B18

# Pharmacodynamic Relationship Between Natural Killer Cells and Daratumumab Exposure in Relapsed/Refractory Multiple Myeloma

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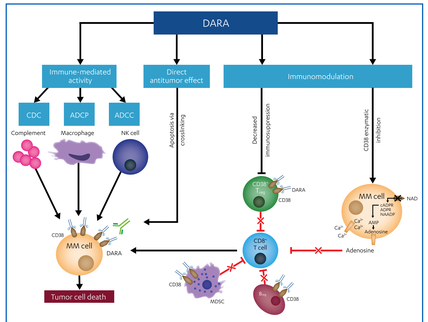
## INTRODUCTION

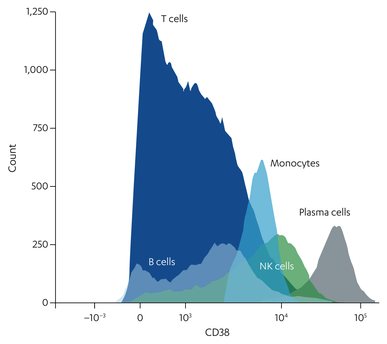
- Daratumumab (DARA) is a human CD38 IgG1κ monoclonal antibody that mediates CD38-expressing tumour cell death through a variety of mechanisms, including complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis, apoptosis through Fc-mediated crosslinking, lysis of myeloid-derived suppressor cells (MDSCs), regulatory B cells and regulatory T cells, and expansion and activation of T cells[1-3] (**Figure 1**)




DARA, daratumumab; CDC, complement-dependent cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; ADCC, antibody-dependent cellular cytotoxicity; NK, natural killer; MM, multiple myeloma; $T_{reg}$, regulatory T cell; MDSC, myeloid-derived suppressor cell; $B_{reg}$, regulatory B cell; NAD, nicotinamide adenine dinucleotide; cADPR, cyclic adenosine diphosphate ribose; ADPR, adenosine diphosphate ribose; NAADP, nicotinic acid adenine dinucleotide phosphate; AMP, adenosine monophosphate.

**Figure 1. Mechanism of action of DARA.**

- CD38 is expressed at high levels on multiple myeloma (MM) cells and, to a lesser extent, on immune effector cells, including natural killer (NK) cells[3] (**Figure 2**), which are important for DARA-mediated ADCC
- Here, clinical and preclinical analyses were conducted to characterise the relationship between NK-cell kinetics, exposure to DARA, and patient outcomes




NK, natural killer; MM, multiple myeloma.
Analysis of a sample from a patient with MM is shown.

**Figure 2. CD38 expression on NK cells.**

## OBJECTIVES

- To understand the effect of DARA on NK cells in the in vitro setting
- To understand the exposure-response relationship between DARA and NK-cell reduction
- To understand the impact of NK-cell reduction on the efficacy and safety profiles of DARA

## METHODS

### Patients

- Data were pooled from 2 studies of single-agent DARA (GEN501 and SIRIUS) in patients treated with 8 or 16 mg/kg
- In both studies, patients had documented relapsed and refractory MM requiring systemic therapy and an Eastern Cooperative Oncology Group performance status ≤2
  - In GEN501, patients had relapsed from or were refractory to ≥2 prior lines of therapy, including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), chemotherapy, or autologous stem cell transplantation
  - In SIRIUS, patients had progressed on their most recent line of therapy and had received ≥3 prior lines of therapy, including a PI and an IMiD, or were double refractory to both a PI and an IMiD

