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Understanding the Dose Regimen for Daratumumab in Patients With Relapsed or Refractory Multiple Myeloma After Prior Proteasome Inhibitors and Immunomodulatory Drugs: A Quantitative Pharmacologic Perspective

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INTRODUCTION

- Daratumumab (DARA) is an IgG1κ human monoclonal antibody that binds to CD38 and inhibits the growth of CD38-expressing tumor cells by inducing the following:
  - Direct apoptosis through Fc-mediated cross-linking[1]
  - Immune-mediated tumor cell lysis through complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP)[2,3]
  - Lysis of myeloid-derived suppressor cells (MDSCs) and a subset of regulatory T cells (CD38+ Tregs) that express CD38[4]
  - Increased CD4+ and CD8+ T-cell absolute counts and total lymphocyte percentages in both peripheral blood and bone marrow[4]
- Identification of optimal dose and schedule is challenging for DARA due to its target (CD38)-mediated drug disposition, which leads to a time-varying and concentration-dependent clearance of the drug, and results in complex interactions between DARA pharmacokinetics (PK) and pharmacodynamics
  - For example, slower clearance at a later time after treatment is expected due to the drug-induced depletion of targets, while a slower clearance at higher drug concentrations is expected due to saturation of the target (discussed in Poster 4222)
- In a phase 2 study of DARA in patients with heavily pretreated relapse or refractory MM (SIRIUS; ClinicalTrials.gov Identifier: NCT01985126), a recommended dose and schedule of 16 mg/kg weekly for 8 weeks, every 2 weeks for 16 weeks, and monthly thereafter was established[5]
- Here, we evaluate PK and efficacy/safety data from 2 clinical studies of DARA as monotherapy in patients with MM relapsed from or refractory to prior proteasome inhibitors (PIs) and/or immunomodulatory drugs (IMiDs), GEN501[6] (NCT00574288) and SIRIUS[5]

OBJECTIVE

- To understand and justify the recommended dose and dosing schedule for DARA in MM patients from a quantitative pharmacologic perspective

METHODS

Patients

- In GEN501, patients were ≥18 years of age, had documented myeloma requiring systemic therapy, had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, had relapsed from or were refractory to ≥2 prior lines of therapy, including PIs, IMiDs, chemotherapy, and autologous stem cell transplantation
- In SIRIUS, patients were ≥18 years of age, had documented myeloma requiring systemic therapy, had an ECOG performance status of ≤2, 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 and Treatment Schedule

- GEN501 was an open-label, phase 1/2, dose-escalation and expansion study[6]
  - A predose of DARA (10% of the full dose, up to 10 mg total) was given the day prior to the first 2 full infusions (in Part 1, and in 2 out of 3 8 mg/kg dose cohorts in Part 2)
  - In Part 1, DARA doses ranged from 0.005 mg/kg to 24 mg/kg

- The first infusion was followed by a 3-week washout period, after which doses were administered weekly for up to 7 full infusions
  - In Part 2, DARA was given as either:
    - 8 mg/kg weekly for 8 weeks, every 2 weeks for 16 weeks, and then monthly until disease progression, or
    - 16 mg/kg, with a 3-week washout after the first infusion, then weekly for 7 weeks, every 2 weeks for 14 weeks, and then monthly until disease progression
- SIRIUS was an open-label, multicenter, phase 2 study[5]
  - Patients received DARA 8 mg/kg every 4 weeks, or
  - 16 mg/kg weekly for 8 weeks, every 2 weeks for 16 weeks, and monthly thereafter

Exposure

- A validated enzyme-linked immunosorbent assay was used to determine serum concentrations (Janssen Research & Development, LLC, Spring House, PA)[7]
- Clearance of DARA was characterized using population PK modeling (NONMEM® 7.2)
  - To understand the association between target saturation and DARA exposure, simulations were conducted to predict DARA PK profiles, target saturation profiles, and exposure metrics based on a previously developed population PK model
- Exposure metrics included: maximal pre-infusion (trough) concentration ($C_{pre-infusion,max}$), maximal end-of-infusion concentration ($C_{post-infusion,max}$), pre-infusion concentration before the last dose received, end-of-infusion concentration after the last dose received, and average concentration during treatment

