Combination of monalizumab and durvalumab as a potent immunotherapy treatment for human solid cancers

Caroline Soulas1, Romain Remark1, Julie Lopez1, Elodie Bonnet1, Flavien Carاغuel1, Ana Lalanne2, Caroline Hoffmann2, Caroline Denis3, Thomas Arnoux1, Clarisse Caïlet1, Fabien Chanuc1, Arnaud Dujardin1, Guillaume Hab1, Olivier Lant2, Cécile Bonnafous3, Eric Vivier1, Pascale André1

1 Institut de Pharma, Marinsa, France; 2 Institut Curie, Paris, France; 3 Centre d'Immunologie de Marseille Luminy, Marseille, France.

**Background**

Monalizumab (PFY0121) is a first-in-class humanized IgG2, targeting NKG2A (Natural Killer Group 2A), which is expressed as a heterodimer with CD94 on subsets of NK cells, γδ T cells and tumor infiltrating CD8 T cells. This inhibitory receptor binds to HLA-E, (Human Leukocyte Antigene), in humans and to Qa-1 in mice. HLA-E is upregulated on cancer cells of several solid tumors, providing a negative regulatory signal to tumor-infiltrating lymphocytes (TIL). Monalizumab prevents binding of NKG2A to HLA-E, reducing inhibitory signaling and thereby enhancing NK and CD8 T cell responses.

PD-1/PD-L1 inhibitors are successfully being used to treat patients with a wide variety of cancers. Combined blockades of NKG2A/HLA-E and PD-1/PD-L1 may be a promising strategy to further fight cancer by activating both the adaptive and innate immune systems.

Here, we describe NK- and CD8 T cell infiltrates in several human solid tumors by immunohistochemistry (IHC) and multicolor flow cytometry. We then studied the effects of a cohort targeting both pathways on primary human NK and CD8 T cells and the efficiency of this combination in a syngeneic mouse model.

**Mechanism of Action**

Monalizumab and durvalumab combination enhances NK and Ag-specific CD8 T cell responses

A. **CD8 T cell infiltration** in human solid tumors. NK and NKG2A+CD8 T cells were determined on paraffin sections and the percentage of NK cells and CD8 T cells was determined and expression of NKG2A and PD1 was analyzed.

**NK2G and PD-1 are expressed on tumor infiltrating NK and CD8 T cells from cancer patients**

**Lung cancer patients**

- NK cells
- CD8 T cells

**Head and Neck cancer patients**

- NK cells
- CD8 T cells

**Conclusions**

- Tumor infiltrating NK and CD8 T cells expressing NKG2A and for PD-1 are present in several cancer types.
- HLA-E is expressed by tumor cells in the large majority of solid tumors compared to PD-L1.
- Blocking both NKG2A/HLA-E and PD-1/PD-L1 pathways could enhance responses of NK and CD8 T cells that are present in close contact to tumor cells and therefore boost innate and adaptive immunity.
- Together, these data support the rationale for ongoing clinical trial investigating the monalizumab/ durvalumab combination (NCT02674353).