# Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial

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## Summary

**Background** Intravenous daratumumab for treatment of patients with multiple myeloma involves a lengthy infusion that affects quality of life, and infusion-related reactions are common. Subcutaneous daratumumab is thought to be easier to administer and to cause fewer administration-related reactions. In this study (COLUMBA), we tested the non-inferiority of subcutaneous daratumumab to intravenous daratumumab.

**Methods** In this ongoing, multicentre (147 sites in 18 countries), open-label, non-inferiority, randomised, phase 3 trial, we recruited adult patients (age ≥18 years) if they had confirmed relapsed or refractory multiple myeloma according to International Myeloma Working Group criteria; received at least three previous lines of therapy, including a proteasome inhibitor and immunomodulatory drug, or were double refractory to both a proteasome inhibitor and immunomodulatory drug; and had an Eastern Cooperative Oncology Group performance status score of 2 or lower. Patients were randomly assigned (1:1) by a computer-generated randomisation schedule and balanced using randomly permuted blocks to receive daratumumab subcutaneously (subcutaneous group) or intravenously (intravenous group). Randomisation was stratified on the basis of baseline bodyweight (≤65 kg, 66–85 kg, >85 kg), previous therapy lines (≤four *vs* >four), and myeloma type (IgG *vs* non-IgG). Patients received 1800 mg of subcutaneous daratumumab co-formulated with 2000 U/mL recombinant human hyaluronidase PH20 or 16 mg/kg of intravenous daratumumab once weekly (cycles 1–2), every 2 weeks (cycles 3–6), and every 4 weeks thereafter (28-day cycles) until progressive disease or toxicity. The co-primary endpoints were overall response and maximum trough concentration ($C_{trough}$; cycle 3, day 1 pre-dose). The non-inferiority margin for overall response was defined using a 60% retention of the lower bound (20·8%) of the 95% CI of the SIRIUS trial. Efficacy analyses were done by intention-to-treat population. The pharmacokinetic-evaluable population included all patients who received all eight weekly daratumumab doses in cycles 1 and 2 and provided a pre-dose pharmacokinetics blood sample on day 1 of cycle 3. The safety population included all patients who received at least one daratumumab dose. This trial is registered with ClinicalTrials.gov, NCT03277105.

**Findings** Between Oct 31, 2017, and Dec 27, 2018, 655 patients were screened, of whom 522 were recruited and randomly assigned (subcutaneous group n=263; intravenous group n=259). Three patients in the subcutaneous group and one in the intravenous group did not receive treatment and were not evaluable for safety. At a median follow-up of 7·5 months (IQR 6·5–9·3), overall response and $C_{trough}$ met the predefined non-inferiority criteria. An overall response was seen in 108 (41%) of 263 patients in the subcutaneous group and 96 (37%) of 259 in the intravenous group (relative risk 1·11, 95% CI 0·89–1·37). The geometric means ratio for $C_{trough}$ was 107·93% (90% CI 95·74–121·67), and the maximum $C_{trough}$ was 593 µg/mL (SD 306) in the subcutaneous group and 522 µg/mL (226) in the intravenous group. The most common grade 3 and 4 adverse events were anaemia (34 [13%] of 260 patients evaluable for safety in the subcutaneous group and 36 [14%] of 258 patients in the intravenous group), neutropenia (34 [13%] and 20 [8%]), and thrombocytopenia (36 [14%] and 35 [14%]). Pneumonia was the only serious adverse event in more than 2% of patients (seven [3%] in the subcutaneous group and 11 [4%] in the intravenous group). There was one death resulting from a treatment-related adverse event in the subcutaneous daratumumab group (febrile neutropenia) and four in the intravenous group (sepsis [n=2], hepatitis B reactivation [n=1], and *Pneumocystis jirovecii* pneumonia [n=1]).

**Interpretation** Subcutaneous daratumumab was non-inferior to intravenous daratumumab in terms of efficacy and pharmacokinetics and had an improved safety profile in patients with relapsed or refractory multiple myeloma. These data could contribute to the approval of the subcutaneous daratumumab formulation by regulatory bodies.

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## Introduction

Daratumumab (a human IgGκ CD38-targeting monoclonal antibody) has been shown to be safe and efficacious in patients with multiple myeloma as monotherapy[1–3] and in combination regimens.[4–8] In the USA, daratumumab monotherapy (16 mg/kg intravenously in 28-day cycles, once weekly for cycles 1 and 2, every 2 weeks for cycles 3–6, then every 4 weeks) is approved in patients with at least three previous therapies including a proteasome inhibitor and an immunomodulatory drug, or who are double-refractory to a proteasome inhibitor and immunomodulatory drug.[9] Daratumumab is approved in combination with other therapies: lenalidomide–dexamethasone (newly diagnosed patients ineligible for transplants and patients with ≥1 previous therapy), bortezomib–melphalan–prednisone (newly diagnosed patients ineligible for transplants), bortezomib–thalidomide–dexamethasone (newly diagnosed patients ineligible for transplants), bortezomib–dexamethasone (patients with ≥1 previous therapy), and pomalidomide–dexamethasone (patients with ≥2 previous therapies including lenalidomide and a proteasome inhibitor).[9]

Administration of intravenous daratumumab takes about 7 h for the first infusion and 3–4 h thereafter.[9] Long infusion times might affect quality of life and strain health-care resources.[10] Intravenous daratumumab is associated with infusion-related reactions, mainly during the first infusion, in approximately half of patients.[9] To shorten the infusion time required for daratumumab administration and possibly decrease the risk of infusion-related reactions, a subcutaneous formulation of daratumumab (1800 mg daratumumab co-formulated with 2000 U/mL recombinant human hyaluronidase PH20 [rHuPH20; ENHANZE drug delivery technology; Halozyme, San Diego, CA, USA]) was developed. Subcutaneous daratumumab has several potential benefits, including shorter administration time (3–5 min), fewer infusion-related reactions, and simplified drug preparation and administration, thereby reducing errors.[11] The phase 1b PAVO study showed the feasibility of subcutaneous daratumumab treatment for patients with multiple myeloma on the basis of pharmacokinetics, durable responses, and an acceptable safety profile.[11–13] Here (COLUMBA study), we investigated whether the efficacy and pharmacokinetics of subcutaneous daratumumab are non-inferior to intravenous daratumumab.

## Methods

### Study design

COLUMBA is an ongoing, multicentre, open-label, non-inferiority, randomised phase 3 trial that includes patients from 147 academic and community health centres in 18 countries (Australia, Brazil, Canada, Czech Republic, France, Greece, Israel, Italy, Japan, Poland, Russia, Spain, South Korea, Sweden, Taiwan, Ukraine, the UK, and the USA; appendix p 4). The study was done in accordance with the principles of the Declaration of Helsinki, International Conference on Harmonisation Guideline for Good Clinical Practice, and applicable region-specific regulatory requirements.

### Research in context

#### Evidence before this study

We searched PubMed for clinical trials that assessed the subcutaneous administration of a monoclonal antibody published in any language from database inception to Jan 28, 2020. All fields were searched for "multiple myeloma", "subcutaneous", and "monoclonal antibody". Our search identified 56 articles published during this timeframe; of them, 13 were clinical trials, but only one of them met our full inclusion criteria. This trial was part one of the phase 1b PAVO study, which evaluated a subcutaneous mix-and-deliver formulation of daratumumab in combination with the recombinant human hyaluronidase PH20 enzyme in patients with relapsed or refractory multiple myeloma. Thus, we identified an unmet need to directly compare subcutaneous daratumumab to intravenous daratumumab.

