1107 ANTI-HVEM MAB THERAPY IMPROVES ANTITUMORAL IMMUNITY BOTH *IN VITRO* AND IN A NOVEL MICE MODEL EXPRESSING HUMAN HVEM AND BTLA MOLECULES USING HVEM EXPRESSING TUMORS

[1]Demerle Clemence, [1]Laurent Gorvel, [2]Marielle Mello, [3]Sonia Pastor, [3]Clara Degos, [2]Ana Zarubica, [2]Frederic Fiore, [3]Geoffrey Guittard, [4]Bernard Malissen, [2]Herve Luche, [5]Jacques Fieschi-Meric, [6]Laurent Greillier, [7]Fabrice Barslesi, [1]Daniel Olive*. [1]*Institute Paoli Calmettes, Marseille, France*; [2]*CiPHE, Marseille, France*; [3]*Cancer Research Center Marseille, Marseille, France*; [4]*Centre d'Immunologie de Marseille-Luminy, Marseille, France*; [5]*Veracyte, Marseille, France*; [6]*Assistance Publique- Hopitaux Universitaires de Marseille, Marseille, France*; [7]*Gustave Roussy, Paris, France*

Background TNFRSF-14/HVEM is a molecule that is the ligand for BTLA and CD160 immune co-inhibitory molecules as well as viral proteins. Its expression is dysregulated with an overexpression in tumors and a connection with tumors of adverse prognosis

Methods We developed models expressing huBTLA and huHVEM in C57/bl6 mice as well as mAbs that completely prevent the interactions of HVEM with its ligands. We also generated mutants of HVEM devoid of the binding sites for BTLA and CD160 binding

Results Here, we show that anti-HVEM18-10 increases primary human alpha beta T cells activity alone (Cis-activity) or in presence of HVEM expressing lung or colorectal cancer cells in vitro (Trans-activity). HVEM18-10 synergizes with anti-PDL1 antibody to activate T cells in presence of $HVEM^{+}PDL\text{-}1^{+}$tumors, but is sufficient to trigger T cell activation in presence of $PD\text{-}L1^{-}$cells. In order to better understand HVEM18-10 effect in vivo and especially CIS and TRANS effects, we developed cutting edge Human BTLA expressing mouse model (BTLA hu KI) and a mouse model expressing both human BTLA and human HVEM ($BTLA^{huKI}$/$HVEM^{huKI}$or DKI). *In vivo*pre-clinical experiments performed in both mouse models showed that HVEM18-10 treatment was efficient to decrease human $HVEM^{+}$ tumor growth. This effect was more pronounced in DKI mice and linked to an increase in $CD8^{+}$cytotoxic T cells tumor infiltration. Interestingly, in both settings, tumor free mice appeared (± 20%) and did not develop tumors upon re-challenge, therefore showing a marked T cell memory effect.

Conclusions Altogether, our preclinical models validate anti-HVEM18-10 as a promising antibody to use in clinics alone or in combination with existing therapies such as anti-PD-L1.

Trial Registration The study presented here is part of the clinical trial PIONeeR BioMarqueurs registered under the number NCT03493581 and part of the RHU PIONeeR ANR-17-RHUS-0007.

Ethics Approval Animal housing and experimental procedures have been conducted according to the French and European Regulations (Parlement Européen et du Conseil du 22 Septembre 2010. Décret n°2013-118 du 1er Février 2013 relatif à la protection des animaux utilisés à des fins scientifiques). All animal procedures (including surgery, anesthesia and euthanasia as applicable) used in the current study have been submitted to the Institutional Animal Care and Use Committee of CIPHE approved by French authorities (CETEA DSV -APA-FIS#6151- 201607202339418-V5).

http://dx.doi.org/10.1136/jitc-2022-SITC2022.1107