

ALD2510: NEXT GENERATION FC-ENHANCED, T_{REG}⁻ SELECTIVE AND IL-2-SPARING ANTI-CD25 ANTIBODY WITH PROMISING POTENTIAL FOR THE TREATMENT OF GYNECOLOGICAL CANCERS

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Background Regulatory T cells (T_{REG}) inhibit immune responses in many solid cancers and are associated with worse prognosis when they infiltrate tumours. ALD2510 is a low-fucose IL-2-sparing anti-CD25 antibody designed for the selective depletion of T_{REG}, allowing the boost of immune effector functions within the tumor micro-environment (TME) and making it a promising candidate for therapy of solid tumors.

Methods ALD2510 potency and mechanisms of action were investigated in T_{REG} depletion, ADCC, ADCP and trogocytosis assays and in syngeneic or humanized animal models of cancer. Characterization of T_{REG} subpopulations within the TME was achieved by flow and mass cytometry followed by t-sne analysis using biopsies from gynecological cancer patients. ALD2510 safety, tolerability and pharmacokinetic (PK) profile were determined in cynomolgus monkey, with doses up to 100mg/kg. ALD2510 manufacturability was assessed through fed-batch production and analytical characterization.

Results ALD2510 showed strong T_{REG} depletion, ADCC and ADCP activities, while sparing CD4⁺ and CD8⁺ T cell compartments, demonstrating its selectivity for T_{REGS} and a mode of action involving multiple effector cell types. ALD2510 also promoted trogocytosis of induced T_{REG}, suggesting that tumour-infiltrating neutrophils may contribute to its function. *In vivo*, as monotherapy, ALD2510 confirmed selective and potent T_{REG} depletion together with significant tumor growth inhibition, which could be further improved when combined with checkpoint inhibitors, leading to complete tumor regressions.

Immunophenotyping of tumor biopsies and related PBMCs from gynecological cancer patients and further t-sne analysis allowed the identification of four T_{REG} subsets. That with the highest CD25 expression was shown to be tumour specific and presented the most immunosuppressive phenotype, thus constituting a preferential target for ALD2510.

In a cynomolgus exploratory toxicology study, ALD2510 showed excellent safety and tolerability with doses up to 100mg/kg. PK and exposition parameters were found in line with those of typical humanized IgG1 in NHP.

The manufacturability of the ALD2510 CHO cell line was demonstrated through 10L fed-batch production, where productivity reached ~4g/L. Analytical characterization of purified ALD2510 materials revealed excellent purity and activity, together with very low levels of process-/cell-related impurities.

Conclusions ALD2510 is a next generation Fc-enhanced, T_{REG}-selective and IL-2-sparing anti-CD25 mAb showing *in vitro* and *in vivo* efficacy, fully satisfactory safety and tolerability in NHP and excellent manufacturability. ALD2510 thus appears as a promising candidate for treatment of solid tumor patients, especially those suffering from gynecological malignancies, where highly immunosuppressive CD25^{high} T_{REGS} were identified in the TME.