Study Endpoints

- Several exposure-response relationships were examined for the efficacy and safety endpoints
  - Efficacy: overall response rate (ORR), duration of response (DOR), and time to progression (TTP)
  - Safety: infusion-related reactions, thrombocytopenia, anemia, neutropenia, lymphopenia, and infections
    - The predicted end-of-infusion concentration after the first infusion ($C_{max,1st}$) was explored for infusion-related reactions because the majority of these adverse events occurred during the first dose
    - The predicted $C_{post-infusion,max}$ was investigated for the other adverse events

Statistical Analyses

- The relationship between exposure and ORR was analyzed with logistic regression; linear models and maximum effect (E_{max}) models were compared; the model predicted probability, along with the 95% confidence band, was plotted and compared to the observed response rate that was grouped by quantiles of DARA exposure
- Cox proportional hazards regression models[8] (implemented in the "survival" package in R) were used to analyze the impact of the decrease in DARA concentration over time on TTP/DOR

RESULTS

- Treatment with DARA 16 mg/kg weekly for 8 weeks, then every 2 weeks for 16 weeks, then every 4 weeks thereafter until progression resulted in ORRs of 36% in GEN501 and 29% in SIRIUS[5,6] (**Table 1**)

Table 1. DARA 16 mg/kg Dosing Regimen: Best Response in GEN501 and SIRIUS Studies

	GEN501 Part 2 (n = 42)	SIRIUS (n = 106)	Total (N = 148)
Best response, n (%)			
sCR	0	3 (2.8)	3 (2.0)
CR	2 (4.8)	0	2 (1.4)
VGPR	2 (4.8)	10 (9.4)	12 (8.1)
PR	11 (26.2)	18 (17.0)	29 (19.6)
Minimal response	4 (9.5)	5 (4.7)	9 (6.1)
Stable disease	22 (52.4)	46 (43.4)	68 (45.9)
Progressive disease	0	18 (17.0)	18 (12.2)
Not evaluable	1 (2.4)	6 (5.7)	7 (4.7)
Overall response (sCR + CR + VGPR + PR)	15 (35.7)	31 (29.2)	46 (31.1)
12-month OS rate (95% CI)	77.0 (58.0–88.2)	64.8 (51.2–75.5)	68.5 (58.1–76.9)

DARA, daratumumab; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; OS, overall survival; CI, confidence interval.

Relationship Between DARA Exposure and Efficacy

- ORR significantly increased with DARA exposure, and there was an E_{max} relationship between DARA exposure based on $C_{pre-infusion,max}$ and ORR (**Figure 1**) and between DARA concentration and target saturation
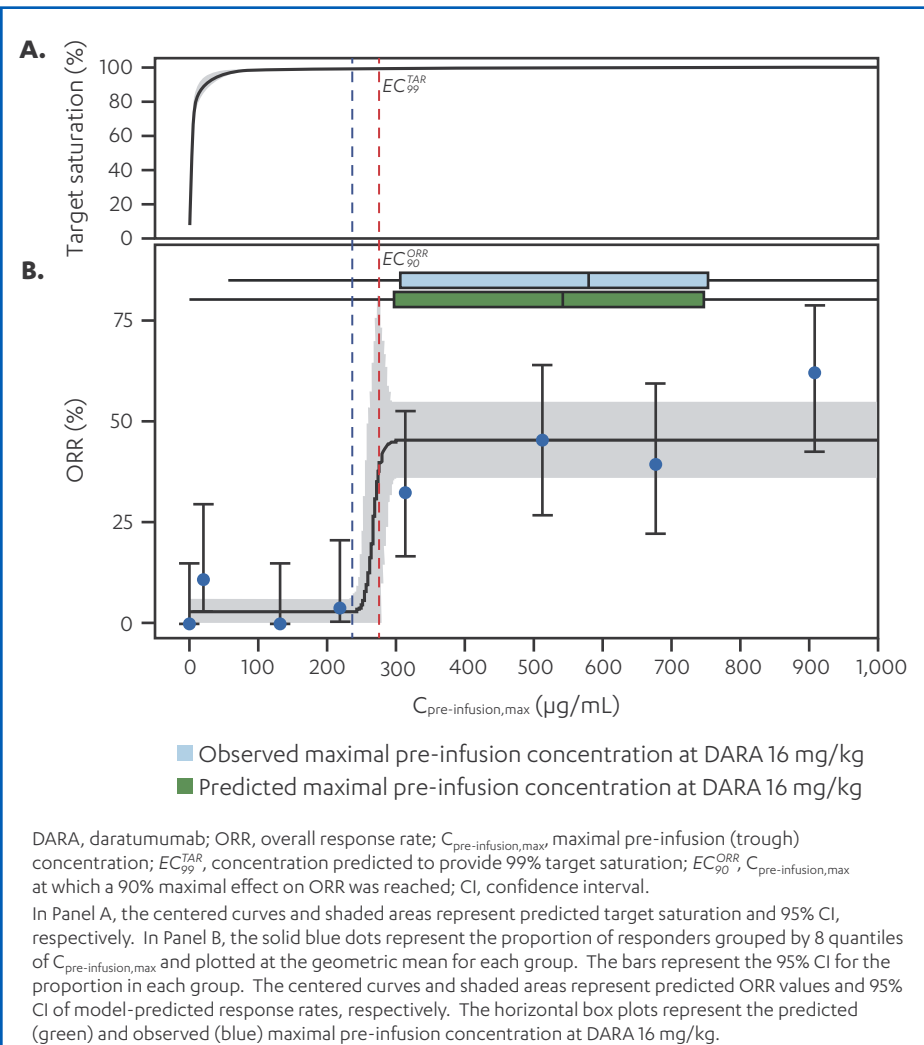

