Background

V-domain Ig suppressor of T cell activation (VISTA), is a type I transmembrane protein that functions as an immune checkpoint. VISTA can be expressed as a wide range of cell types. Malignant pleural mesothelioma (MPM) is a tumor with high expression of VISTA (PMID: 30322867). However, it remains unclear if VISTA could be a predictive or prognostic marker in patients with MPM following PD-1 blockade.

Methods

The phase III PROMISE-meso study randomized 144 patients with MPM to either chemotherapy (vinorelbine or gemcitabine) or pembrolizumab. We analysed the tumor from 62 patients from the pembrolizumab arm and 57 patients from the chemotherapy arm (Figure 1), with available tissue. We performed multiplex IHC for the following markers: cell types: c-aretin or WT1, CD8, CD14, CD66b, CD11c, VISTA, and DAPI (Figure 2).

Results

Figure 3. Most of the VISTA expression originated from the mesothelioma cells

- A) VISTA expression in cell types according to location; B) VISTA expression in tumor-infiltrating cells; C) VISTA expression in the function of total VISTA in tumors; D) Frequency of VISTA+ cells with cell types; E) correlation of total VISTA expression and cell types

Figure 4. Lack of correlation between best objective response (BOR) and VISTA expression in

- A) overall tumors B) cancer cells C) CD8 T cells D) CD11c dendritic cells E) CD14+ monocytess

Figure 5. VISTA expressing neutrophils but not total neutrophils predict response and PFS but not OS median value of > 1.0/cm2 was used as threshold for the VISTA+/CD66b+. A significant interaction of VISTA+/CD66b+ with treatment for PFS (p=0.0051) was detected. B) BOR versus neutrophil count; C) VISTA expressing neutrophils versus PFS in pembrolizumab arm; D) VISTA expressing neutrophils versus PFS in chemo arm; E) Neutrophils versus PFS in pembrolizumab arm; F) VISTA expressing neutrophils versus OS in pembrolizumab arm; G) VISTA expressing neutrophils versus OS in chemo arm

Figure 6. VISTA is expressed in a subset of neutrophils

Acknowledgment & Contact: The ETOP-IBCSG Partners Foundation and co-institutionalized with the Spanish Lung Cancer Group (SOCLC) and the Swiss Group for Clinical Cancer Research (SAKK) with financial support of Merck Sharp & Dohme and the Swiss National Accident Insurance Fund (SVA). This translational lab project was sponsored and coordinated by the ETOP-IBCSG Partners Foundation. Conflict: Financial: VHS for permission to report the research findings. This reclassification of VISTA+ neutrophils might be a viable therapeutic option in a subset of MPM patients.

Conclusions

1. Although most VISTA expression was detected on cancer cells, no correlation was identified with clinical outcomes.
2. VISTA expressing neutrophils but not total neutrophil counts negatively correlate with PFS for PD1-blockade but not for chemotherapy.
3. Our data support the complex biology of VISTA and suggest that specific targeting of a subset of VISTA+ neutrophils might be a viable therapeutic option in a subset of MPM patients.

Disclosure: K.Homicko receives research funding from Roche/Geneva, Merck, Pantera SA.

Figure 2. Example of a sample and markers

Presented at the ESMO Immuno-Oncology Annual Congress, Geneva, Switzerland, 7-9 December 2022