (irAEs). The unpredictable nature and severity of irAEs highlight the urgent need to conduct comprehensive translational studies to elucidate the role of tumour microenvironment in outcomes of ICI therapy.

Methods This pilot analysis was conducted as part of NCT04631731 prospective study. To conduct in-depth characterisation of MPM tissue we utilised Visium (10x Genomics) spatial transcriptomic assay and Sentis+ mutational panel (BGI Genomics) on FFPE cancer tissues from four males with metastatic MPM treated with IPI (1 mg/kg Q6W) + NIVO (3 mg/kg Q2W).

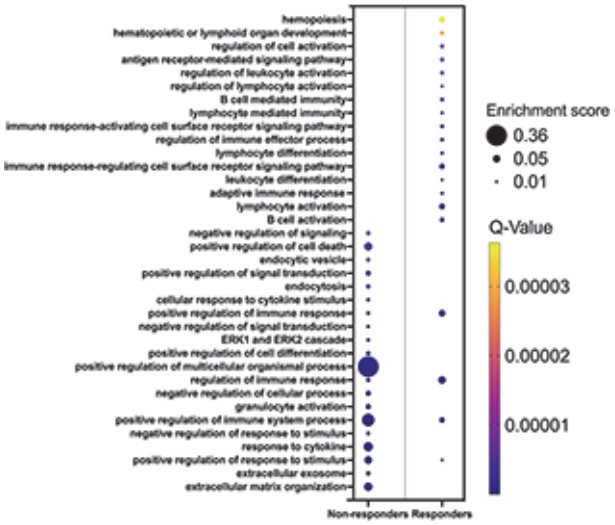
Results To determine the location of tumour-infiltrating T cells within Visium spatially profiled FFPE tissues we utilized an *ImSig*package in R as we have shown before. Tissues A1 and C1 possessed a greater number of spatial spots assigned to T cells as compared to non-responders: n=250 and n=137 respectively. The percentage of tumour spots directly surrounded by T cells was A1=3.8%, B1=0.61%, C1=4.75%, D1=6.76% with no significant difference between responders and non-responders (p=0.85). We next conducted a differential gene expression analysis that identified n=122 dysregulated genes in tumour-infiltrating T cells (n=70 and n=52 significantly upregulated in non-responders and responders respectively). Annotation of gene sets based on response status identified different biological processes that have the potential to contribute to therapy response (figure 1). In addition, we selectively examined the expression of immune-checkpoint inhibitor genes. Interestingly, no differences in cancer or T cells were identified. Further analysis revealed significant differences in expression of *HAVCR2* in infiltrating macrophages. Specifically, the expression of *HAVCR2* was higher in non-responders. Finally, we aimed to determine a tissue mutational landscape using the SENTIS+ panel. Our analysis established that gene *PTCH1* was exclusively mutated (deletion of triplet GCC on 9q22.32) in tumour tissues of non-responders.

Conclusions This pilot analysis provides valuable insights into the tumour-based molecular signatures associated with the response to IPI + NIVO therapy in MPM patients. The ongoing recruitment in NCT04631731 holds promise for successful validation of preliminary data thus providing new perspectives on establishing risk factors of ICI therapy in near future.

Trial Registration NCT04631731

Ethics Approval Research sample collection and analysis was conducted as part of the NCT04631731 study (ICEMELT), which has been approved by the Western Sydney Local Health District (WSLHD) Human Research Ethics Committee (Ethics reference number: 2020/ETH02285).

Consent Written informed consent was obtained from each patient recruited to NCT04631731 study. A copy of the written consent is available for review upon the request to a corresponding author.



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