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Target-mediated Drug Disposition of Daratumumab Following Intravenous Infusion in Relapsed or Refractory Multiple Myeloma After Prior Proteasome Inhibitors and Immunomodulatory Drugs: A Population Pharmacokinetic Analysis

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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, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis[2,3]
  - Lysis of myeloid-derived suppressor cells and a subset of regulatory T cells that express CD38[4]
  - Increased $CD4^+$ and $CD8^+$ T-cell absolute counts and total lymphocyte percentages in both peripheral blood and bone marrow[4]
- Population pharmacokinetic (PK) analyses were performed based on data from 2 clinical studies of DARA as monotherapy in patients with multiple myeloma (MM) relapsed from or refractory to prior proteasome inhibitors (PIs) and/or immunomodulatory drugs (IMiDs): GEN501[5] (ClinicalTrials.gov Identifier: NCT00574288) and SIRIUS[6] (NCT01985126)

OBJECTIVES

- To characterize the target-mediated drug disposition (TMDD) and variability associated with DARA disposition
- To predict target (CD38) saturation and its relationship with DARA exposure
- To evaluate the effects of individual demographic characteristics and other factors on the disposition of DARA
- To understand DARA exposure and target saturation in subpopulations

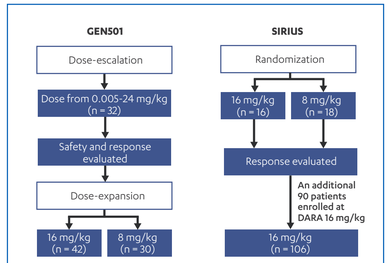
METHODS

Patients

- In both studies, patients were ≥18 years of age, had documented myeloma requiring systemic therapy, and had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2
- In GEN501, patients had relapsed from or were refractory to ≥2 prior lines of therapy, including PIs, IMiDs, chemotherapy, and autologous stem cell transplantation
- In SIRIUS, patients had progressed on their most recent line of therapy, and had received ≥3 prior lines of therapy that included a PI and an IMiD or were double refractory to both a PI and an IMiD

Study Design

- GEN501 was a phase 1/2, open-label, multicenter study conducted in 2 parts (**Figure 1**)
  - Part 1 was a dose-escalation phase
  - Part 2 was a dose-expansion phase
- SIRIUS was a phase 2, open-label, international, multicenter study of Simon 2-stage design (**Figure 1**)



DARA, daratumumab.

Figure 1. Study design for GEN501 and SIRIUS.

Treatment Schedule

- In GEN501, DARA treatment was administered as follows:
  - 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)
  - Part 1 (n = 32)
    - Sequential cohorts received doses ranging from 0.005 mg/kg to 24 mg/kg
    - The first infusion was followed by a 3-week washout period; doses were then administered weekly for up to 7 full infusions
  - Part 2 (n = 72)
    - 8 mg/kg weekly for 8 weeks, then every other week for 16 weeks, and then monthly until disease progression, or
    - 16 mg/kg, with a 3-week washout period between the first and second infusions, then weekly for 7 weeks, every other week for 14 weeks, and then monthly until disease progression
- In SIRIUS, DARA was administered as follows:
  - 8 mg/kg monthly (n = 18), or
  - 16 mg/kg weekly for 8 weeks, every other week for 16 weeks, and then every 4 weeks thereafter (n = 106)
  - 16 mg/kg, administered as described above, was established as the recommended dose

Population PK Analyses

- The population PK analyses were performed on pooled datasets from the GEN501 and SIRIUS studies
- A validated enzyme-linked immunosorbent assay (BioAnalytical Research Corporation Global Central Laboratory, Ghent, Belgium; Janssen Research & Development, LLC, Spring House, PA, USA) was used to assess serum DARA concentrations
- Serum samples were screened for antibodies binding to DARA; for positive serum samples, the serum titer was evaluated using validated assay methods
- Population PK modeling was performed using NONMEM® 7.2 (ICON, Dublin, Ireland)
  - The software package R (version 2.15.3) was used for data management, post-processing, and graphic analyses of NONMEM® runs
- Model-based covariate analyses and simulations were conducted to evaluate the influence of individual characteristics/factors on exposure to DARA

