

AB053. SOH21AS146. Cooperation between chemotherapy and immunotherapy to enhance anti-tumour T-cell mediated immunity in oesophageal adenocarcinoma: implications for synergistic combination regimens

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Background: Combining immunostimulatory chemotherapies with immune checkpoint inhibitors (ICIs) to stimulate anti-tumour immunity and prevent immune-exhaustion is an attractive approach to improve outcomes in oesophageal adenocarcinoma (OAC), in particular those with 'cold and immune-excluded' tumours.

Methods: Immune checkpoint (IC) expression was profiled on circulating and tumour-infiltrating T-cells perioperatively and correlated with clinical outcomes (n=16). Immunostimulatory and immunoinhibitory effects of chemotherapy regimens (FLOT, CROSS, MAGIC) on T-cells was investigated following 48 h-treatment, via assessment of T-cell activation markers (CD69, ICOS), inhibitory ICs (PD-1, TIGIT, TIM-3, CTLA-4, LAG-3, KLRG-1, PD-L1, PD-L2), T-cell cytokine profiles (TH1-IL-12, IFN- γ , TNF- α , TH2-IL-4, TH17-IL-17A and Treg-IL-10) and T-cell subsets (naïve, effector

and central memory) with/without nivolumab and atezolizumab. The effect of chemotherapy regimens on immunogenic cell death (ICD) in OAC cells was also assessed by flow cytometry (calreticulin, HMGB1, MIC-AB, HLA-DR).

Results: ICs were increased on tumour-infiltrating T-cells compared with peripheral T-cells. Pre-treatment, ICs correlated with worse treatment response and advanced tumours (P<0.05). Paradoxically, post-treatment ICs correlated with better treatment response (P<0.05). FLOT and CROSS increased OAC T-cell activation markers (CD69, ICOS), TH1 and TH17 profiles and also increased several ICs. FLOT and CROSS enhanced anti-tumour cytokine production more substantially in healthy donor T-cells versus OAC T-cells. The frequency of effector memory T-cells was increased by FLOT and CROSS and addition of nivolumab/atezolizumab promoted terminal differentiation. FLOT and CROSS induced ICD compared with MAGIC in OAC cells.

Conclusions: A link between chemotherapy and immune-resistance is highlighted. ICIs may enhance the efficacy of immunostimulatory chemotherapies in OAC patients boosting response rates. As FLOT and CROSS induced ICD in OAC cells these regimens may synergise with ICIs in patients.

Keywords: Chemotherapy; immune checkpoints; immunogenic cell death (ICD); immunostimulatory; oesophageal adenocarcinoma (OAC)

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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