PHOSPHONATE-ANTIBODY-DRUG CONJUGATES: A NOVEL IMMUNOSTIMULATORY CLASS OF ADCS DRIVING INSIDE-OUT ACTIVATION OF Vγ9Vδ2 T CELLS LEADING TO SELECTIVE TUMOR CELL KILLING


Byondis BV, Nijmegen, Gelderland, Netherlands

Background Gamma delta (γδ) T cells are cytotoxic effector cells that can recognize and kill tumor cells in a major histocompatibility complex (MHC)-independent fashion. Their infiltration into malignant tissue correlates with a favorable prognosis in a broad range of cancers. Vγ9Vδ2 T cells are the predominant γδ T cell population in human peripheral blood and can sense accumulated phosphoantigens (pAgs) bound intracellularly to the BTN3A/BTN2A complex. Early clinical studies using aminobisphosphonates or synthetic pAgs, alone or in combination with a low dose of IL-2, have demonstrated expansion and activation of peripheral Vγ9Vδ2 T cells. Clinical efficacy, however, was variable, possibly due to the absence of tumor targeting and a very short half-life of these compounds.

Methods To circumvent these problems, we generated antibody-drug conjugates (ADCs) that deliver synthetic phosphonates selectively to tumor cells and drive inside-out activation of Vγ9Vδ2 T cells. The antibody moiety binds to a tumor-associated antigen (TAA), triggering internalization. The linker conjugating the phosphonate to the antibody is cleaved in lysosomes by proteases releasing the phosphonate payload which is then free to activate BTN3A/BTN2A complexes. The payload was conjugated to various TAA-targeting antibodies, including anti-CD123, anti-CD20, and anti-HER2 mAbs.

Results Multiple phosphonate-ADC-pretreated TAA-positive tumor cell lines were able to activate Vγ9Vδ2 T cells in a BTN3A-dependent fashion, leading to cytokine production, degranulation and killing of the tumor cells. The phosphonate-ADCs specifically activated Vγ9Vδ2 T cells in all tested healthy donors (N>40), but not other T cells. Stimulation of FcγR-positive immune cells through Fc-tail interactions were preserved.

Conclusions Overall, these immunostimulatory phosphonate-ADCs represent a promising novel approach to targeted therapy in the field of cancer.

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