**Introduction**

Daratumumab is a human IgGκ monoclonal antibody targeting CD38 with a direct on-tumor [[1](https://www.nature.com/articles/s41408-024-01030-w#ref-CR1),[2](https://www.nature.com/articles/s41408-024-01030-w#ref-CR2),[3](https://www.nature.com/articles/s41408-024-01030-w#ref-CR3),[4](https://www.nature.com/articles/s41408-024-01030-w#ref-CR4)] and immunomodulatory [[5](https://www.nature.com/articles/s41408-024-01030-w#ref-CR5),[6](https://www.nature.com/articles/s41408-024-01030-w#ref-CR6),[7](https://www.nature.com/articles/s41408-024-01030-w#ref-CR7)] mechanism of action, demonstrating greater cytotoxicity toward multiple myeloma (MM) cells ex vivo compared with analogs of other CD38 antibodies [[8](https://www.nature.com/articles/s41408-024-01030-w#ref-CR8)]. Daratumumab is approved as a monotherapy and in combination with standard-of-care regimens for patients with relapsed or refractory MM and a part of combination therapy for patients with newly diagnosed MM (NDMM) [[9](https://www.nature.com/articles/s41408-024-01030-w#ref-CR9)].

Induction therapy with a triplet regimen consisting of a proteasome inhibitor, immunomodulatory drug, and dexamethasone is standard of care for transplant-eligible patients with NDMM [[10](https://www.nature.com/articles/s41408-024-01030-w#ref-CR10)]. Recent studies have examined the addition of daratumumab to these triplet regimens. The single-arm, phase 2 MASTER study (ClinicalTrials.gov Identifier: NCT03224507) evaluated daratumumab plus carfilzomib, lenalidomide, and dexamethasone (D-KRd) and demonstrated promising clinical efficacy in transplant-eligible patients with NDMM [[11](https://www.nature.com/articles/s41408-024-01030-w#ref-CR11)]. The primary analysis (median follow-up, 25.1 months) showed that minimal residual disease (MRD) negativity at the 10–5 threshold was achieved by 80% of D-KRd patients, as determined at the end of MRD-directed treatment [[11](https://www.nature.com/articles/s41408-024-01030-w#ref-CR11)]. The final analysis of MASTER was recently reported, and data continued to demonstrate a benefit of D-KRd in this setting in the overall population and suggested a possible pathway for treatment cessation among responding patients exhibiting sustained MRD negativity [[12](https://www.nature.com/articles/s41408-024-01030-w#ref-CR12)]. The randomized, phase 2 GRIFFIN study (ClinicalTrials.gov Identifier: NCT02874742) evaluated daratumumab plus lenalidomide, bortezomib, and dexamethasone (D-RVd) or lenalidomide, bortezomib, and dexamethasone (RVd) alone in transplant-eligible patients with NDMM [[13](https://www.nature.com/articles/s41408-024-01030-w#ref-CR13)]. The primary analysis (median follow-up, 13.5 months) showed that the rate of stringent complete response (CR) by the end of post-autologous stem cell transplant (ASCT) consolidation was significantly higher for D-RVd versus RVd (42.4% vs 32.0%; 1-sided *p* = 0.068, which met the pre-specified 1-sided α of 0.10) [[13](https://www.nature.com/articles/s41408-024-01030-w#ref-CR13)]. At the time of GRIFFIN final analysis, which occurred after all patients completed ≥1 year of long-term follow-up after the end of study treatment, death, or withdrawal (median follow-up, 49.6 months), responses continued to deepen over time for D-RVd versus RVd, and there was an improvement in progression-free survival (PFS) for the D-RVd group versus the RVd group (hazard ratio, 0.45; 95% confidence interval, 0.21–0.95; *p* = 0.032) [[14](https://www.nature.com/articles/s41408-024-01030-w#ref-CR14)]. The safety profiles of D-KRd and D-RVd were previously reported [[11](https://www.nature.com/articles/s41408-024-01030-w#ref-CR11), [13](https://www.nature.com/articles/s41408-024-01030-w#ref-CR13)]. No unexpected safety concerns occurred for these daratumumab-based quadruplet therapies, and adverse events in each regimen were consistent with previous reports of the individual regimen components.

