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Discovery of JNJ-89853413, a First-in-Class CD33xVδ2 T-cell Engager for the Treatment of Acute Myeloid Leukemia

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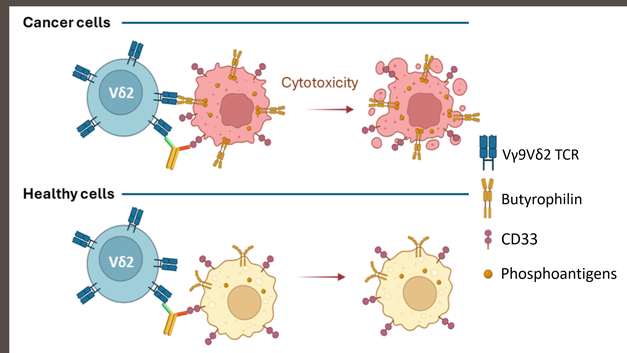
Key Takeaways

JNJ-89853413 is a novel first-in-class bispecific Vδ2 T-cell engaging antibody under investigation for the treatment of myeloid malignancies. JNJ-89853413 is currently being advanced for clinical investigation in patients with AML.



Schematic representation explaining mechanism of action: JNJ-89853413 is a T-cell engaging bispecific antibody that binds the Vδ2 antigen on T lymphocytes and CD33 on AML cells. Target cancer cell recognition is mediated by sensing phosphoantigen-induced conformational changes in the butyrophilin complexes. Figure created with BioRender.

Conclusions

- JNJ-89853413 binding and T cell-mediated cytotoxicity were selective to CD33-expressing cells. JNJ-89853413 showed potent in *vitro* cytotoxicity to AML patient-derived BM blast.
- JNJ-89853413 induced preferential cancer cells cytotoxicity over healthy myeloid cells with low cytokine secretion profile, compared to CD3 engagement.
- No impact on the viability of healthy hematopoietic cells after JNJ-89853413 treatment was observed, suggesting low risk of on-target off-tumor toxicities.
- JNJ-89853413 mediated robust anti-tumor activity in a disseminated MOLM-13 *in vivo* model.

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Supplementary material

https://jsh.epg-digital.com/ASH2024/Oncology/EarlyAssets/Ashkar

The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

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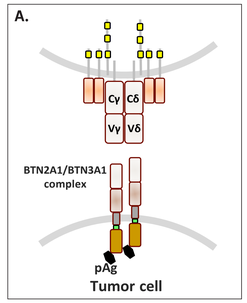
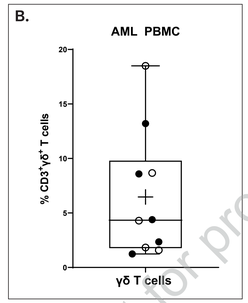
Disclosures
Sara El Ashkar[1,2], Lorena Kallal[2], Kavita Raman[1,2], Ranjeet Prasad Dash[1,2], Nirav Shah[1,2], Lore Delbroek[1], Lénárd Kertész[1], Heleen Van Acker[1], Steffie Junius[1], Ivo Cornelissen[1,2], Surendar Arumugam[1], Lauren Gerloff[1], Kathryn Bradford[1,2], E. Christine Pietsch[1], Leopoldo Luistro[1], Bethany Mattson[2], Christina Guttke[2], Karim Safer[1], Janine Arts[1,2], Sonal Patel[1], Ulrike Philippar[1,2,3]

1: Current employment at Janssen; 2: Current equity holder in Janssen; 3. Membership on an entity's board of directors or advisory committees and patent & royalties

Background

- Targeted immunotherapy in acute myeloid leukemia (AML) remains a substantial clinical challenge due to the heterogeneous nature of the AML cancer cells and the lack of AML-specific antigens. While several immunotherapies targeting CD33, including CAR-T and NK cell therapies, are being evaluated clinically, challenges have been experienced with immunotherapies targeting CD33 due to lack of tolerability. In addition, on-target off-tumor toxicities due to target expression on normal myeloid cells represent a major concern.
- Vδ2 T-cells represent a promising subset of T-cells to explore for novel and innovative cancer immunotherapy. They represent ~5% of the T-cell population in the peripheral blood of healthy donors and are prevalent in a broad set of cancers. In addition, differential expression of phosphoantigen-activated butyrophilins contributes to greater activity of Vδ2 T-cells against cancer cells over normal cells.
- Targeting CD33 (a well validated AML target that is expressed in ~90% of AML cases) with Vδ2 T-cell engagement could potentially provide advantages with regards to safety and efficacy compared to the existing therapies



