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Discovery of JNJ-87562761, a novel anti-GPRC5D enhanced effector function antibody with multiple mechanisms of action for the treatment of multiple myeloma

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Key Takeaways

JNJ-87562761 is a next-generation anti-GPRC5D monoclonal antibody with ADCP, enhanced-ADCC, and enhanced-CDC (immune cell-independent) mechanisms of action, being developed for the treatment of relapsed/refractory multiple myeloma

Conclusions for JNJ-87562761:

- Demonstrated dose-dependent ADCC, ADCP, and CDC against GPRC5D$^+$ MM cells; no NK cell fratricide was observed
- Significant *in vivo* anti-tumor efficacy observed in two human GPRC5D$^+$ MM xenograft models in NSG-IL15 mice engrafted with human NK-92.CD16 cells
- Currently being evaluated in a Phase 1 study of participants with relapsed/refractory MM (NCT06604715)

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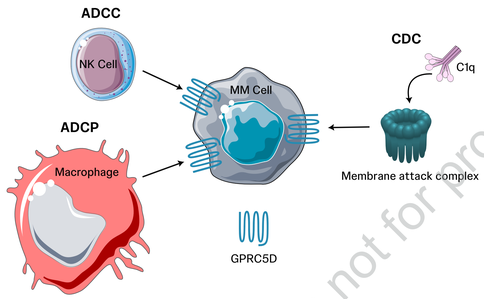
Disclosures

BH, XLS, HH, JR, AM, KS, BMC, NH, AZ, KR, WR, TP, SL, AD, MPY, WCC, JS, and **UP:** employees of Johnson & Johnson; employees may hold stock or stock options in Johnson & Johnson. **JT:** former Johnson & Johnson employee and may hold stock or stock options in Johnson & Johnson

Background

- Antibody and T-cell engaging therapies have reshaped the multiple myeloma (MM) therapeutic landscape in recent years resulting in significantly improved clinical outcomes
- Monoclonal antibodies (mAbs) such as daratumumab (anti-CD38) demonstrate the effector function (EF) mechanisms: antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC)[1,2]
  - While EF mAbs targeting CD38 have shown clinical benefit, NK cell fratricide is a known liability due to CD38 expression on NK cells[3,4], potentially reducing the full antitumor effect of the ADCC mechanism
- Targeting plasma cell-specific antigens in the hematopoietic compartment, such as GPRC5D, with an EF antibody may avoid NK cell fratricide, optimizing ADCC activity, while simultaneously mediating ADCP and CDC mechanisms

Figure 1: JNJ-87562761 mediates ADCP, enhanced-ADCC, and enhanced-CDC mechanisms against GPRC5D$^+$ MM cell lines

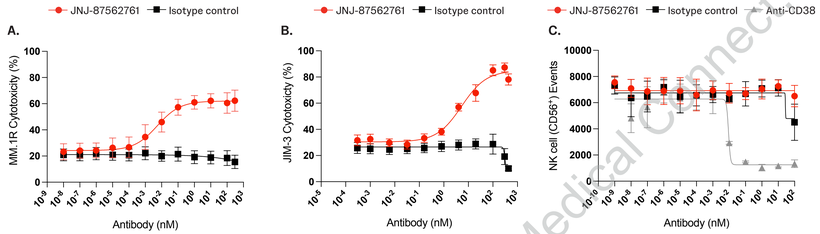


Methods

- JNJ-87562761
  - Is a first-in-class anti-GPRC5D enhanced-EF human IgG1 antibody that targets GPRC5D-positive MM plasma cells
  - Was purposefully designed to elicit ADCP, enhanced-ADCC, and enhanced-CDC
- Assays
  - ADCC and ADCP assays were performed using isolated peripheral blood healthy donor NK cells or monocytes (M1 phenotype differentiated with M-CSF [6 days] and IFN-γ [1 day]), respectively and co-cultured with MM cells
  - CDC assays were performed using 40% qualified pooled human serum
  - *In vivo* efficacy was evaluated in human MM disseminated models using NSG-IL-15 mice with and without engraftment of human NK-92.CD16 effector cells to evaluate ADCC from mouse effector cells and human NK effector cells