#### Added value of this study

To our knowledge, our study is the first head-to-head comparison of subcutaneous and intravenous daratumumab. Subcutaneous administration offers numerous benefits over intravenous, including shorter administration time, fewer infusion-related reactions, and simplified drug preparation. We found subcutaneous daratumumab to be non-inferior to intravenous daratumumab in efficacy and pharmacokinetics, thus adding to the knowledge of subcutaneous delivery of daratumumab.

#### Implications of all the available evidence

The availability of subcutaneous daratumumab, with a markedly shorter administration time and reduced rate of infusion-related reactions compared with intravenous daratumumab, will have extensive implications for patients, caregivers, and health-care professionals. The quality of life and safety benefits of subcutaneous daratumumab, combined with the non-inferior efficacy, over intravenous daratumumab could contribute to the approval of the subcutaneous daratumumab formulation by regulatory bodies. Further data are needed to confirm these findings for subcutaneous daratumumab use in combination regimens.

Study protocol and amendments (appendix pp 19–330) were reviewed by independent ethics committees and institutional review boards at each centre.

### Participants

Eligible patients were aged 18 years or older; had a documented diagnosis of multiple myeloma according to the International Myeloma Working Group (IMWG) diagnostic criteria,[14] and measurable disease based on increased serum or urine M-protein concentrations or increased serum immunoglobulin free light chain; and an Eastern Cooperative Oncology Group (ECOG) performance status score of 2 or lower (appendix p 50). Patients with relapsed or refractory multiple myeloma had received at least three previous lines of therapy, including a proteasome inhibitor and an immunomodulatory drug, or were double refractory to both a proteasome inhibitor and an immunomodulatory drug, and had evidence of response to at least one previous treatment regimen. Pretreatment clinical laboratory values during the screening phase were required to show adequate bone marrow, liver, and kidney function: (haemoglobin ≥7·5 g/dL [≥5 mmol/L], absolute neutrophil count ≥$1·0 \times 10^9$ per L, platelet count ≥$50 \times 10^9$ per L, aspartate aminotransferase ≤2·5 × the upper limit of normal [ULN], alanine aminotransferase ≤2·5 × ULN, total bilirubin ≤2·0 × ULN, and estimated creatinine clearance >20 mL per min per 1·73 $m^2$). Women of childbearing potential had to agree to use two methods of birth control at least 4 weeks before first treatment dose and had to have a negative pregnancy test 2 weeks before randomisation.

The exclusion criteria included previous treatment with daratumumab or other anti-CD38 therapies; anti-myeloma treatment within 2 weeks or five pharmacokinetic half-lives before randomisation; receipt of an autologous stem cell transplant within 12 weeks before randomisation; malignancies other than multiple myeloma, unless all treatment of that malignancy had been completed at least 2 years before consent and the patient had no evidence of the disease; meningeal involvement of the myeloma; chronic obstructive pulmonary disease with a forced expiratory volume in 1 s of less than 50% of the predicted normal; moderate or severe persistent asthma or a history of asthma within the last 2 years; clinically significant cardiac disease; seropositivity for HIV, hepatitis B, or hepatitis C; and known allergies to study-relevant compounds and any other conditions that might interfere with the study protocol (appendix pp 51–53). All patients provided written informed consent.

### Randomisation and masking

Enrolment of patients was determined by investigators and screened by the study sponsor. Eligible patients were randomly assigned (1:1) to receive either subcutaneous daratumumab (subcutaneous group) or intravenous daratumumab (intravenous group). Randomisation was via a computer-generated randomisation schedule (Signant Health; Wayne, PA, USA) and balanced using randomly permuted blocks. The randomisation schedule was prepared before the study and done under the supervision of the sponsor. Individuals directly involved in the trial conduct and analysis did not have access to the randomisation schedule. Randomisation was stratified on the basis of baseline bodyweight (≤65 kg, 66–85 kg, >85 kg), previous therapy lines (≤four *vs* >four), and myeloma type (IgG *vs* non-IgG). Because of the different daratumumab administration routes, patients and investigators could not be masked to treatment allocation.

### Procedures

Patients in the subcutaneous group received a flat dose of 1800 mg of daratumumab co-formulated with rHuPH20 2000 U/mL. Patients in the intravenous group received 16 mg/kg of daratumumab (appendix p 15). Patients received daratumumab once weekly (cycles 1 and 2), every 2 weeks (cycles 3–6), and then every 4 weeks (28-day cycles) until progressive disease or toxicity. Dose delays were permitted for daratumumab-related toxicities. Dose modification was prohibited. Patients received pre-dose and post-dose medications to prevent infusion-related reactions (appendix p 2).

Disease assessments were done every 28 (±7) days until progressive disease by IMWG response criteria[14] and a validated computerised algorithm.[3] Cytogenetic abnormalities were assessed at screening (local laboratories) by fluorescence in-situ hybridisation or karyotyping; high-risk chromosomal mutations were del(p17), t(p4;q14), and t(p14;q16). Blood samples were collected for pharmacokinetics and immunogenicity analyses (appendix p 2).

Patient therapy satisfaction was evaluated using the modified Cancer Therapy Satisfaction Questionnaire (CTSQ). The CTSQ is a 16-item patient-reported outcome measure that assesses satisfaction with therapies on the basis of efficacy, tolerability, and convenience. The CTSQ was developed to compare intravenous with oral administration of medication.[15,16] The modified CTSQ used in the COLUMBA study was adapted to contain nine items (two items for "Thoughts about cancer therapy" and seven items in a defined domain of "Satisfaction with therapy") specific to satisfaction with therapy and for comparison of subcutaneous and intravenous administration. At least five of the seven items within the "Satisfaction with therapy" domain had to be completed to calculate a domain score. No domain score was calculated for "Thoughts about cancer therapy". The modified CTSQ was completed before any other study procedure at treatment visits (days 8, 15, and 22 of cycles 1 and 2, and day 1 of each cycle starting from cycle 2), and at 4 weeks (+7 days) post-treatment.

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See **Online** for appendix

### Outcomes

The non-inferiority co-primary endpoints were overall response (partial response or better) and the maximum trough concentration ($C_{trough}$), defined as the serum pre-dose concentration of daratumumab on cycle 3, day 1 (after 8 weekly doses). Secondary endpoints were proportion of patients with very good partial response or better; proportion of patients with complete response or better (ie, complete response plus stringent complete response; stringent complete response as defined by the IMWG criteria); time to response; duration of response (the time between date of first response and disease progression or death); progression-free survival (the time between randomisation and disease progression or death); overall survival (the time between randomisation and death from any cause); time to next therapy; patient-reported treatment satisfaction; and incidence of infusion-related reactions (systemic infusion-related reactions were classified as infusion-related reactions regardless of administration route; for the subcutaneous group, localised reactions were classified as injection-site reactions). Other analyses were for safety and immunogenicity, evaluated through incidence of anti-daratumumab and anti-rHuPH20 antibodies (appendix pp 41, 42).

