1408

JNJ-87801493 (CD20xCD28), a Potential First-in-Class CD20 Targeted CD28 Costimulatory Bispecific Antibody, Enhances the Activity of B-cell Targeting T-cell Engagers in Preclinical Models

Lorena Fontan,[1] Adam Zwolak,[2] Irene Guimerans-Lorenzo,[1] Mariette Bekkers,[1] Nicholas Hein,[2] Nele Vloemans,[1] Emanuele Trella,[1] Tina Smets,[1] Ivo Cornelissen,[1] Alemu Assefa,[1] Bie Verbist,[1] Ricardo Amorim,[1] Pankaj Seth,[2] Ranjeet Prasad Dash,[2] Leo Luistro,[2] Bethany Mattson,[2] Matthew A. Dragovich,[3] Michael Hedvat,[3] Gregory L. Moore,[3] John R. Desjarlais,[3] Olivia Kutlu,[4] Joseph Erhardt,[2] Ulrike Philippar[1]

[1]Janssen Research & Development, Beerse, Belgium; [2]Janssen Research & Development, Spring House, PA, USA; [3]Xencor, Inc., Pasadena, California; [4]Janssen Research & Development, Los Angeles, CA, USA.

Key Takeaway

- These data establish the preclinical proof-of-concept that JNJ-87801493 (CD20xCD28) enhances the *in vitro* and *in vivo* efficacy of TCEs through improved T-cell function
- A clinical trial (NCT06139406) is underway to characterize the safety and clinical activity of JNJ-87801493 in combination with JNJ-80948543 (CD79bxCD20xCD3) in participants with previously treated B-cell NHL

Conclusions

- *In vitro*, JNJ-87801493 enhanced JNJ-80948543 target specific T-cell mediated cytotoxicity, T-cell activation, and proliferation in a concentration-dependent manner
- JNJ-87801493 alone had no effect on T-cell activation or T-cell–mediated cytotoxicity *in vitro* or *in vivo*
- *In vivo*, JNJ-87801493 enhanced tumor growth inhibition by JNJ-80948543, resulting in complete tumor regression and significantly extended survival in a DLBCL xenograft mouse model

Please scan QR code

Poster

https://www.congresshub.com/ASH2024/Oncology/EarlyAssets/Fontan

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

Acknowledgments

This study was funded by Janssen Research & Development. Priya Ganpathy, MPH, CMPP (SIRO Clinpharm UK Limited) and Jennifer Han, MS (Janssen Global Services) provided editorial support. Amit Kavle (SIRO Medical Writing Pvt. Ltd. India) provided graphic designing support.

Disclosures

LF, AZ, IGL, MB, NH, NV, ET, TS, IC, AA, BV, RA, PS, RPD, LL, BM, OK, JE, UP: employee of Janssen Research & Development, LLC, a Johnson & Johnson company; employees may hold stock or stock options in Johnson & Johnson. **MAD, MH, GLM, JRD:** employees of Xencor Inc.

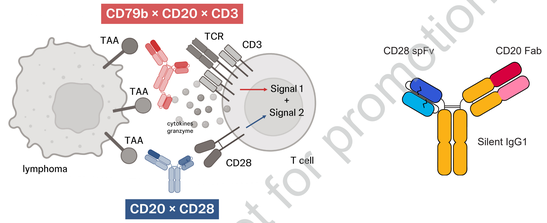
Introduction

- Recent approvals validate immune T cell-engagement (tumor-associated antigen [TAA] x cluster of differentiation [CD]3) as a promising therapeutic strategy for relapsed/refractory B-cell malignancies[1]
- Despite treatment advances, activation of the CD3 axis alone is not curative in a large proportion of cases[2,3], potentially due to the absence of costimulatory signals
- Costimulatory signals are required for optimal T-cell activation along with T-cell receptor (TCR)/CD3 activation ('Signal 1')
- CD28 is a costimulatory signal and its engagement ('Signal 2') initiates pathways important for T-cell activation, differentiation, persistence, and survival[4]
- Mimicking 'Signal 2' with a bispecific costimulatory antibody targeting CD28 and TAAxCD28, administered together with a T-cell engager (TCE), may enable optimal activation and persistence of T-cells[5]
- Combination therapy TAAxCD3 ('Signal 1') + TAAxCD28 ('Signal 2') may enhance TAAxCD3 activity leading to deeper, more durable antitumor responses