Results

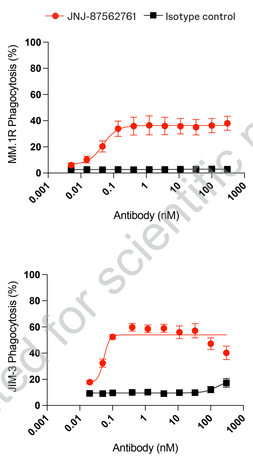
Figure 2: JNJ-87562761 mediated ADCC in GPRC5D$^+$ MM cell lines but not NK cell fratricide



NK cells were isolated from healthy donors (n=5, ADCC) and co-cultured with GPRC5D$^+$ MM cells (MM.1R and JIM-3) at a 5:1, E:T ratio or alone (n=3, NK fratricide). After 48 hours, ADCC of MM.1R and JIM-3 cells (**Figure 2A** and **2B**) or 96 hours, NK cell fratricide (**Figure 2C**) was measured by flow cytometry. Mean ± SEM is shown.

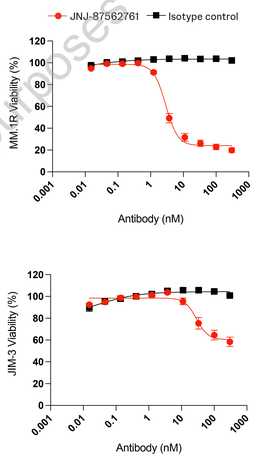
E:T, effector to target ratio; SEM, standard error of the mean.

Figure 3: JNJ-87562761 mediated ADCP in GPRC5D$^+$ MM cell lines



Monocytes were isolated from healthy donors (n=5) and co-cultured with GPRC5D$^+$ MM cells at a 3:1, E:T ratio. After 2 hours, phagocytosis was measured by flow cytometry. Mean ± SEM is shown.

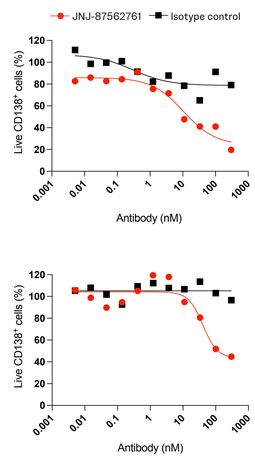
Figure 4: JNJ-87562761 mediated CDC in GPRC5D$^+$ MM cell lines



40% healthy donor pooled human serum was cocultured with dartumumab CDC-resistant MM cells[5] and JNJ-87562761. After 24 hours, CellTiter-Glo® reagent was added to all the wells and luminesce values were quantified as percent viability, calculated as [RLU treated/RLU untreated] ×100. Each experiment was performed with 3 replicate wells. Mean ± SEM is shown.

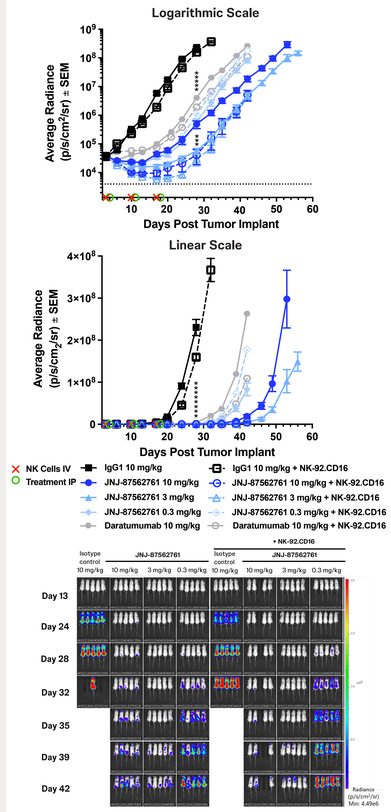
RLU, relative light units.

Figure 5: JNJ-87562761 mediated ADCC and CDC in MM patient cells



NK cells were isolated from a healthy donor (n=1) and co-cultured with bone marrow mononuclear cells containing CD138$^+$ MM cells that were GPRC5D$^+$ at ~5:1, E:T ratio (NK cells/MM cells). After 24 hours, ADCC-mediated cytotoxicity (top) and after 2 hours, CDC-mediated cytotoxicity (bottom) were measured by flow cytometry.