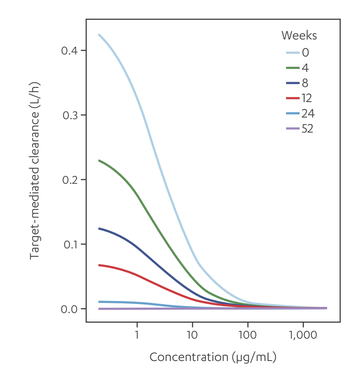
RESULTS

Patients

- A total of 2,572 DARA serum concentration measurements from 223 patients enrolled in GEN501 and SIRIUS were included in the population PK modeling
- DARA doses ranged from 0.1 mg/kg to 24 mg/kg, and 150 patients received the recommended dose of 16 mg/kg
  - Five patients were excluded from the population PK analyses because they did not have measurable concentrations of DARA, including 1 patient who received only 1 dose at 16 mg/kg and 4 patients who received doses of <0.1 mg/kg
- No patients were positive for antibodies to DARA

Population PK Modeling of DARA

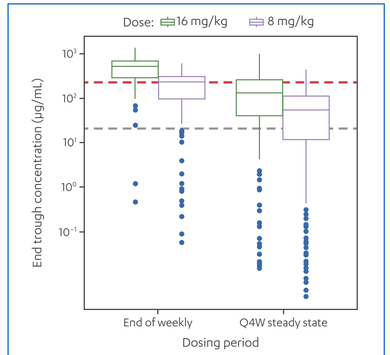
- The data were best described by a 2-compartment population PK model with parallel linear and nonlinear Michaelis-Menten eliminations
- This model suggested that the nonlinear (target-mediated) clearance of DARA was both concentration- and time-dependent, likely due to saturation and depletion of the target (**Figure 2**)
- At steady state, the target-mediated clearance of DARA approached zero; therefore, by the end of the weekly dosing period, the (nonspecific) linear clearance became the dominant clearance pathway
- The concentration- and time-dependency of DARA clearance suggested that the dynamics of target/tumor burden significantly influenced DARA disposition in patients



DARA, daratumumab.
Target-mediated clearance decreases with increasing concentration and time due to target saturation and depletion, respectively.

Figure 2. Concentration- and time-dependency of target-mediated clearance of DARA.

- The population PK model predicted that concentrations of 21.4 μg/mL and 236 μg/mL would be needed to achieve 90% and 99% target saturation, respectively (**Figure 3**)
  - At the end of every 4 weeks (Q4W) dosing, 82% and 67% of patients achieved >90% target saturation at doses of DARA 16 mg/kg and 8 mg/kg, respectively

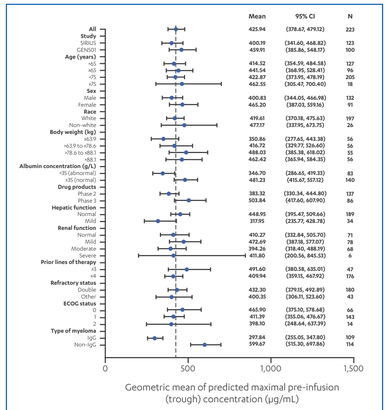


Q4W, every 4 weeks; DARA, daratumumab; Q2W, every 2 weeks; EC_{99}^{Ss}, concentration at which 99% of target saturation is reached; EC_{90}^{Ss}, concentration at which 90% of target saturation is reached.
Red and gray dashed lines represent the concentration of DARA at which the 99% (EC_{99}^{Ss}) and 90% (EC_{90}^{Ss}) target saturation is achieved, respectively.
The simulations were performed assuming the dosing schedule of weekly for 8 weeks, Q2W for 16 weeks, and then Q4W (8 doses for the current simulation) thereafter. The sampling time for end of weekly dosing was the pre-infusion of the 1st dose in the Q2W dosing period; it was the pre-infusion of the 8th dose in the Q4W dosing period for Q4W steady state.
EC_{99}^{Ss} was obtained by solving $\frac{EC^{Ss}}{E_{C^{Ss}}+EC_{50}}$ = 99%, and EC_{90}^{Ss} was obtained by solving $\frac{EC^{Ss}}{E_{C^{Ss}}+EC_{50}}$ = 90%. The percentage of patients who achieved >99% target saturation at the end of weekly dosing with DARA 16 mg/kg and 8 mg/kg was 83% and 48%, respectively.

Figure 3. Box plot for the predicted pre-infusion (trough) concentrations at the end of weekly and Q4W steady-state dosing at DARA 16 mg/kg and 8 mg/kg.

