SELECTIVE TREG DEPLETION IN SOLID TUMORS WITH ALD2510, A NOVEL HUMANIZED CD25-SPECIFIC, IL-2 SPARING MONOCLONAL ANTIBODY

¹Jemila Houacine, ²Anne Marie-Cardine, ¹Aude Le Roy, ³Jérôme Giustiniani, ¹Riad Abes, ⁴Anne-Sophie Chrétien, ⁴Stéphane Fattori, ⁴Laurent Gorvel, ²Armand Bensussan, ⁴Daniel Olive, ¹Arnaud Foussat*. ¹Alderaan Biotechnology, Paris, France; ²INSERM U976, Paris, France; ³Inserm U955, Créteil, France; ⁴Inserm UMR1068, Institut Paoli Calmettes, Marseille, France

Background Regulatory T cells (Tregs) inhibit immune responses in solid cancers using cell-cell contacts and anti-inflammatory cytokine release. Also, due to high and constitutive levels of IL2Ralpha chain (CD25) expression, Tumor infiltrating (TIL)-Tregs cells preferably consume local Interleukin-2 (IL2), thus depriving conventional T cells from IL2-induced activation and proliferation. Therefore, the selective depletion of TIL-Tregs using therapeutic antibodies targeting CD25 represents a promising strategy to unleash tumor-specific immune responses in solid cancers.

Methods CD25 expression was evaluated by flow and mass cytometry on T-cell subsets from tumor biopsies collected in patients with various solid cancers (Breast, Endometrial and Cervix). ALD2510 potency was demonstrated in vitro and in vivo in human CD25 Knock-In huGEMM (huCD25-KI) MC38-bearing mice and in CD34+ humanized NSG mice grafted with human cancer cell lines (MDA-MB-231 and HT29).

Results In tumor biopsies, CD25 is highly and homogeneously expressed by TIL-Tregs, while being much less expressed by only a fraction of conventional CD4+ T cells and barely expressed by TIL-CD8+ cells. This confirms CD25 as the most selective marker to target TIL-Tregs in cancer patients. In vitro, ALD2510 shows potent ADCC and ADCP as well as strong Treg depletion capacity. Importantly, CD8+ and CD4+ conventional T cells are not impacted by ALD2510 even after activation confirming ALD2510 ability to selectively deplete Tregs. Accordingly, ALD2510 neither blocks IL-2 binding to CD25 nor inhibits IL-2 induced proliferation of activated T cells. In CD34+-humanized mice, ALD2510 efficiently depletes human Tregs but spares conventional T cells. Also, in the MC38 model in huCD25-KI mice, ALD2510 shows a strong anti-tumor activity as a single agent with 60% overall tumor growth inhibition together with massive Treg depletion 7 days after a single administration. In addition, combination of ALD2510 with anti-PD1 leads to complete tumor regression and strong activation of conventional T cells. Importantly, Basiliximab, a CD25-specific IL-2 blocking antibody, although efficient at depleting Treg cells, did not impact tumor growth, thus demonstrating that the IL-2 sparing feature of ALD2510 is critical to elicit anti-tumour response in vivo.

Conclusions This preclinical data package supports CD25 as a potent and selective Treg marker allowing Tregs depletion while sparing conventional T cells. In this context, ALD2510, a novel humanized CD25-specific and IL-2 sparing antibody presents all the required attributes for selective and efficient TIL-Tregs depletion, making it a promising drug candidate to treat a broad range of solid tumor patients.

Ethics Approval The studies involving human material were approved by the ethical committee "Comité de Protection des Personnes Sud Méditerranée" under approval numbers 1362 and 1048. All participants gave informed consent before taking part.

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