Safety analyses included adverse event assessments (National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03), electrocardiograms, clinical laboratory testing, physical examinations, and vital signs. A serious adverse event was defined, on the basis of the International Council on Harmonisation and European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use, as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is a suspected transmission of any infectious pathogen via a medicinal product, or is medically important. All adverse events were reported from the time a signed and dated informed consent form was obtained until 30 days after the last dose of daratumumab, unless the patient withdrew consent or started subsequent anti-cancer therapy.

### Statistical analysis

The non-inferiority margin for overall response of subcutaneous versus intravenous daratumumab was defined using a 60% retention of the lower bound (20·8%) of the 95% CI of the SIRIUS trial.[3] The study needed to randomly assign (1:1) at least 480 patients to show non-inferiority, with a power of 80% and a one-sided alpha of 0·025, assuming that the true overall response is the same for both groups. For maximum $C_{trough}$, the geometric means ratio and the corresponding 90% CI of log-transformed $C_{trough}$ were estimated. Non-inferiority of subcutaneous versus intravenous daratumumab was met if the lower limit of the 90% CI of the geometric means ratio exceeded 80%. Both co-primary endpoints needed to be met to show subcutaneous daratumumab non-inferiority. Secondary endpoints (incidence of infusion-related reactions, progression-free survival, very good partial response or better, overall survival) were tested sequentially for superiority using a hierarchical procedure to control the type I error rate at a two-sided significance level of 0·05.

Analyses of the co-primary efficacy endpoint of overall response and the secondary efficacy endpoints included all randomly assigned patients (intention-to-treat population). Non-inferiority analysis of the co-primary pharmacokinetics endpoint of $C_{trough}$ included all patients who had received all eight weekly full daratumumab doses in cycles 1 and 2, within the dosing timeframe, and provided a pre-dose pharmacokinetics blood sample on day 1 of cycle 3, 8 h before the start of dose administration (population evaluable for pharmacokinetics analysis). Safety analyses included all treated patients (patients who received at least one dose of daratumumab). Summary statistics for pharmacokinetics included patients who had received at least one dose of daratumumab and had at least one pharmacokinetics concentration measurement (pharmacokinetics population) within specified dosing and sampling windows (appendix p 2). The immunogenicity-evaluable dataset included all patients who received at least one dose of daratumumab and had at least one sample after the start of dosing (appendix p 2).

The Kaplan-Meier method was used to estimate time-to-event distributions. Hazard ratios (HRs) and 95% CIs were estimated using a stratified Cox proportional-hazards regression model. The infusion-related reaction rate and rates of very good partial response or better were compared between groups using a stratified Cochran-Mantel-Hansel test. Pharmacokinetics data were summarised using descriptive statistics. Modified CTSQ item scores and the "Satisfaction with therapy" domain scores at each timepoint were summarised using descriptive statistics. The mean differences of the "Satisfaction with therapy" domain scores with 95% CIs were compared between groups at each timepoint. Safety was analysed descriptively. Prespecified subgroup analyses were done in age, sex, race, geographical region, bodyweight, International Staging System staging, number of previous lines of therapy, type of myeloma, baseline renal function, cytogenetic risk, and ECOG performance status score subgroups. An independent data monitoring committee reviewed safety data during the study. SAS version 9.4 was used for all analyses. This trial is registered with ClinicalTrials.gov, NCT03277105.

### Role of the funding source

The trial was designed by the study sponsor. All authors, including those from Janssen, were responsible for data collection, analysis, and interpretation and the development of the Article, and approved the final

version. Professional medical writers who were funded by the sponsor prepared the manuscript. The lead author had full access to all data in the study and had final responsibility for the decision to submit for publication.

## Results

Between Oct 31, 2017, and Dec 27, 2018, 655 patients were screened, of whom 522 were randomly assigned to the subcutaneous group (n=263) or the intravenous group (n=259; figure 1). Four patients (three in the subcutaneous group and one in the intravenous group) were not treated after randomisation as they no longer met the eligibility criteria on day 1; these patients were included in the efficacy analysis only (figure 1). The immunogenicity-evaluable population for daratumumab antibody analysis included 204 patients in the intravenous group and 205 in the subcutaneous group; for the anti-rHuPH20 analysis, the subcutaneous group included 202 patients.

Patient baseline demographics and disease characteristics were generally well balanced between groups (table 1), except that more patients in the subcutaneous group had an ECOG performance status score of 1 or higher and high-risk cytogenetic abnormalities than in the intravenous group (appendix p 3). At the primary data cutoff on Jan 8, 2019 (median follow-up 7·5 months, IQR 6·5–9·3; range 0·03–13·9), 222 (43%) patients were receiving treatment (111 patients per group). Overall, 296 patients discontinued daratumumab, mainly because of progressive disease (112 [43%] of 260 patients who received treatment in the subcutaneous group and 114 [44%] of 258 who received treatment in the intravenous group; figure 1). Patients received a median of six cycles per group (IQR for intravenous 3–9, range 1–14; IQR for subcutaneous 3–8, range 1–15). Dose intensity and administration duration are shown in the appendix (p 3).

Overall responses were seen in 108 (41%) of 263 patients in the subcutaneous group (95% CI 35·1–47·3) and in 96 (37%) of the 259 patients in the intravenous group (31·2–43·3; relative risk 1·11, 95% CI 0·89–1·37; table 2), meeting the non-inferiority criterion. Overall response results were consistent across prespecified subgroups (appendix p 16). Overall responses in the subcutaneous group were consistent in all bodyweight subgroups: overall response in 29 (44%) of 66 patients in the heaviest subgroup (>85 kg) was similar to the overall response for all patients (108 [41%] of 263).

In the patients evaluable for pharmacokinetics (149 in the subcutaneous group and 146 in the intravenous group), the mean maximum $C_{trough}$ was 593 µg/mL (SD 306) in the subcutaneous group and 522 µg/mL (226) in the intravenous group (figure 2). The geometric means ratio of maximum $C_{trough}$ for the subcutaneous group versus the intravenous group was 107·93% (90% CI 95·74–121·67), with the lower limit of the 90% CI exceeding 80%, thereby meeting the non-inferiority criterion (figure 2; appendix p 7). Subcutaneous daratumumab flat dosing had adequate exposure for all bodyweight subgroups, as maximum $C_{trough}$ with subcutaneous daratumumab was similar to or higher than that with intravenous daratumumab (figure 2). Within each bodyweight subgroup, there was considerable overlap in maximum $C_{trough}$ for both treatment groups, although the lightest subgroup (≤65 kg) had about 60% higher mean maximum $C_{trough}$, and the heaviest subgroup (>85 kg) had about 12% lower values, with subcutaneous daratumumab than intravenous daratumumab (figure 2). In the overall population, $C_{trough}$ values with subcutaneous daratumumab were consistently higher or similar to intravenous daratumumab for all follow-up visits (appendix p 17).

