TARGETING OVARIAN CARCINOMA WITH GDT002, A FIRST-IN-CLASS γδT-CELL-BASED T CELL THERAPY

Esther Drent, Sabine Middendorp*, Andrea Bisso, Sjoerd Baardman, Dagmar Verweij, Estefania Salcedo, Christopher Cotmans, Steven Brem, Sander van de Weg, Menno Meijer, Natalie Proost, Marieke van de Ven, Haakan Norell, Marleen van Loenen, Nia Emami, Sara Melef, Stefania Gobessi, Mark Throsby. 1Gadeta, Utrecht, Netherlands; The Netherlands Cancer Institute, Amsterdam, Netherlands

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 γδTCRs combined with the proliferative capacity and robust tumor killing of αβT cells to develop tumor-specific cell therapies. 1 The most abundant peripheral γδT cells express Vγ9Vδ2 TCRs, which sense the presence of phosphoantigens (pAgs) upregulated in malignant cells due to a dysregulated mevalonate pathway.2-4 The Vγ9Vδ2 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. 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.

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.

REFERENCES
5. Grunder C et al. gamma9 and d2CDR3 domains regulate functional avidity of T cells harboring gamma9d2TCRs. Blood. 2012; 120:5153-62