Figure 1. Maximum effect relationship between DARA concentration and target saturation (A) and between ORR and predicted $C_{pre-infusion,max}$ (B).

DARA, daratumumab; ORR, overall response rate; $C_{pre-infusion,max}$, maximal pre-infusion (trough) concentration; EC_{90}^{ORR}, concentration predicted to provide 99% target saturation; EC_{99}^{TAR}, $C_{pre-infusion,max}$ at which a 90% maximal effect on ORR was reached; CI, confidence interval.
In Panel A, the centered curves and shaded areas represent predicted target saturation and 95% CI, respectively. In Panel B, the solid blue dots represent the proportion of responders grouped by 8 quantiles of $C_{pre-infusion,max}$ and plotted at the geometric mean for each group. The bars represent the 95% CI for the proportion in each group. The centered curves and shaded areas represent predicted ORR values and 95% CI of model-predicted response rates, respectively. The horizontal box plots represent the predicted (green) and observed (blue) maximal pre-infusion concentration at DARA 16 mg/kg.

- The $C_{pre-infusion,max}$ at which a 90% maximal effect on ORR was reached (EC_{90}^{ORR}) was 274 μg/mL and was similar to the concentration predicted to provide 99% target saturation (EC_{99}^{TAR}; 236 μg/mL)
  - Based on observed and predicted PK parameters, after ≥8 weekly infusions of 16 mg/kg, approximately 80% of patients achieved serum concentrations above the EC_{90}^{ORR} threshold
- Across all dose levels, separation in the observed trough concentration over time was apparent between responders and non-responders, with maximal separation around the time of maximal trough concentrations in both groups (**Figure 2**)
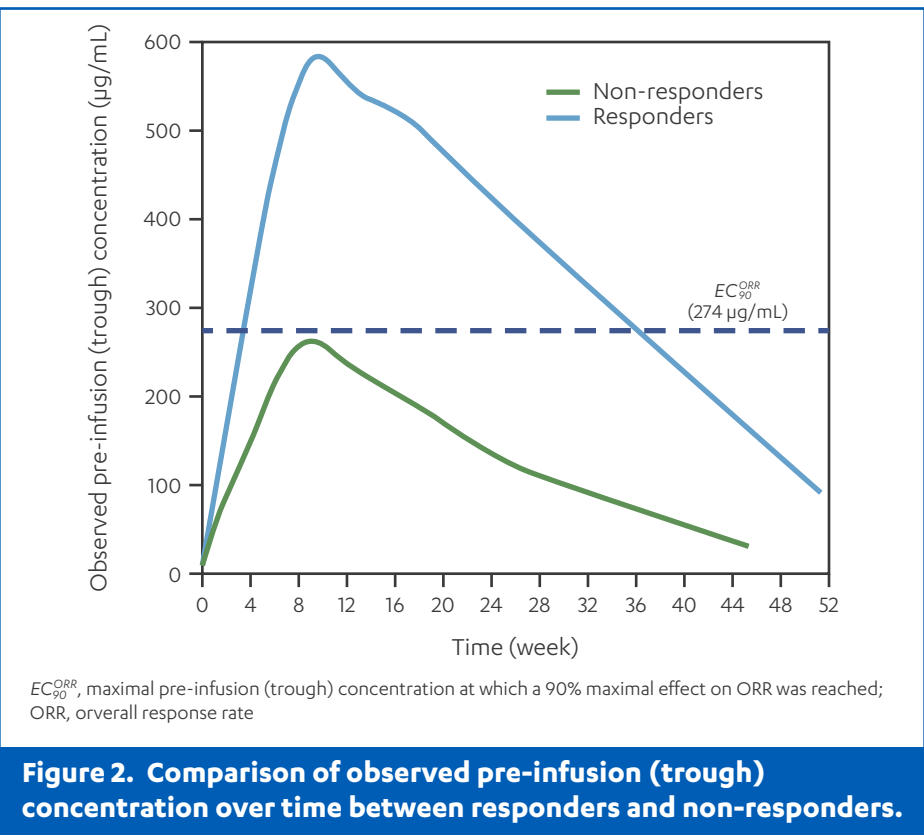

