

215 **TARGETING OVARIAN CARCINOMA WITH GDT002, A FIRST-IN-CLASS $\gamma\delta$ TCR-BASED T CELL THERAPY**

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Background Broad application of cell therapies like CAR-T have been hampered by a lack of tumor-specific targets. Gadeta leverages the natural HLA-independent tumor recognition capabilities of $\gamma\delta$ TCRs combined with the proliferative capacity and robust tumor killing of $\alpha\beta$ T cells to develop tumor-specific cell therapies.¹ The most abundant peripheral $\gamma\delta$ T cells express V γ 9V δ 2 TCRs, which sense the presence of phosphoantigens (pAgs) upregulated in malignant cells due to a dysregulated mevalonate pathway.²⁻⁴ The V γ 9V δ 2 TCR expressed by GDT002 was selected for its broad and strong tumor reactivity.⁵ In addition, GDT002 demonstrated effective control of tumor growth in an aggressive systemic xenograft MM mouse model.

Currently GDT002 is being evaluated in a multicenter first-in-human phase 1/2 study for the treatment of multiple myeloma (NCT04688853). This ongoing FIH trial has completed the first dose cohort of 7E7 GDT002 cells without any safety concerns. To broaden the applicability of GDT002, we conducted preclinical studies to identify potential solid tumor indications.

Methods The specificity and anti-tumor activity of GDT002 was evaluated in various cell lines from solid cancer types and primary cells from healthy tissues. Tumor reactivity was tested in 2D co-cultures in the presence or absence of pamidronate, a clinically approved aminobisphosphonate that boosts pAgs levels. Target killing was determined by an xCELLigence-based cytotoxicity assay and T cell activity by cytokine release. Furthermore, GDT002 tumor reactivity and infiltration capacity was assessed in more complex 3D co-culture systems, such as a broad panel of patient-derived tumor organoids and ovarian carcinoma tumoroids, which were subjected to high-content imaging.

Results Significant GDT002 reactivity was observed against 10/15 adherent tumor targets in the presence of pamidronate. In contrast, no GDT002 reactivity was observed against primary cells from healthy tissue. In 3D organoid co-culture assays, GDT002 displayed significant reactivity towards most organoids, with an exceptionally high (90%) response rate towards ovarian cancer organoids. In addition, high-content quantitative imaging showed efficient aminobisphosphonate- and CD277-dependent cytotoxic activity of GDT002 in tumoroids with evidence of infiltration and expansion of GDT002 in the 3D cellular matrix.

Conclusions We demonstrate that GDT002 has potent anti-tumor activity across a broad spectrum of solid tumors. Based on the unmet clinical need and preclinical studies, recurrent ovarian cancer was selected as the first solid tumor indication to evaluate the efficacy of GDT002.

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Ethics Approval This study was approved by the Ethics Board of the Mouse Clinic for Cancer and Aging (MCCA), The Netherlands Cancer Institute, Amsterdam, The Netherlands; approval number AVD3010020165407 -165001, study EGP 1.1.9705, 1.5.9012 and 1.5.9421

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