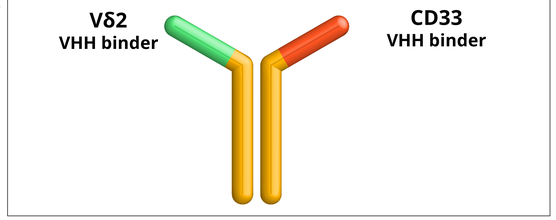


(A) The Vδ2 TCR chain binds directly to BTN2A1/BTN3A1 complex on cells. In the case of healthy cells, no activation of Vδ2 T cells occurs. Full activation is only achieved when BNT3A1 is recruited in a pAg-dependent manner where accumulation leads to increased mobilization of intracellular BTN3A1. Conformational changes in BTN3A1 extracellular domain subsequently stabilizes the immunological synapse. (B) Frequency of γδ T cells in AML patient-derived PBMC. Relapsed/Refractory donors are indicated as closed circles, newly diagnosed patients are indicated as open circles.

Methods

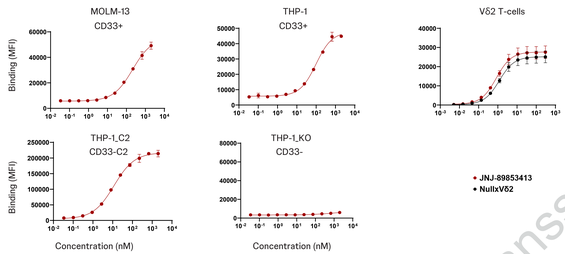
- JNJ-89853413 is a fully human IgG1 antibody that binds to the IgC2 domain of CD33 and Vδ2 T cells. Anti-CD33 VHH arm was combined with anti-Vδ2 VHH arm (generated by LAVA Therapeutics). Humanized and post-translation modification (PTM) risk mitigation was performed at Janssen.

Schematic Representation of JNJ-89853413



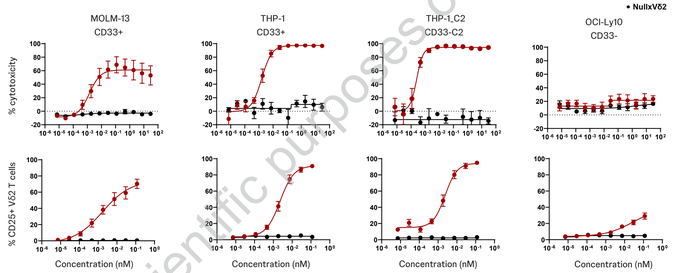
Results

JNJ-89853413 selectively binds to CD33-expressing cells and Vδ2+T cells



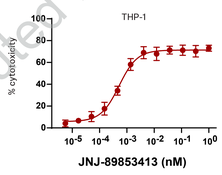
One hour binding of JNJ-89853413 antibody to a panel of CD33-expressing cell lines and Vδ2+ T cells, detected with a AF647-labeled secondary antibody. MFI; median fluorescence intensity.

JNJ-89853413 mediates selective cytotoxicity of CD33+ cancer cells



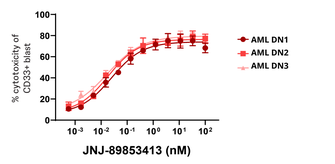
T cells from healthy donors were evaluated in T-cell cytotoxicity assays with the indicated antibodies and target cell lines. Cytotoxicity of cancer cells and T-cell activation were measured after 72 hours. The assay was conducted at a relative E:T ratio of 0.5:1.

JNJ-89853413 mediates cytotoxicity using AML-derived Vδ2+ T cells



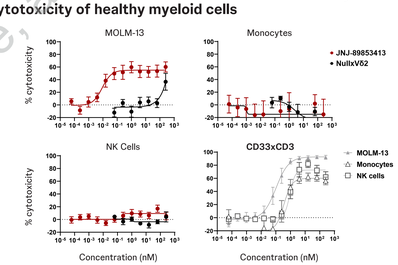
Vδ2+ T cells were expanded from AML patient-derived PBMCs and tested in a T-cell cytotoxicity assay with JNJ-89853413 and THP-1 target cells at an E:T ratio of 1:1. Cytotoxicity of THP-1 cells was evaluated after 24 hours.