Subcutaneous daratumumab was well tolerated; the proportion of patients experiencing an infusion-related reaction was significantly lower for subcutaneous daratumumab (33 [13%] of 260 patients) than intravenous daratumumab (89 [34%] of 258 patients; odds ratio 0·28,

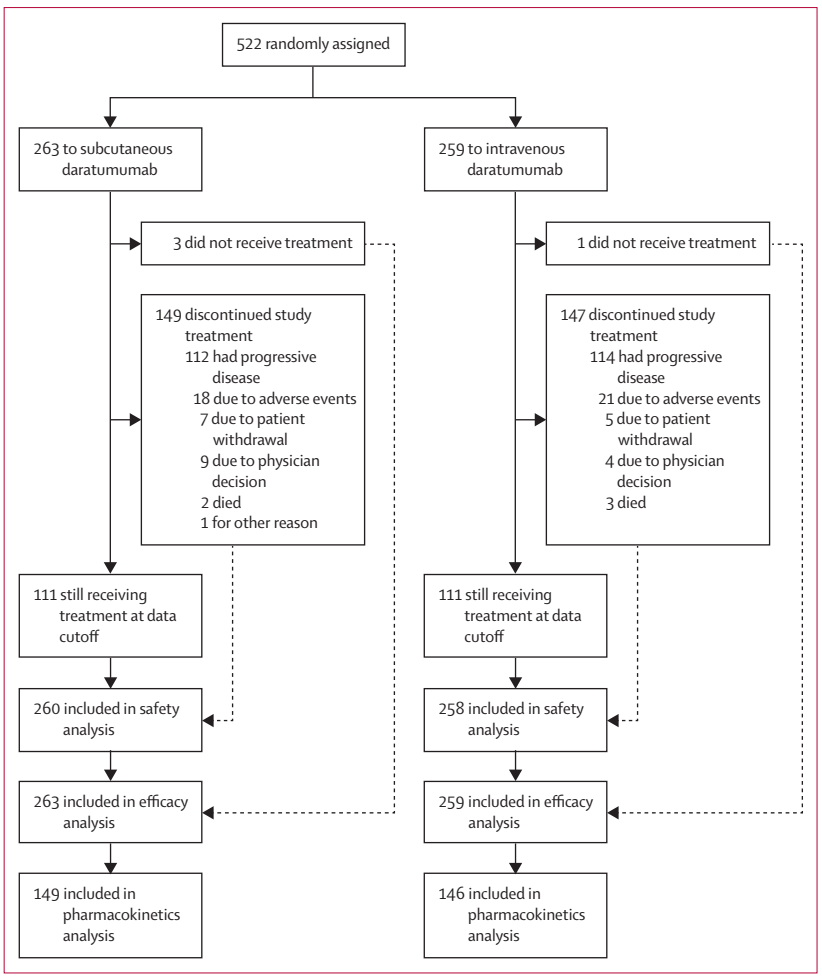


***Figure 1:*** **Study profile**
Pharmacokinetics analyses for both groups only included patients who received all 8 doses in cycles 1 and 2 within the protocol-specified timeframe and who provided a pre-dose blood sample on day 1 of cycle 3 within the sampling window of 8 h before the start of dose administration.

| | Subcutaneous group (N=263) | Intravenous group (N=259) |
|---|---|---|
| Sex | | |
| Male | 136 (52%) | 149 (58%) |
| Female | 127 (48%) | 110 (42%) |
| Median age, years | 65 (42–84) | 68 (33–92) |
| 18 to <65 | 121 (46%) | 100 (39%) |
| 65 to <75 | 95 (36%) | 100 (39%) |
| ≥75 | 47 (18%) | 59 (23%) |
| Race | | |
| White | 207 (79%) | 201 (78%) |
| Black or African American | 9 (3%) | 5 (2%) |
| Asian | 32 (12%) | 40 (15%) |
| American Indian or Alaska Native | 1 (<1%) | 0 |
| Native Hawaiian or other Pacific Islander | 0 | 1 (<1%) |
| Not reported | 14 (5%) | 12 (5%) |
| Median weight, kg* | 72·4 (39·0–130·0) | 73·0 (28·6–138·0) |
| ≤65 | 94 (36%) | 92 (36%) |
| >65–85 | 102 (39%) | 105 (41%) |
| >85 | 66 (25%) | 61 (24%) |
| Baseline ECOG performance status score | | |
| 0 | 64 (24%) | 88 (34%) |
| 1 | 152 (58%) | 132 (51%) |
| 2 | 47 (18%) | 38 (15%) |
| >2† | 0 | 1 (<1%) |
| International Staging System stage at study entry‡ | | |
| I | 82 (31%) | 94 (36%) |
| II | 101 (38%) | 89 (34%) |
| III | 79 (30%) | 76 (29%) |
| Median time since initial diagnosis, years | 6·01 (0·8–21·1) | 5·36 (0·6–39·0) |
| Median number of previous therapies | 4·0 (2–12) | 4·0 (1–15) |
| ≤4 | 174 (66%) | 175 (68%) |
| >4 | 89 (34%) | 84 (32%) |
| Refractory to last previous therapy | 209 (79%) | 220 (85%) |
| (Continued from previous column) | | |
| Type of measurable disease | | |
| Serum-only | 144 (55%) | 137 (53%) |
| IgG | 109 (41%) | 109 (42%) |
| IgA | 31 (12%) | 25 (10%) |
| Other | 4 (2%) | 3 (1%) |
| Serum and urine | 47 (18%) | 45 (17%) |
| Urine-only | 44 (17%) | 45 (17%) |
| Serum free light-chain only | 28 (11%) | 32 (12%) |
| Cytogenetic risk§ | | |
| Standard risk | 146 (74%) | 167 (83%) |
| High risk | 52 (26%) | 35 (17%) |
| Del(p17) | 32 (16%) | 22 (11%) |
| t(p4;q14) | 22 (11%) | 15 (7%) |
| t(p14;q16) | 7 (4%) | 4 (2%) |
| Bone marrow proportion of plasma cells¶ | | |
| <10% | 53 (21%) | 64 (25%) |
| 10–30% | 107 (42%) | 112 (44%) |
| >30% | 95 (37%) | 79 (31%) |

Data are n/N (%) patients or median (range). ECOG=Eastern Cooperative Oncology Group. The International Staging System score was derived on the basis of the combination of serum β2-microglobulin and albumin. *n=262 for the subcutaneous group, and n=258 for the intravenous group. †One patient in the intravenous group who met the eligibility criteria with an ECOG performance status score of 1 at baseline was assessed with a baseline score of 3 on cycle 1, day 1. ‡Missing data for one patient in the subcutaneous group. §n=198 for the subcutaneous group, and n=202 for the intravenous group. ¶n=255 for both treatment groups.

***Table 1:*** **Baseline characteristics**

95% CI 0·18–0·44, p<0·0001). Most infusion-related reactions occurred following the first dose and were predominantly grade 1 and grade 2. Grade 3 infusion-related reactions occurred in four (2%) patients in the subcutaneous group and 14 (5%) patients in the intravenous group. No grade 4 and grade 5 infusion-related reactions were reported. The most common infusion-related reactions (subcutaneous group *vs* intravenous group) were chills (12 [5%] *vs* 30 [12%] patients), pyrexia (12 [5%| vs seven [3%]), and dyspnoea (three [1%] *vs* 17 [7%]; appendix p 8). Incidence of infusion-related reactions was lower with subcutaneous daratumumab than intravenous daratumumab regardless of bodyweight (appendix p 9). Median time to onset for infusion-related reactions after administration of the first dose was longer in the subcutaneous group (3·4 h, IQR 1·5–4·4, range 1–47·8) than the intravenous group (1·5 h, 1–1·8, 0–24·5). Most infusion-related reactions in both treatment groups occurred during or shortly after the first administration of daratumumab. One patient in the subcutaneous group and three patients in the intravenous group had an infusion-related reaction on the second or subsequent administrations. No patients had an infusion-related reaction following the fourth or later administrations. One patient in the subcutaneous group and two in the intravenous group had at least one infusion-related reaction on non-treatment days (delayed-onset infusion-related reactions). All delayed-onset infusion-related reactions were grade 1 or grade 2 and non-serious.