Figure 2. Comparison of observed pre-infusion (trough) concentration over time between responders and non-responders.

EC_{90}^{ORR}, maximal pre-infusion (trough) concentration at which a 90% maximal effect on ORR was reached; ORR, overall response rate.

DARA Pharmacokinetics and Target Saturation

- Clearance was concentration- and time-dependent, resulting in a clearance that decreased with increasing dose/concentration and with multiple doses over time (**Figure 3**)
  - Intensive weekly dosing was used at the beginning of treatment to overcome the high initial clearance and to rapidly establish the efficacious concentration
  - Thereafter, 16 mg/kg dosing intervals every 2 weeks, followed by every 4 weeks, were adequate to saturate the target and maintain the total clearance close to the nonspecific linear clearance
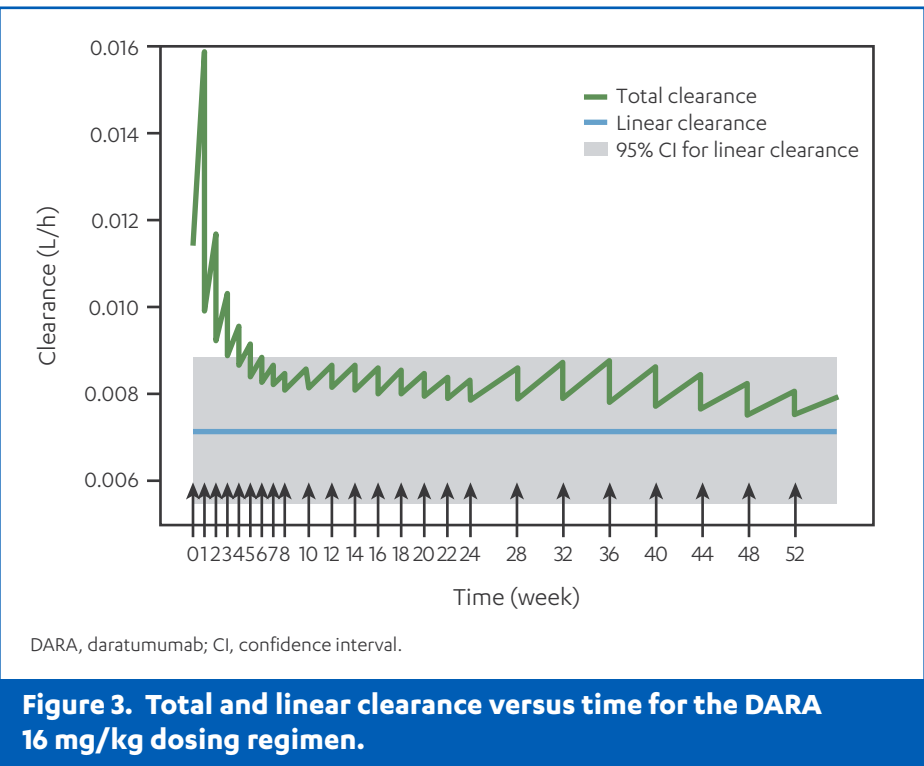

Figure 3. Total and linear clearance versus time for the DARA 16 mg/kg dosing regimen.

DARA, daratumumab; CI, confidence interval.