JNJ-89853413 induces potent cytotoxicity of AML BM blast



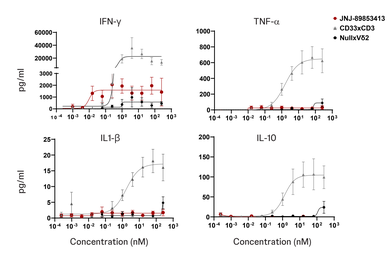
T cells from healthy donors were tested in T-cell cytotoxicity assays with JNJ-89853413 and AML patient-derived BM cells, performed at a relative E:T ratio of 2:1. Cytotoxicity of CD33+ blast was assessed after 24 hours. BM, bone marrow; DN, donor.

JNJ-89853413 mediates preferential cancer cells cytotoxicity over cytotoxicity of healthy myeloid cells



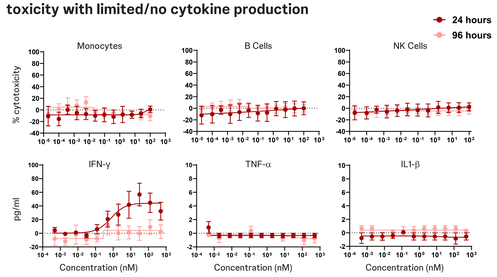
Healthy donor PBMCs were evaluated in cytotoxicity assays with the indicated antibodies and target cells. Cytotoxicity of cancer cells and healthy immune cells were assessed after 96 hours at 20:1 E:T ratio. CD33xCD3 comparator antibody was evaluated in parallel.

JNJ-89853413 induces low cytokine secretion



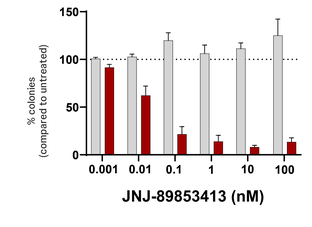
Cytokine production was assessed from supernatant of PBMC cytotoxicity assays after 96 hours. Cytokine levels upon CD33xCD3 engagement are depicted for comparison.

JNJ-89853413 shows no evidence of on-target off-tumor toxicity with limited/no cytokine production



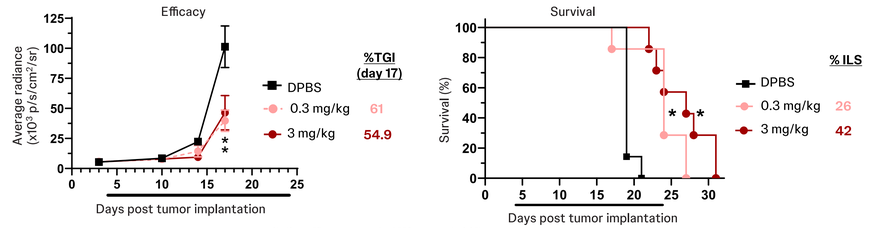
Whole blood from healthy donors was tested in a T-cell cytotoxicity assay with JNJ-89853413 for 24 or 96 hours in the absence of cancer cells. The percent cytotoxicity of monocytes, B cells and NK cells, and secreted cytokines were determined.

JNJ-89853413 shows low risk of hematopoietic toxicity



Naïve Vδ2+ T cells were isolated from healthy donor PBMCs and used as effectors at 1:1 relative E:T ratio with CD34+ cells or THP-1 cells as target cells in CFU assays. CFU, colony forming unit; HSPC, hematopoietic stem/progenitor cells.

JNJ-89853413 mediates anti-tumor activity in disseminated MOLM-13 *in vivo model*



* *Significant difference compared to DPBS treatment (p<0.05)*

MOLM-13 cancer cells were implanted on Day 0. γδ T cell injection was performed on Day 3 and 16. Dosing of JNJ-89853413 occurred on Days 4, 7, 10, 14, 17, 21, and 24 (represented by black line). ILS, increased life span; TGI, tumor growth inhibition.

References
1. Laszlo et al. (2014), Blood Reviews; **2.** Bonneville M, et al. (2010) Nat Rev Immunol; **3.** Fichtner AS et al. (2020) Cells; **4.** Künkele et al. (2020), Cells; **5.** Vyborova et al, 2020 J Clin Invest; **6.** Nair-Gupta et al. (2020), Blood Adv.

Myeloid Malignancies

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