With intravenous daratumumab, infusion-related reactions led to dose interruptions for 79 (31%) patients, one instance of a terminated infusion, decreases in infusion rate in 26 (10%) patients, and two treatment discontinuations. No infusion-related reactions with subcutaneous daratumumab led to treatment discontinuation, dose interruption, or incomplete dose administration. Injection-site reactions, all grade 1 and grade 2, were seen in 18 (7%) patients in the subcutaneous group, with no treatment discontinuations. The only

| | Subcutaneous group (N=263) | | Intravenous group (N=259) | | RR (95% CI)* | OR (95% CI) |
|---|---|---|---|---|---|---|
| | Proportion of patients or median | 95% CI or IQR | Proportion of patients or median | 95% CI or IQR | | |
| Overall response† | 108 (41%) | 35·1–47·3 | 96 (37%) | 31·2–43·3 | 1·11 (0·89–1·37) | 1·19 (0·83–1·69) |
| Best overall response† | | | | | | |
| Complete response or better | 5 (2%) | 0·6–4·4 | 7 (3%) | 1·1–5·5 | .. | 0·71 (0·22–2·27) |
| Stringent complete response | 2 (1%) | 0·1–2·7 | 2 (1%) | 0·1–2·8 | .. | 1·02 (0·14–7·31) |
| Complete response | 3 (1%) | 0·2–3·3 | 5 (2%) | 0·6–4·4 | .. | 0·59 (0·14–2·48) |
| Very good partial response or better | 50 (19%) | 14·5–24·3 | 44 (17%) | 12·6–22·1 | .. | 1·16 (0·73–1·85) |
| Very good partial response | 45 (17%) | 12·8–22·2 | 37 (14%) | 10·3–19·1 | .. | 1·25 (0·77–2·03) |
| Partial response | 58 (22%) | 17·2–27·6 | 52 (20%) | 15·4–25·5 | .. | 1·13 (0·73–1·74) |
| Minimal response | 25 (10%) | 6·2–13·7 | 28 (11%) | 7·3–15·2 | .. | 0·87 (0·49–1·53) |
| Stable disease | 102 (39%) | 32·9–45·0 | 94 (36%) | 30·4–42·5 | .. | 1·11 (0·78–1·58) |
| Progressive disease | 19 (7%) | 4·4–11·1 | 27 (10%) | 7·0–14·8 | .. | 0·66 (0·35–1·22) |
| Not evaluable | 9 (3%) | 1·6–6·4 | 14 (5%) | 3·0–8·9 | .. | 0·63 (0·27–1·49) |
| Median time to first response, months‡ | 1·0 | 1·0–1·9 | 1·0 | 1·0–1·9 | .. | .. |
| Median time to very good partial response or better, months§ | 1·9 | 1·0–3·1 | 1·1 | 1·0–3·8 | .. | .. |

OR=odds ratio. RR=relative risk. *Farrington-Manning estimates of RR of subcutaneous over intravenous daratumumab. †Clopper-Pearson exact CIs for response rates. ‡n=108 for the subcutaneous group, n=96 for the intravenous group. §n=50 for the subcutaneous group, n=44 for the intravenous group.

***Table 2:*** **Best response according to International Myeloma Working Group criteria**

injection-site reaction in more than two patients of this group was erythema (four [2%] patients; appendix p 10).

At the median follow-up of 7·5 months, disease progression or death had occurred in 133 (51%) of 263 patients in the subcutaneous group and 133 (51%) of 259 in the intravenous group. Median progression-free survival was 5·6 months (95% CI 4·7–7·6) for subcutaneous daratumumab and 6·1 months (4·7–8·3) for intravenous daratumumab (HR 0·99, 95% CI 0·78–1·26, p=0·93; figure 3). The proportion of patients with very good partial response or better was similar between the subcutaneous and intravenous groups (50 [19%] *vs* 44 [17%]); odds ratio 1·16, 95% CI 0·73–1·85, p=0·53). Complete response or better was also similar between the subcutaneous and intravenous groups (five [2%] patients *vs* seven [3%]; table 2). The median time to next anti-myeloma therapy was similar between the subcutaneous group (9·72 months, 95% CI 7·59–not reached) and the intravenous group (8·67 months, 7·69–11·14). Follow-up was short and therefore overall survival data were not mature: 45 (17%) of 263 patients in the subcutaneous group and 48 (19%) of 259 in the intravenous group died by data cutoff (HR 0·90, 95% CI 0·59–1·35, p=0·60; figure 3). 6-month survival was 88% (95% CI 83–91) with subcutaneous daratumumab and 83% (78–87) with intravenous daratumumab (figure 3). Median time to first response was 1 month in both groups (table 2). Median duration of response was not reached for either group (95% CI not reached–not reached).

Patient completion of the modified CTSQ was high (>88%) throughout dosing in both treatment groups.

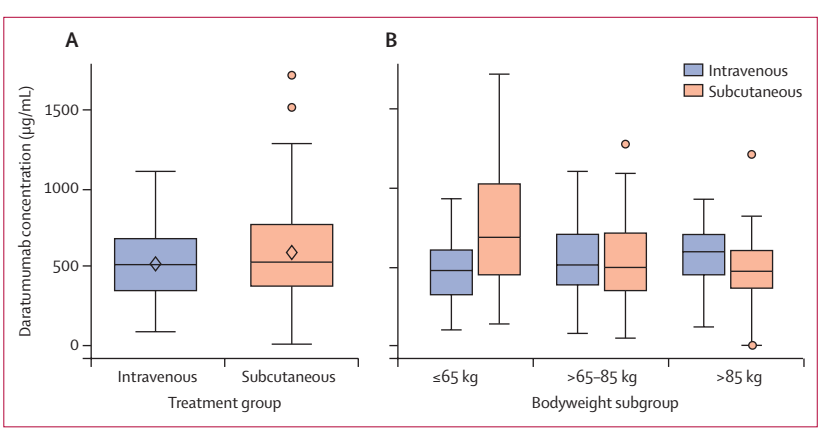


***Figure 2:*** **Daratumumab trough concentration before cycle 3, day 1 dosing**
(A) Overall population. (B) Bodyweight subgroups. The boxes represent the 25th, 50th, and 75th percentile, and the whiskers represent the furthest values from the median that did not exceed 1·5 × IQR. Data above or below the respective whisker ends are considered outliers.

Mean scores for the "Satisfaction with therapy" domain were consistently higher in the subcutaneous group than in the intravenous group (figure 4). Patients in the subcutaneous group responded more positively to individual components of "Satisfied with form of cancer therapy (intravenous/subcutaneous)", "Taking cancer therapy as difficult as expected", and "Were side effects as expected" (appendix p 18) than those in the intravenous group.