### Study Design

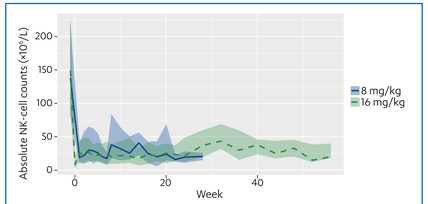
- GEN501 was an open-label, phase 1/2, dose-escalation and dose-expansion study
  - In Part 1, patients received DARA doses ranging from 0.005 to 24 mg/kg
  - In Part 2, patients received the following:
    - DARA 8 mg/kg once weekly (QW) for 8 weeks, every 2 weeks (Q2W) for 16 weeks, and every 4 weeks (Q4W) until disease progression, or
    - DARA 16 mg/kg once, followed by a 3-week washout period, then QW for 7 weeks, Q2W for 14 weeks, and Q4W until disease progression
- SIRIUS was an open-label, phase 2 study
  - Patients were randomized to receive the following:
    - DARA 8 mg/kg Q4W, or
    - DARA 16 mg/kg QW for 8 weeks, Q2W for 16 weeks, and Q4W thereafter (the recommended dose)

### Clinical Correlative Analyses

- A validated enzyme-linked immunosorbent assay was used to assess serum concentrations of DARA
- NK cells, both total ($CD16^+CD56^+$) and activated ($CD16^+CD56^{dim}$), were measured by flow cytometry in peripheral whole blood and bone marrow aspirates; absolute cell numbers per μL and the percentage of lymphocytes were both calculated
- The correlation between DARA exposure (dose and serum concentrations) and change in NK cells after DARA treatment was examined to investigate exposure-response relationships
- The kinetics of total ($CD16^+CD56^+$) and activated ($CD16^+CD56^{dim}$) NK cells following DARA infusions were explored
- The relationship between change in NK cells following DARA treatment and clinical efficacy (as measured by overall response rate [ORR]) and safety (as measured by grade ≥3 adverse events [AEs] and incidence of infections such as herpes zoster) was studied

## RESULTS

- In peripheral blood and bone marrow, total and activated NK-cell counts were reduced rapidly after initial treatment with DARA in all patients, regardless of clinical response, and remained low over the course of treatment (**Figure 3**)
  - The ORRs among patients receiving DARA 8 or 16 mg/kg are shown in **Table 1**
  - Patients received DARA 8 or 16 mg/kg; while NK cells showed some recovery in patients receiving 8 mg/kg, this recovery did not translate to improved efficacy, as measured by ORR. Because ORR was greater in patients receiving DARA 16 mg/kg, subsequent analyses focused on the 16 mg/kg dose




NK, natural killer; DARA, daratumumab.

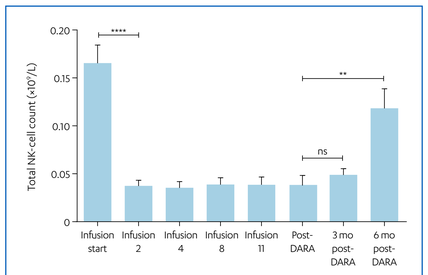
**Figure 3. NK cells in the peripheral blood after DARA treatment.**

**Table 1. ORRs With DARA 16 mg/kg Versus DARA 8 mg/kg**

| | DARA 16 mg/kg (n = 148) | DARA 8 mg/kg (n = 48) |
|---|---|---|
| ORR, n (%) | 46 (31.1) | 5 (10.4) |
| Stringent complete response | 3 (2.0) | – |
| Complete response | 2 (1.4) | – |
| Very good partial response | 12 (8.1) | 1 (2.1) |
| Partial response | 29 (19.6) | 4 (8.3) |
| Minimal response | 9 (6.1) | 8 (16.7) |
| Stable disease | 68 (45.9) | 24 (50.0) |
| Progressive disease | 18 (12.2) | 7 (14.6) |
| Not evaluable | 7 (4.7) | 3 (6.3) |

ORR, overall response rate; DARA, daratumumab.

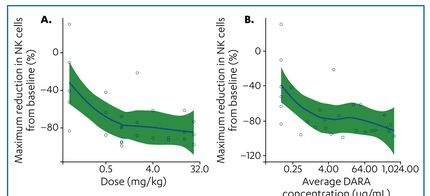
- Although total NK cells were significantly reduced during DARA infusion, they recovered after treatment ended (**Figure 4**)




NK, natural killer; DARA, daratumumab; ns, not significant; mo, month; s.e.m., standard error mean.
NK-cell counts from the peripheral blood samples of 21 patients are presented as mean ± s.e.m.
*P* values were calculated using a paired Student *t* test; $^{**}P<0.01$, $^{****}P<0.0001$.