Objectives

- To characterize the preclinical efficacy and mechanism of action of JNJ-87801493 (CD20xCD28) in combination with JNJ-80948543 (CD79bxCD20xCD3), in diffuse large B-cell lymphoma (DLBCL) models

Figure 1: Structure and mechanism of action of JNJ-87801493 in combination with JNJ-80948543



CD, cluster of differentiation; Fab, fragment antigen binding; IgG1, immunoglobulin G1; spFv, stapled single-chain fragment variable; TAA, tumor-associated antigen; TCR, T-cell receptor.

Methods

- JNJ-87801493 is a novel, fully-human, IgG1 bispecific costimulatory antibody that binds to CD20 on B-cells and the CD28 receptor on T-cells
- JNJ-87801493 features a disulfide-stapled single-chain fragment variable (scFv) that binds to CD28 monovalently with relatively weak affinity and without superagonism

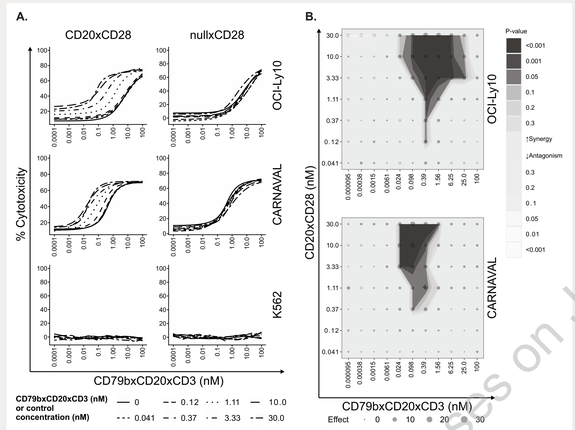
Table 1: Tumor associated antigen expression in lymphoma cell lines

Receptor density (receptors/cell)	CD20	CD79b
CARNAVAL	198K	110K
OCI-Ly10	140K	41K
WILL-2	4K	2K
NALM6	bdl	130
K562	-	-

bdl, below detection limit; CD, cluster of differentiation; K, thousand.

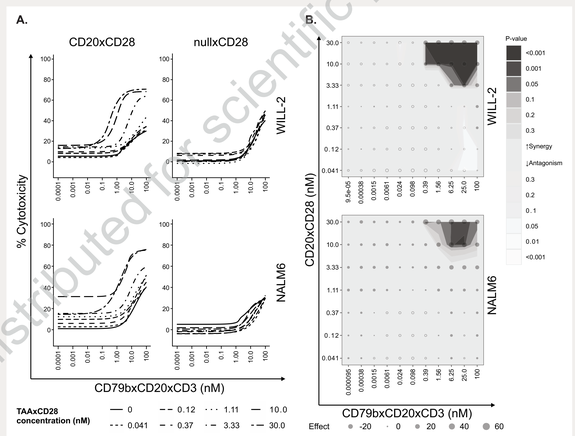
Results

Figure 2: CD28 co-stimulation synergistically enhanced CD79bxCD20xCD3–induced T-cell mediated cytotoxicity of B-cell lymphoma cell lines