The safety profiles of subcutaneous and intravenous daratumumab were similar: 228 (88%) and 230 (89%) patients reported at least one treatment-emergent adverse event (table 3); 119 (46%) and 126 (49%) reported at least one grade 3 or higher treatment-emergent

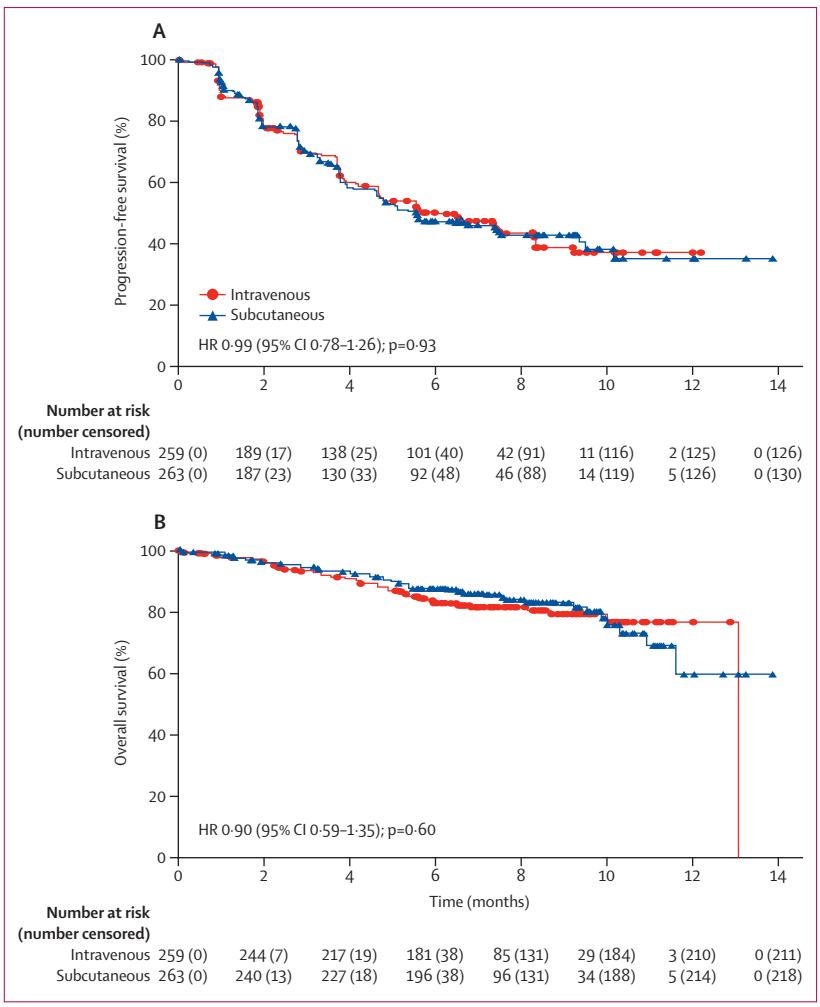


***Figure 3:*** **Survival outcomes after daratumumab treatment**
(A) Progression-free survival. (B) Overall survival. HR=hazard ratio.

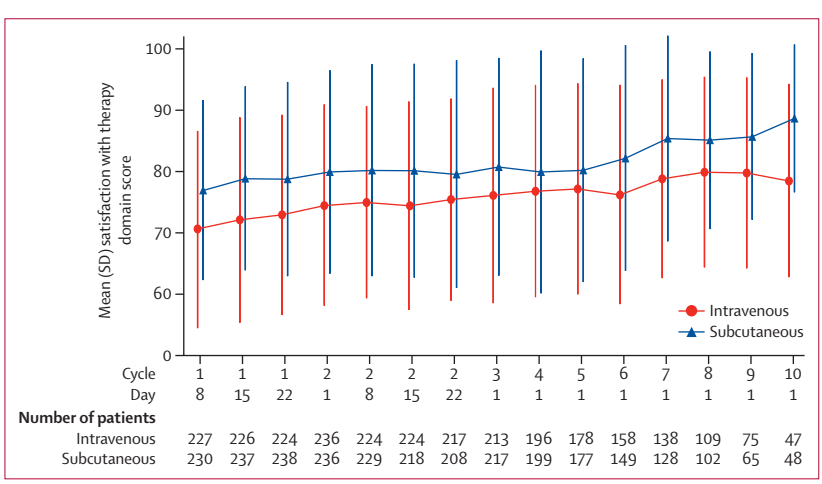


***Figure 4:*** **Mean scores for "Satisfaction with therapy" domain of modified Cancer Therapy Satisfaction Questionnaire**
Whiskers represent the SD for every mean.

adverse event. In both groups, the most common grade 3 or 4 treatment-emergent adverse events were anaemia (34 [13%] of 260 patients evaluable for safety in the subcutaneous group and 36 [14%] of 258 patients in the intravenous group), neutropenia (34 [13%] and 20 [8%]), and thrombocytopenia (36 [14%] and 35 [14%]; table 3).

The safety profiles were also broadly consistent (<5% difference in adverse event incidence between groups) when assessed by bodyweight (appendix p 9). One exception was neutropenia, which was higher in the subcutaneous daratumumab group than the intravenous group (appendix pp 3, 9). Compared with intravenous daratumumab, the incidence of adverse events with subcutaneous daratumumab was lower in the heaviest subgroup (51 [78%] of 65 patients *vs* 54 [89%] of 61 patients) and higher in the lightest subgroup (88 [95%] of 93 patients *vs* 82 [89%] of 92 patients).

Serious adverse events occurred in 68 (26%) patients in the subcutaneous group and 76 (29%) patients in the intravenous group. Pneumonia was the only serious adverse event in more than 2% of patients (seven [3%] patients in the subcutaneous group *vs* 11 [4%] in the intravenous group). Treatment discontinuations because of adverse events occurred in 18 (7%) patients in the subcutaneous group and 21 (8%) in the intravenous group. The most common adverse events leading to discontinuation were thrombocytopenia (two patients in the subcutaneous group *vs* five in the intravenous group), anaemia (two *vs* three), and septic shock (two *vs* three). Neutropenia in one patient and sepsis in two patients in the intravenous group led them to discontinue treatment. Adverse events leading to death (within 30 days of the last dose) occurred in 14 (5%) patients in the subcutaneous group and 17 (7%) in the intravenous group. Adverse events leading to death in more than one patient (subcutaneous daratumumab *vs* intravenous daratumumab) included general deterioration of physical health (n=4 *vs* n=3), septic shock (n=2 *vs* n=3), sepsis (n=0 *vs* n=2), and respiratory failure (n=2 *vs* n=0; appendix pp 11–14). There was one death judged to be treatment-related in the subcutaneous group (febrile neutropenia; table 3) and four in the intravenous group (two from sepsis, one from hepatitis B reactivation, and one from *Pneumocystis jirovecii* pneumonia; appendix pp 11–14). The incidence of grade 3 and grade 4 adverse events, serious adverse events, and adverse events leading to discontinuation were similar across bodyweight subgroups (appendix p 9).

