AB073. SOH24AB_228. Immunomodulatory effect of epigenetic modification on T cell phenotype and checkpoint receptor expression in oesophageal adenocarcinoma

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Background: Histone deacetylase inhibitors (HDACi) are immunotherapy agents demonstrating efficacy in malignancies such as T-cell lymphoma and Multiple Myeloma. This study aims to characterise the effects of HDACi on T-cell phenotype and function, both in health and in oesophageal adenocarcinoma (OAC), and identify opportunities for synergism with immune checkpoint inhibitors (ICIs).

Methods: Through *ex-vivo* models, activated T-cells isolated from healthy donors and OAC patients, were treated with four HDACi (panobinostat, romidepsin, tubacin & PCI-34051). T-cell activation, immune checkpoint receptor expression and cytokine production were assessed by flow cytometry, under normal conditions and those of the microenvironment (glucose deprivation, glutamine deprivation and hypoxia).

Results: HDACi did not affect activation of T-cells. Under normal conditions in both healthy and OAC T-cells, reductions in PD-1, LAG-3 and TIGIT were noted for all HDACi. Romidepsin significantly reduced TIGIT expression on helper CD4+ T-cells in OAC samples ($P<0.01$). Tumour microenvironment conditions further enhanced these effects, notably hypoxia. Significant reductions in PD-1, LAG-3 and TIGIT were noted in deprivation states in T-cells treated with panobinostat ($P<0.05$), romidepsin ($P<0.05$) and tubacin ($P<0.05$), while PCI-34051 displayed significant reductions of LAG-3 only ($P<0.05$). OAC samples demonstrated significantly reduced PD-1 expression at baseline on helper CD4+ T-cells, and significant increases in LAG-3 and TIGIT expression on cytotoxic CD8+ T-cells compared to healthy donors ($P<0.05$).

Conclusions: OAC donor T-cells displayed significant differences in checkpoint expression compared to healthy donors. PCI-34051 maintained checkpoint expression in both healthy and OAC T-cells which could be crucial to understanding the potential of combinational therapeutic strategies with ICIs and epidrugs.

Keywords: Oesophageal cancer; immunotherapy; histone deacetylase inhibitors (HDACi); tumour microenvironment; immune checkpoint inhibitors (ICIs)

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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