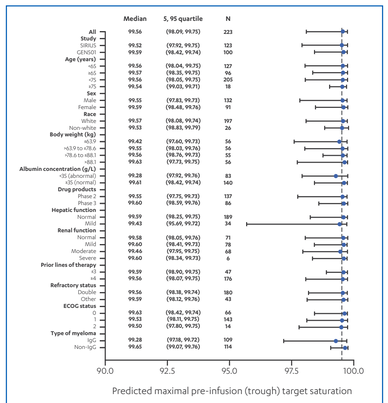
Effect of Patient Covariates on DARA Disposition and Exposure

- The linear clearance and volume of distribution of DARA significantly increased with increasing body weight
  - As a result, after administration on a mg/kg basis, exposure to DARA was relatively consistent across the range of body weights of MM patients
- Exposure to DARA was not significantly affected by age, race, renal impairment, or mild hepatic impairment (**Figures 4** and **5**)
  - These variables did not have clinically relevant covariates
  - No patients developed antibodies to DARA; thus, immune response was not evaluated as a covariate
- Exposure to DARA was consistent across patients stratified by ECOG status, refractory status, and number of prior therapies (**Figures 4** and **5**)
- A statistically significant difference in DARA exposure was observed with sex, myeloma subtype, and baseline albumin levels (**Figures 4** and **5**), but these differences did not have a clinically relevant impact on efficacy (**Figure 6**) or safety
  - Supporting analyses of the relationship between DARA exposure and efficacy and safety are presented in Poster 4254



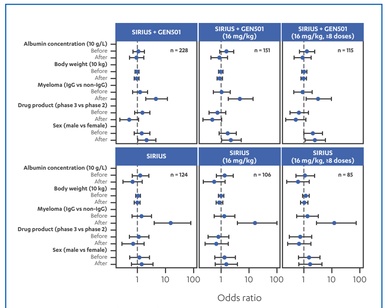
CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; DARA, daratumumab; Q2W, every 2 weeks; Q4W, every 4 weeks.
Solid blue circles represent geometric means and error bars represent 95% CIs. The dashed gray line represents the geometric mean value (ie, 425.94 μg/mL) of all subjects.
Analyses assumed that all patients in SIRIUS and GEN501 received DARA 16 mg/kg weekly for 8 weeks (8 doses), Q2W for 16 weeks (8 doses), and Q4W thereafter. Maximal pre-infusion (trough) concentration was derived as the pre-infusion concentration of the 1st dose of the Q2W dosing period.
Among the investigated exposure metrics, maximal pre-infusion (trough) concentration had the strongest correlation with the efficacy endpoints.

Figure 4. Forest plot of subgroup analyses on the predicted maximal pre-infusion (trough) concentration.



CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; DARA, daratumumab; Q2W, every 2 weeks; Q4W, every 4 weeks.
Solid blue circles represent medians (50th quantile). Error bars represent 5th to 95th quantile ranges. The dashed gray line represents the median value (ie, 99.56) of all subjects.
Analyses assumed that all patients in SIRIUS and GEN501 received DARA 16 mg/kg weekly for 8 weeks (8 doses), Q2W for 16 weeks (8 doses), and Q4W thereafter. Maximal pre-infusion (trough) concentration was derived as the pre-infusion concentration of the 1st dose of the Q2W dosing period. Target saturation was calculated as 100*C/(Km + C), where C is the maximal pre-infusion (trough) concentration.
Among the investigated exposure metrics, maximal pre-infusion (trough) concentration had the strongest correlation with the efficacy endpoints.

Figure 5. Forest plot of subgroup analyses on the predicted target saturation at the predicted maximal pre-infusion (trough) concentrations.



PK, pharmacokinetic; DARA, daratumumab.

Figure 6. Effects of covariates identified from population PK analysis on overall response rate before and after adjusting for DARA exposure: estimated odds ratio and 95% confidence interval.

CONCLUSIONS

- **A 2-compartment population PK model with parallel linear and nonlinear Michaelis-Menten eliminations adequately described the observed patient data**
- **The model suggested that DARA clearance was concentration- and time-dependent, and that DARA nonlinear (target-mediated) clearance decreased over time**
- **Linear clearance and volume of distribution of DARA significantly increased with increasing body weight, resulting in similar DARA exposure across patients with a range of body weights, indicating that body-weight–based dosing is a feasible strategy**
- **Aside from body weight, none of the examined patient covariates had a clinically relevant effect on DARA disposition or exposure**
- **Age and gender do not have clinically important effects on DARA PK. No dosage adjustment is necessary for patients with pre-existing renal or mild hepatic impairment**

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DISCLOSURES

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