No patients in the subcutaneous daratumumab group were positive for anti-daratumumab antibodies, whereas one (<1%) of 204 patients in the intravenous group who were evaluable for immunogenicity was positive for non-neutralising, anti-daratumumab antibodies of low titre. These antibodies were not associated with an infusion-related reaction or clinically relevant adverse events and had no effect on pharmacokinetics. 12 (6%) of 202 patients in the subcutaneous group had treatment-emergent

| | Subcutaneous group (n=260) | | | | Intravenous group (n=258) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1 and 2 | Grade 3 | Grade 4 | Grade 5 | Grade 1 and 2 | Grade 3 | Grade 4 | Grade 5 |
| Any adverse events | 109 (42%) | 83 (32%) | 22 (8%) | 14 (5%) | 104 (40%) | 81 (31%) | 28 (11%) | 17 (7%) |
| Haematological adverse events | | | | | | | | |
| Anaemia | 34 (13%) | 34 (13%) | 0 | 0 | 24 (9%) | 34 (13%) | 2 (1%) | 0 |
| Neutropenia | 16 (6%) | 29 (11%) | 5 (2%) | 0 | 15 (6%) | 13 (5%) | 7 (3%) | 0 |
| Thrombocytopenia | 12 (5%) | 26 (10%) | 10 (4%) | 0 | 13 (5%) | 19 (7%) | 16 (6%) | 0 |
| Leukopenia | 8 (3%) | 10 (4%) | 0 | 0 | 8 (3%) | 1 (<1%) | 1 (<1%) | 0 |
| Lymphopenia | 6 (2%) | 10 (4%) | 3 (1%) | 0 | 1 (<1%) | 11 (4%) | 5 (2%) | 0 |
| Febrile neutropenia | 0 | 2 (1%) | 0 | 1 (<1%)* | 0 | 5 (2%) | 1 (<1%) | 0 |
| Non-haematological adverse events | | | | | | | | |
| Hypertension | 5 (2%) | 8 (3%) | 0 | 0 | 6 (2%) | 16 (6%) | 0 | 0 |
| Hyponatraemia | 2 (1%) | 6 (2%) | 0 | 0 | 0 | 2 (1%) | 0 | 0 |
| Bone pain | 13 (5%) | 5 (2%) | 0 | 0 | 7 (3%) | 2 (1%) | 0 | 0 |
| Pneumonia | 2 (1%) | 5 (2%) | 2 (1%) | 0 | 6 (2%) | 8 (3%) | 1 (<1%) | 1 (<1%) |
| Back pain | 23 (9%) | 4 (2%) | 0 | 0 | 25 (10%) | 7 (3%) | 0 | 0 |
| Lower respiratory tract infection | 4 (2%) | 4 (2%) | 0 | 0 | 3 (1%) | 2 (1%) | 0 | 0 |
| Acute kidney injury | 3 (1%) | 4 (2%) | 0 | 0 | 3 (1%) | 3 (1%) | 1 (<1%) | 0 |
| Diarrhoea | 36 (14%) | 2 (1%) | 0 | 0 | 27 (10%) | 1 (<1%) | 0 | 0 |
| Fatigue | 26 (10%) | 2 (1%) | 0 | 0 | 25 (10%) | 2 (1%) | 0 | 0 |
| Cough | 20 (8%) | 2 (1%) | 0 | 0 | 33 (13%) | 0 | 0 | 0 |
| Dyspnoea | 12 (5%) | 2 (1%) | 0 | 0 | 26 (10%) | 2 (1%) | 0 | 0 |
| Nausea | 20 (8%) | 1 (<1%) | 0 | 0 | 27 (10%) | 1 (<1%) | 0 | 0 |
| Chills | 14 (5%) | 1 (<1%) | 0 | 0 | 30 (12%) | 2 (1%) | 0 | 0 |
| Hypokalaemia | 10 (4%) | 1 (<1%) | 0 | 0 | 11 (4%) | 4 (2%) | 0 | 0 |
| Upper respiratory tract infection | 35 (13%) | 0 | 0 | 0 | 23 (9%) | 2 (1%) | 0 | 0 |
| Pyrexia | 33 (13%) | 0 | 0 | 0 | 31 (12%) | 2 (1%) | 0 | 0 |
| General physical health deterioration | 0 | 0 | 1 (<1%) | 4 (2%) | 1 (<1%) | 3 (1%) | 0 | 3 (1%) |

Data are n (%). See appendix pp 11–14 for table with all grade 3, 4, and 5 treatment-emergent adverse events. *Treatment-related grade 5 adverse event.

***Table 3:*** **Most common maximum-toxicity grade 1 and 2 (≥10% of patients in either group) and grade 3, 4, and 5 (≥2% in either group) treatment-emergent adverse events in the safety population**

non-neutralising anti-rHuPH20 antibodies that were not associated with an infusion-related reaction or clinically relevant treatment-emergent adverse events, and the antibodies had no effect on pharmacokinetics.

## Discussion

The COLUMBA data suggested non-inferiority of subcutaneous daratumumab compared with intravenous daratumumab for both efficacy (overall response) and pharmacokinetics (maximum $C_{trough}$) parameters. Depth of response (very good partial response or better) and progression-free survival were similar between groups. Moreover, higher patient satisfaction and significantly reduced infusion-related reactions with subcutaneous daratumumab and similar safety profiles between treatment groups support the use of subcutaneous daratumumab.

The similarity of overall responses with subcutaneous and intravenous daratumumab is particularly encouraging. A conservative overall response estimate was used for the retention-of-benefit calculation, leading to a large number of patients required to show non-inferiority. Results showed a lower bound of 89% retention of the overall response, exceeding the prespecified non-inferiority criteria (60% retention) by a large margin. Importantly, similar overall responses were observed across prespecified subgroups, including bodyweight categories, despite the subcutaneous group not receiving a bodyweight-based dose. The intravenous group, as the comparator group in COLUMBA, performed similarly or better than in previous investigations of daratumumab monotherapy (intravenous daratumumab overall response: COLUMBA 37% [95% CI 31·2–43·3]; SIRIUS 29% [20·8–38·9]; GEN501 part 2 36% [21·6–52·0]),[1–3] possibly reflecting study population differences or improved clinical experience with daratumumab. A key finding from COLUMBA was that depth and time to response were not affected by the administration route; depth of response is associated with prolonged long-term multiple myeloma outcomes.[17,18] Median progression-free survival in COLUMBA (5·6 months for subcutaneous daratumumab; 6·1 months for intravenous daratumumab) was also similar to previous investigations of intravenous daratumumab (SIRIUS, 3·7 months; GEN501 part 2, 6·2 months).[2,3] Although COLUMBA overall survival data are immature, the similar overall response and median

progression-free survival between subcutaneous and intravenous daratumumab are encouraging.

Maximum $C_{trough}$ was selected as a co-primary endpoint since this parameter was strongly correlated with efficacy.[19] In COLUMBA, mean $C_{trough}$ for subcutaneous daratumumab was consistently similar or slightly higher than for intravenous daratumumab throughout the dosing regimen. Peak daratumumab concentrations in the subcutaneous group were lower than in the intravenous group and occurred about 72 h after dose administration,[12] rather than at the end of infusion as with intravenous daratumumab, thereby minimising peak-to-trough concentration fluctuation. The estimated bioavailability for subcutaneous daratumumab is about 70% (data from Janssen not shown), consistent with other monoclonal antibodies dosed subcutaneously.[20] The range of daratumumab concentrations we used across bodyweights for flat dosing in the subcutaneous group were within the range that was previously seen for 16 mg/kg of intravenous daratumumab.[19] As previously reported for monoclonal antibodies,[21] variability in exposure between flat dosing and bodyweight-based dosing is generally moderate compared with pharmacodynamic, safety, or efficacy effects.