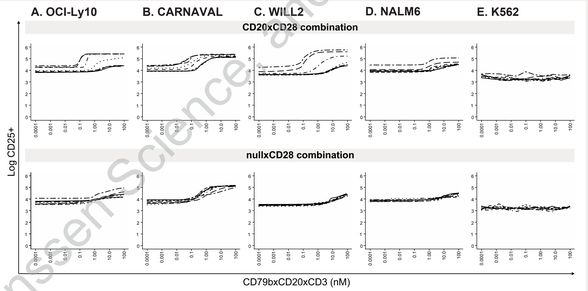
CD, cluster of differentiation; E:T effector to target.
A. Pan T-cell and lymphoma cell line cocultures at E:T ratio 1:1 (n=3 T-cell donor). Cytotoxicity was measured over 6 days.
B. Synergy was analyzed under HSA null model using MaxR from BIGL R package. Open circles represent negative effect; closed circles represent positive effect on cytotoxicity.

Figure 3: CD20xCD28 synergistically enhanced CD79bxCD20xCD3–induced T-cell–mediated cytotoxicity of low CD20-expressing B-cell lymphoma cell lines



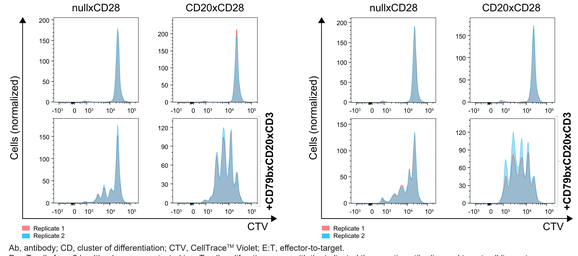
CD, cluster of differentiation; E:T effector to target
A. Pan T-cell and lymphoma cell line cocultures at E:T ratio 5:1 (n=3 T-cell donor). Cytotoxicity was measured over 6 days.
B. Synergy was analyzed under HSA null model using MaxR from BIGL R package. Open circles represent negative effect; closed circles represent positive effect on cytotoxicity.

Figure 4: CD28 co-stimulation enhanced CD79bxCD20xCD3–induced T-cell activation



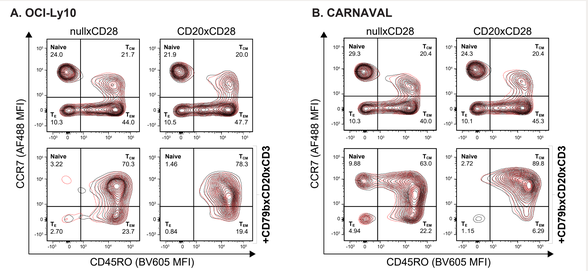
CD, cluster of differentiation; E:T, effector-to-target.
T-cells from 3 healthy donors were tested in T-cell/tumor co-culture cytotoxicity assays at an E:T ratio of 1:1 with the indicated antibodies and target cell lines expressing mKate2 and at an E:T ratio of 5:1 with the indicated antibodies and target cell lines WILL-2 and NALM6 expressing mKate2. OCI-Ly10 and CARNAVAL are CD20+CD79b+ and K562 is CD20-CD79b−. CD25 expression was measured over 6 days.

Figure 5: CD28 costimulation enhanced CD79bxCD20xCD3–induced T-cell proliferation



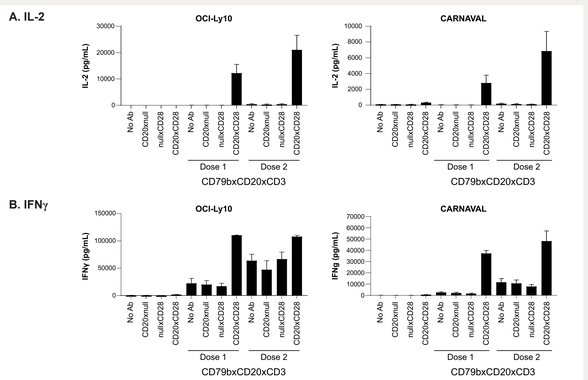
Ab, antibody; CD, cluster of differentiation; CTV, CellTrace™ Violet; E:T, effector-to-target.
Pan T-cells from 2 healthy donors were tested in a T-cell proliferation assay with the indicated therapeutic antibodies and target cell lines at a 5:1 E:T ratio. T-cell proliferation, measured as CTV dilution, was assessed after 72 hours incubation. Representative histograms showing cell division peaks by dilution of CellTrace™ Violet from a representative T-cell donor run in duplicate. Gating cell/singlets/live/CD3+.