**Figure 4. Rapid reduction of total NK-cell counts and recovery after DARA treatment.**

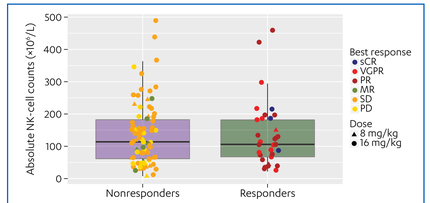
- There was a clear maximum effect ($E_{max}$) relationship between the maximum reduction in NK cells in peripheral blood and DARA dose (**Figure 5A**) and concentration (**Figure 5B**)




$E_{max}$, maximum effect; DARA, daratumumab; NK, natural killer.
The blue curves represent smoothing lines and the green shaded areas represent the 95% confidence interval around the smoothing curves.

**Figure 5. $E_{max}$ exposure-response relationship between DARA exposure and maximum NK-cell reduction.**

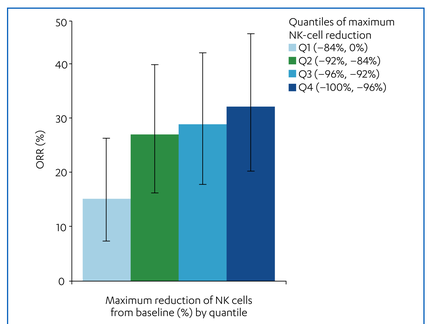
- No significant difference in NK-cell counts (total or activated) was observed between responders and nonresponders prior to treatment with DARA (ie, at baseline; **Figure 6**)




NK, natural killer; sCR, stringent complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PD, progressive disease.
Data from 1 outlier not shown.

**Figure 6. Baseline activated NK-cell levels for responders versus nonresponders in SIRIUS.**

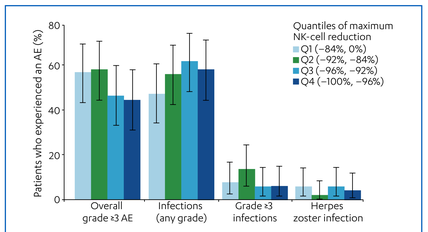
- A trend toward higher ORR was observed in quantiles with a greater maximum reduction in NK cells following DARA treatment (**Figure 7**)




ORR, overall response rate; NK, natural killer.

**Figure 7. Relationship between ORR and maximum reduction in NK cells.**

- No relationship between the reduction in NK cells and safety profile (ie, overall grade ≥3 AEs, infections of any grade, grade ≥3 infections, and herpes zoster infection) was observed (**Figure 8**)




NK, natural killer; AE, adverse event.

**Figure 8. No relationship between NK-cell reduction and safety.**

## CONCLUSIONS

- **NK cells express CD38 and are sensitive to DARA treatment in the clinic and in vitro**
- **ADCC, a robust in vitro mechanism of action for DARA-mediated MM cell killing, is heavily dependent on NK effector cells**
  - **Although NK cells are reduced following treatment, they are not completely depleted and may still contribute to ADCC and, thus, clinical efficacy**
- **Peripheral blood and bone marrow NK cells (total and activated) decreased with increasing DARA exposure in all patients, regardless of response, and exhibited an $E_{max}$-type exposure-response relationship, supporting NK cells as a pharmacodynamic marker for DARA**
- **Baseline NK-cell (total and activated) counts in peripheral blood and bone marrow were not different between responders and nonresponders**
- **NK-cell reduction during DARA treatment was not clinically relevant, with no apparent relationship with incidence of AEs (grade ≥3), infection (any grade or grade ≥3), and herpes zoster infection**
- **The multifaceted mechanism of action of DARA may contribute to the remarkable depth of clinical response in patients with MM**

### REFERENCES

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