Importantly, subcutaneous and intravenous daratumumab had similar safety profiles. In keeping with previous daratumumab monotherapy studies (SIRIUS and GEN501),[1–3] the most common adverse events in each treatment group were haematological (anaemia, neutropenia, and thrombocytopenia). Fewer treatment-related deaths occurred in the subcutaneous group than in the intravenous group. This observation further supports the use of subcutaneous daratumumab for multiple myeloma. The safety profiles of subcutaneous and intravenous daratumumab were also generally consistent among bodyweight subgroups. Neutropenia was the only adverse event differing by bodyweight, with an increased incidence of any-grade and grade 3 or 4 neutropenia in the subcutaneous subgroup with lowest bodyweight (≤65 kg). However, these events did not translate into differences in serious adverse events, treatment discontinuations, or deaths.

One challenge with intravenous daratumumab is management of infusion-related reactions. Approximately half of patients treated with intravenous daratumumab experience infusion-related reactions.[9] Although infusion-related reactions are generally mild and mainly occur during the first administration, management of infusion-related reactions with infusion interruptions and rate reductions results in prolonged infusion times causing additional burden to patients and health-care resources. Albeit rare, severe cases of infusion-related reactions could lead to treatment discontinuation.[9] In COLUMBA, subcutaneous daratumumab had a markedly reduced administration time (about 5 min) for all dose administrations and a significant reduction in infusion-related reactions compared with intravenous daratumumab. With grade 3 infusion-related reactions occurring in 2% of patients in the subcutaneous group and no grade 4 or 5 infusion-related reactions reported, the monitoring period after administration of subcutaneous daratumumab should be determined by the treating physicians on the basis of patient fitness and ability to seek medical assistance in a timely manner in case an adverse event occurs after discharge.

An important finding in COLUMBA was that patients in the subcutaneous group had a consistently more positive perception and greater satisfaction with treatment than those in the intravenous group. More positive scores with subcutaneous than intravenous daratumumab in "Satisfied with form of cancer therapy (intravenous/subcutaneous)" and "Taking cancer therapy as difficult as expected" are particularly pertinent as these are the most relevant to subjective treatment experience and might reflect the shorter administration times. Moreover, fewer infusion-related reactions with subcutaneous daratumumab might have contributed to more positive scores in "Were side effects as expected". A 2019 publication reported the positive effect of subcutaneous dosing over intravenous dosing of oncology biologics on health-related quality of life, use of health-care resources, and economic outcomes.[22]

Overall, COLUMBA showed the feasibility of a flat-dose of 1800 mg subcutaneous daratumumab. Flat dosing offers several advantages, including increased convenience to patients and health-care providers, improved compliance, reduced costs, and favourable safety due to the potential reduction of dosing errors.[23] With patients from 147 study sites across 18 countries in North and South America, Europe, and the Asia-Pacific region, and the inclusion of patients with a wide range of bodyweights, ages, and number of previous lines of therapy, the results from COLUMBA are generalisable.

This trial has several limitations. Since patients and physicians were not masked to treatment, bias cannot be excluded in adverse-event reporting or responses to the modified CTSQ. Additionally, baseline characteristics were imbalanced, with a higher proportion of patients in the subcutaneous daratumumab group with high-risk cytogenetic abnormalities and worse ECOG performance status scores than the intravenous group. However, this imbalance would favour intravenous daratumumab. Furthermore, intravenous daratumumab is approved and commonly used in combination with other anti-myeloma drugs (eg, proteasome inhibitors or immunomodulatory drugs) to treat newly diagnosed patients or those with relapsed or refractory multiple myeloma. Further data are needed to confirm our findings for combination regimens.

**Contributors**

All authors contributed to the study design, study execution, data analysis, and manuscript writing. All authors provided a full review of the article and are fully responsible for all content and editorial decisions, were involved in all stages of manuscript development, and have approved the final version. Professional medical writers who were funded by the sponsor prepared the manuscript.

#### Declaration of interests

M-VM has received honoraria for lectures and advisory boards from Janssen, Celgene, Amgen, Takeda, AbbVie, GlaxoSmithKline, Adaptive, EDO-Mundipharma, and PharmaMar, outside the submitted work. VV has received honoraria for lectures and advisory boards from Janssen, Bristol-Myers Squibb, Celgene, Amgen, Takeda, AbbVie, Roche, and AstraZeneca, outside the submitted work. IS has received honoraria and consulting and lecture fees from Celgene, Amgen, Janssen-Cilag, Takeda, and Novartis; consulting and lecture fees from Sanofi; and lecture fees from Bristol-Myers Squibb, all outside the submitted work. VH has received fees for lectures and advisory boards from Janssen, AbbVie, Amgen, Bristol-Myers Squibb, Celgene, and Takeda, outside the submitted work. NB has received personal fees from Janssen, Celgene, Amgen, Takeda, and AbbVie; and a grant from Celgene. JB has received honoraria for lectures and advisory boards from Janssen during the conduct of the study; and grants and personal fees from Celgene and personal fees from Amgen, Takeda, and AbbVie, outside the submitted work. PM reports personal fees from Janssen, during the conduct of the study; and personal fees from Celgene, Takeda, and Amgen, outside the submitted work. MK has received consultancy fees from AbbVie, Celgene, Takeda, Janssen, Amgen, and Karyopharm; research funding from Celgene and Janssen; and honoraria and travel expenses from Takeda, Janssen, Celgene, and Amgen, all outside the submitted work. SI has received a grant and honoraria from Janssen, during the conduct of the study; grants and personal fees from Celgene, Takeda, Ono, Daiichi Sankyo, Bristol-Myers Squibb, and Novartis, and grants from Chugai, Kyowa Kirin, Sanofi, AbbVie, MSD, Gilead, Astellas, and Teijin Pharma, outside the submitted work. MC has received personal fees from Janssen, during the conduct of the study, and personal fees from Celgene, Amgen, Takeda, Sanofi, and Bristol-Myers Squibb, outside the submitted work. CHu has received honoraria from Janssen, Celgene, Amgen and Takeda, outside the submitted work. DW has received honoraria for lectures and advisory boards from Amgen, Celgene, Janssen, Karyopharm, Sanofi, and Takeda, outside the submitted work. VDS reports grants, personal fees, and non-financial support from Amgen, Celgene, and Novartis, outside the submitted work. PLC, TM, KL, LO'R, CHe, XQ, DAP, ZY, and MQ are Janssen employees and hold Johnson & Johnson stocks and shares, during the conduct of the study. SX was a Janssen employee at the time COLUMBA was conducted and holds Johnson & Johnson stocks and shares. SZU has grants and personal fees from Amgen, Celgene, Sanofi, Seattle Genetics, Janssen, Takeda, and SkylineDX; grants from Bristol-Myers Squibb and Pharmacyclics; and personal fees from MundiPharma, all outside the submitted work. HN, WL, SG, SK, MF, JL, and HM declare no competing interests.

#### Data sharing

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access Project site at http://yoda.yale.edu.

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