Figure 6: CD28 costimulation enhanced CD79bxCD20xCD3-mediated increase in CD8+ T_{CM} (CD45RO+CCR7+) T-cells *in vitro*



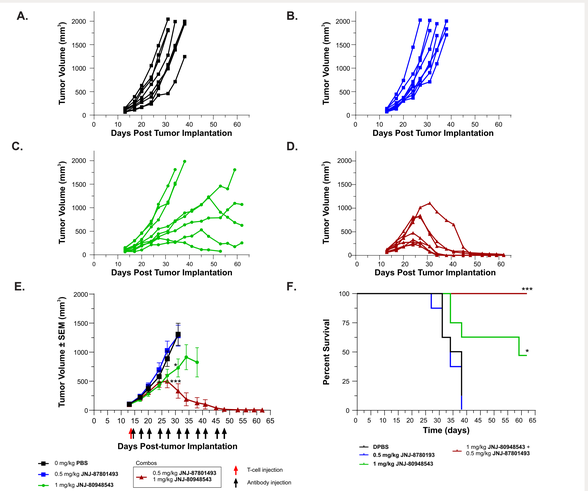
CD, cluster of differentiation; E:T, effector-to-target; T_{CM}, central memory T-cells; T_{EM}, effector memory T-cells; T_E, T effector cells. Pan–T-cells from 2 healthy donors were tested in a T-cell/tumor co-culture at a 1:1 E:T ratio with the indicated antibodies and T-cell differentiation was assessed at 72 hours. Gating cell/singlets/live/CD3+/CD8+.

Figure 7: CD28 costimulation enhanced CD79bxCD20xCD3–induced T-cell Th1 cytokine secretion



CD, cluster of differentiation; E:T, effector-to-target; IFNγ, interferon gamma; IL-2, interleukin-2.
Pan–T-cells from 2 healthy donors were tested in a in T-cell/tumor co-culture at a 1:1 E:T ratio with the indicated antibodies. Cytokine secretion was assessed at 72 hours.

Figure 8: Combination treatment of CD20xCD28 and CD79bxCD20xCD3 resulted in complete tumor regression and 100% survival in established OCI-Ly10–subcutaneously-injected DLBCL xenografts in T-cell–humanized mice



DPBS, Dulbecco's phosphate buffered saline; SEM, standard error of the mean.
Tumor volume spider plots showing tumor volume over time for individual mice in each treatment group (n=8 mice/treatment group). (A) PBS, (B) 0.5 mg/kg JNJ-87801493, (C) 1 mg/kg JNJ-80948543, (D) combination of 1 mg/kg JNJ-80948543 and 0.5 mg/kg JNJ-87801493. (E) Average tumor volume ±SEM for indicated groups. Data displayed up until two thirds of animals remained in the group. (F) Survival plot for the study. *p<0.05; **p<0.01; ***p<0.001.

References

1. Dalle IA, et al. *Blood Cancer J.* 2024;25;14:2; **2.** Dickinson MJ, et al. *N Engl J Med.* 2022;387:2220; **3.** Thieblemont C, et al. *J Clin Oncol.* 2023;41:2238; **4.** Boise LH, et al. *Immunity*. 1995;3:87; **5.** Skokos D, et al. *Sci Transl Med.* 2020;12:eaaw7888.

B-cell Malignancies

Presented by Dr Fontan at the American Society of Hematology (ASH) Annual Meeting; December 7 to 10, 2024; San Diego, California.