- Although the concentration of DARA tended to decrease following every 2-week and every 4-week dosing intervals until reaching steady state, the reduction in target saturation over time in the study population was minimal, with a median above 98% at Week 52 (**Figure 4**)
- The reduction in concentration over time that was observed in the studies was not associated with either shorter duration of response or higher risk of disease progression (**Figure 5**)
  - This finding corroborates the clinical analysis, which indicated that the rate of patients experiencing disease progression was consistent in the every 2-week and every 4-week dosing intervals
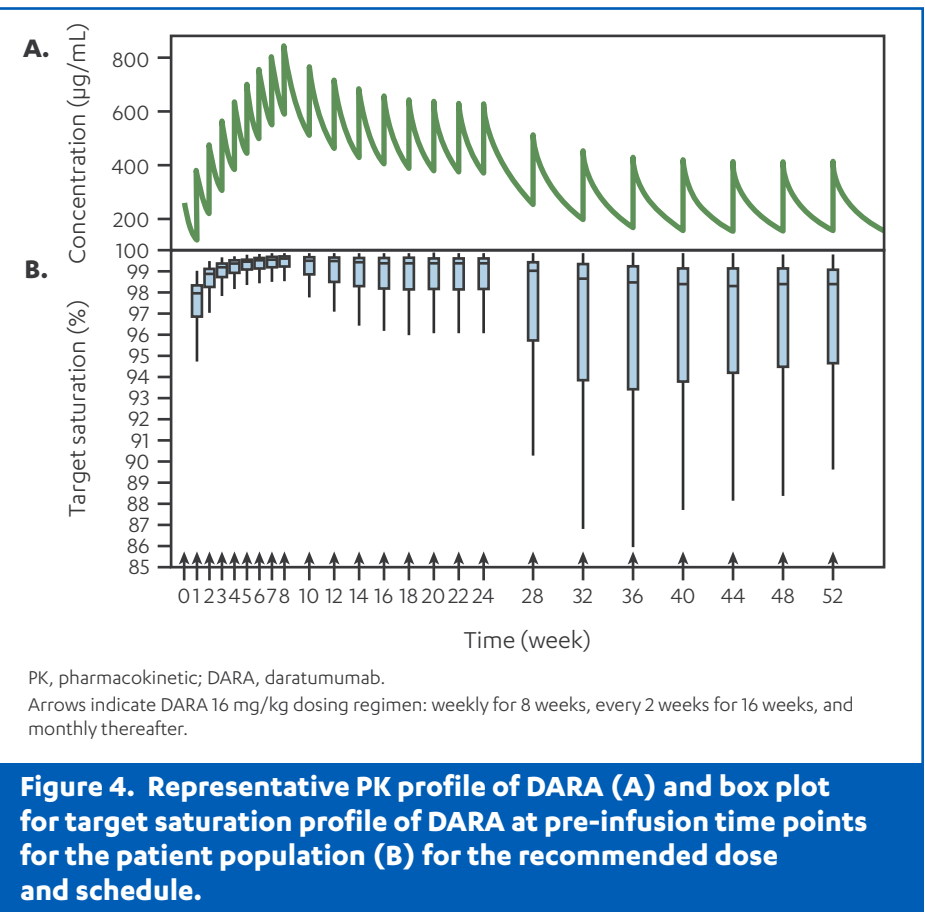

Figure 4. Representative PK profile of DARA (A) and box plot for target saturation profile of DARA at pre-infusion time points for the patient population (B) for the recommended dose and schedule.