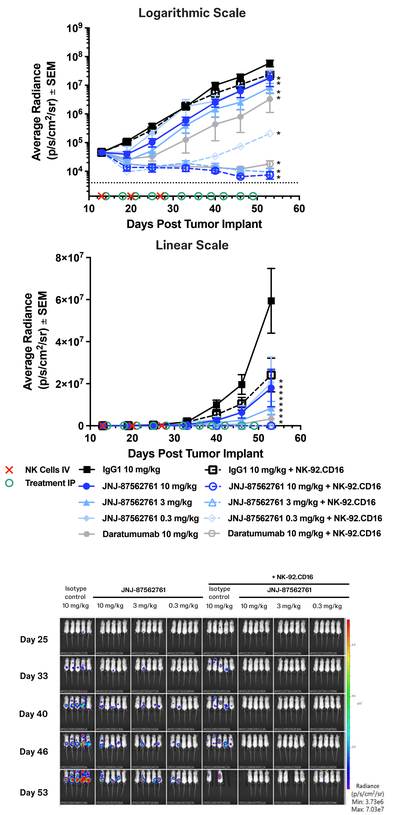
Figure 6: JNJ-87562761 demonstrates significant anti-tumor in vivo activity in a disseminated MM.1S-luc model that is superior to daratumumab



Efficacy of JNJ-87562761, IgG1 isotype control, and daratumumab (anti-CD38) was evaluated in disseminated MM.1S transduced to express luciferase in NSG-IL-15 mice with and without human NK-92.CD16 effector cell engraftment. Average radiance ± SEM from IVIS® was plotted over time using Living Image software when at least 2/3 of mice remained in each group (logarithmic scale/top, linear scale/middle, n=10 mice/group) and representative dorsal BLI images from 4-5 mice/group (bottom).
*Denotes significant difference (ps0.05) of JNJ-87562761-treated groups on Day 28 versus the respective control group. Dotted line represents background signal from naïve animal. One animal each in the JNJ-87562761 0.3 mg/kg and 10 mg/kg group were found dead or euthanized for body weight loss between Days 10-13 due to NK-92.CD16 cell injections. JNJ-87562761 treatment decreased tumor burden as assessed by BLI with significant activity from mouse effector cells (no NK-92.CD16 engraftment), which was further enhanced with engraftment of human NK-92.CD16 cells.

BLI, bioluminescence; IP, intraperitoneal; IV, intravenous; P, photon; S, steradian.

Figure 7: JNJ-87562761 demonstrates significant anti-tumor in vivo activity in a disseminated OPM-2-luc model



Efficacy of JNJ-87562761, IgG1 isotype control, and daratumumab (anti-CD38) was evaluated in disseminated OPM-2 transduced to express luciferase in NSG-IL-15 mice with and without human NK-92.CD16 effector cell engraftment. Average radiance ± SEM from IVIS® was plotted over time using Living Image software when at least 2/3 of mice remained in each group (logarithmic scale/top, linear scale/middle, n=10 mice/group) and representative dorsal BLI images from 5 mice/group (bottom).
*Denotes significant difference (ps0.05) of JNJ-87562761-treated groups on Day 53 versus the respective control group. Dotted line represents background signal from naïve animal. JNJ-87562761 treatment decreased tumor burden as assessed by BLI with even greater enhanced efficacy observed with engraftment of human NK-92.CD16 cells compared to the MM.1S-Luc model possibly due to higher GPRC5D receptor density in this model compared to MM.1S-Luc.

References

1. de Weers M, et al. *J Immunol.* 2011;186(3): 1840–48. 2. Overdijk MB, et al. *MAbs.* 2015;7(2): 311–21. 3. Casneuf T, et al. *Bood Adv.* 2017;1(23): 2105–2114. 4. Verkleij CPM, et al. *Hemasphere.* 2023;7(5): e881. 5. Nijhof IS, et al. *Blood. 2016;*128(7): 959–70.

Multiple Myeloma

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