PK, pharmacokinetic; DARA, daratumumab.
Arrows indicate DARA 16 mg/kg dosing regimen: weekly for 8 weeks, every 2 weeks for 16 weeks, and monthly thereafter.
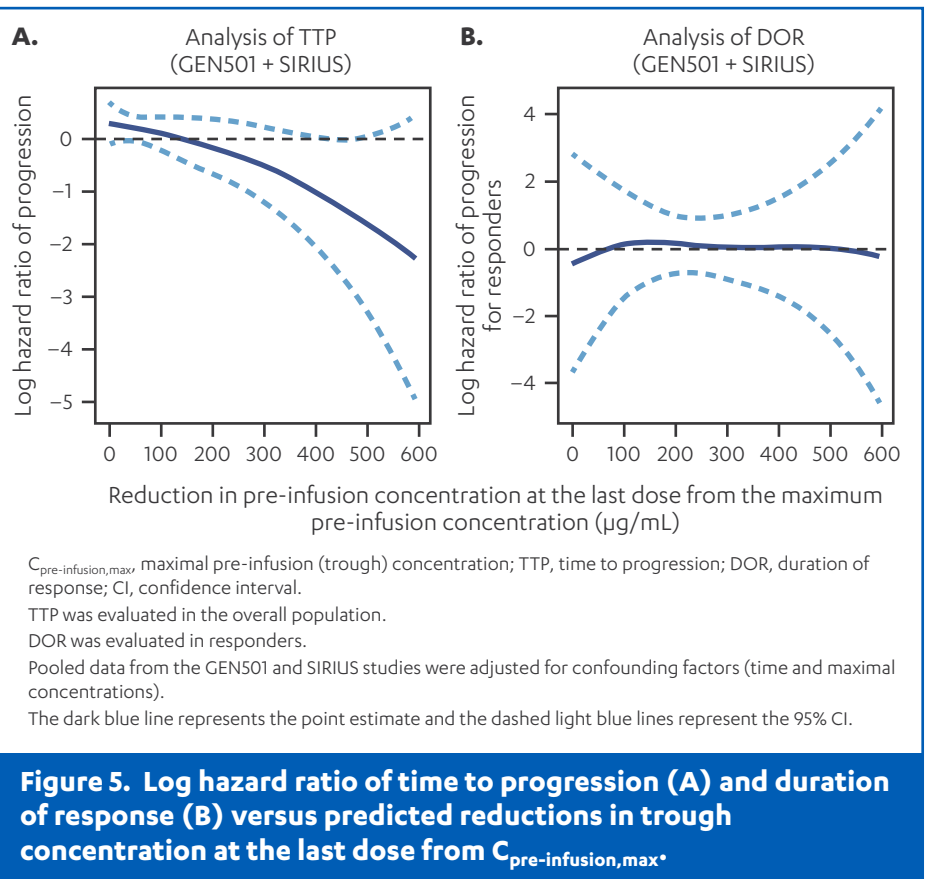

Figure 5. Log hazard ratio of time to progression (A) and duration of response (B) versus predicted reductions in trough concentration at the last dose from $C_{pre-infusion,max}$*

$C_{pre-infusion,max}$, maximal pre-infusion (trough) concentration; TTP, time to progression; DOR, duration of response; CI, confidence interval.
TTP was evaluated in the overall population.
DOR was evaluated in responders.
Pooled data from the GEN501 and SIRIUS studies were adjusted for confounding factors (time and maximal concentrations).
The dark blue line represents the point estimate and the dashed light blue lines represent the 95% CI.

Relationship Between Exposure and Safety

- There was no apparent relationship between DARA exposure and infusion-related reactions, thrombocytopenia, anemia, neutropenia, or lymphopenia (**Figure 6**)
  - Although the overall event rate of infection increased numerically with DARA exposure, this trend was not observed for infections of grade 3 or higher
- The safety profile of the 16-mg/kg dose was consistent with the total population
  - There was no observed trend toward higher overall incidence of treatment-emergent adverse events in higher dose groups
- No patients were positive for antibodies to DARA

Figure 6. Comparison of overall (A) and grade ≥3 (B) adverse event rates between predicted DARA exposure quartiles.*

DARA, daratumumab; IRR, infusion-related reaction; $C_{max,1st}$, end-of-infusion concentration after the first infusion; $C_{post-infusion,max}$, maximal end-of-infusion concentration.
*$C_{max,1st}$ was used as the exposure measure for analyses on IRRs; error bars represent 95% CIs.
$C_{post-infusion,max}$ was used as the exposure measure for analyses on other adverse events.
The quartiles for $C_{max,1st}$ were: 1st quartile (434 μg/mL), 2nd quartile (134-245 μg/mL), 3rd quartile (245-310 μg/mL), and 4th quartile (310-470 μg/mL).
The quartiles for $C_{post-infusion,max}$ were: 1st quartile (470 μg/mL), 2nd quartile (270-511 μg/mL), 3rd quartile (511-907 μg/mL), and 4th quartile (907-1,840 μg/mL).
Data were pooled from GEN501 and SIRIUS studies.

CONCLUSIONS

- These analyses demonstrate that the recommended dose regimen of DARA is appropriate for patients with relapsed or refractory MM
  - Lower doses would be expected to reduce efficacy, and higher doses do not appear to improve the benefit-risk profile
- DARA 16 mg/kg rapidly establishes efficacious concentrations during the initial intense, weekly dosing period
  - The recommended dosing schedule is 16 mg/kg weekly for 8 weeks, every 2 weeks for 16 weeks, and monthly thereafter
- Target saturation is maintained, reducing the risk of disease progression at the later, less frequent dosing intervals of every 2 weeks and every 4 weeks
- Overall and grade 3 adverse events do not appear to correlate with DARA exposure

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