Patients with MM may have high-risk disease characteristics, such as the presence of extramedullary disease, International Staging System stage III disease, advanced age, and/or the presence of high-risk cytogenetic abnormalities (HRCAs) [[15](https://www.nature.com/articles/s41408-024-01030-w#ref-CR15),[16](https://www.nature.com/articles/s41408-024-01030-w#ref-CR16),[17](https://www.nature.com/articles/s41408-024-01030-w#ref-CR17)]. These high-risk disease characteristics are associated with a poor overall prognosis and shorter survival, and patients with high-risk features constitute a population with high unmet medical need [[15](https://www.nature.com/articles/s41408-024-01030-w#ref-CR15), [18](https://www.nature.com/articles/s41408-024-01030-w#ref-CR18), [19](https://www.nature.com/articles/s41408-024-01030-w#ref-CR19)]. The consensus from the International Myeloma Working Group (IMWG) advises that cytogenetic risk should be evaluated using bone marrow aspirate–based fluorescence in situ hybridization panels for t(4;14), del(17p), and t(14;16), with an extended panel for clinical trials that includes t(11;14), t(14;20), gain(1q), del(1p), del(13q), and ploidy status [[18](https://www.nature.com/articles/s41408-024-01030-w#ref-CR18)]. While risk stratification is important for understanding overall prognosis, much remains to be learned about how HRCAs impact clinical outcomes and influence optimal therapy selection and treatment sequencing. The objective of this study is to better understand clinical outcomes for daratumumab-based treatment among patients with NDMM by HRCA risk stratifications, according to a revised definition inclusive of the cytogenetic abnormalities del(17p), t(4;14), t(14;16), t(14;20), and/or gain/amp(1q21) (≥3 copies of chromosome 1q21). Here, we present a post hoc analysis of side-by-side results including patients from MASTER (D-KRd) and GRIFFIN (D-RVd) with 0, 1, or ≥2 HRCAs, noting the goal is not to compare D-KRd and D-RVd but rather to evaluate the overall value of frontline daratumumab-based therapy.

**Methods**

Patients and study design

The full details of the MASTER (ClinicalTrials.gov Identifier: NCT03224507) [[11](https://www.nature.com/articles/s41408-024-01030-w#ref-CR11)] and GRIFFIN (ClinicalTrials.gov Identifier: NCT02874742) [[13](https://www.nature.com/articles/s41408-024-01030-w#ref-CR13)] studies have been previously reported. Briefly, in the multicenter, single-arm, phase 2 MASTER study, D-KRd was evaluated in transplant-eligible patients with NDMM. Patients had no upper age limit and an Eastern Cooperative Oncology Group performance status score of ≤2. Patients received up to 4 D-KRd induction cycles; high-dose therapy and ASCT; and up to 2 phases of D-KRd consolidation therapy (Cycles 5–8 and 9–12). MRD assessments in MASTER occurred post-induction, post-ASCT, and after each consolidation phase, and patients achieving 2 consecutive MRD negative (10–5) assessments transitioned to treatment-free observation. Patients who completed consolidation without 2 consecutive MRD-negative assessments transitioned to lenalidomide maintenance. The study design included enrichment for patients with MM harboring HRCAs to meet the criteria that ≥35% of participants would have t(4;14), t(14;16), and/or del(17p). In both studies, cytogenetic risk was assessed at baseline by fluorescence in situ hybridization via local testing.

In the multicenter, randomized, open-label, phase 2 GRIFFIN study, D-RVd was evaluated versus RVd alone in transplant-eligible patients with NDMM. Patients were 18–70 years of age and had an Eastern Cooperative Oncology Group performance status score of ≤2. Prior to the randomized phase of GRIFFIN, a safety run-in was conducted in 16 patients to assess D-RVd dose-limiting toxicities [[20](https://www.nature.com/articles/s41408-024-01030-w#ref-CR20)]. Following completion of the safety run-in, the study proceeded to the randomization phase in which patients were randomized 1:1 to the D-RVd or the RVd group. In this phase, patients received 4 D-RVd or RVd induction cycles, followed by high-dose therapy and ASCT, then 2 D-RVd or RVd consolidation cycles, followed by up to 2 years of maintenance therapy consisting of daratumumab plus lenalidomide or lenalidomide alone. Patients in the safety run-in phase of GRIFFIN received the same treatment as patients in the randomized phase in the D-RVd group. MRD negativity was measured at baseline, at first evidence of suspected CR or stringent CR (including patients with very good partial response or better and suspected daratumumab interference), after induction therapy, at the post-transplant consolidation disease evaluation, and after 1 and 2 years of maintenance therapy.

For both studies, the protocols and appropriate related documents were approved by the institutional review board or independent ethics committee at each participating site, and all patients gave written informed consent. The studies were conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, the principles originating from the Declaration of Helsinki, as well as study site–specific regulations. The MASTER study followed the University of Alabama at Birmingham O’Neal Comprehensive Cancer Center Data and Safety Monitoring Plan. Each study established an independent Data Monitoring Committee for oversight for study conduct.

Endpoints, objectives, and analyses

The primary endpoint of the MASTER study was the achievement of MRD negativity at any time during therapy and was previously reported [[11](https://www.nature.com/articles/s41408-024-01030-w#ref-CR11)]. The primary endpoint of GRIFFIN was the stringent CR rate by the end of post-ASCT consolidation treatment and was also previously published [[13](https://www.nature.com/articles/s41408-024-01030-w#ref-CR13)]. Both studies also assessed additional endpoints, including response rates, MRD-negativity rates (minimum sensitivity threshold of 1 in 100,000 cells [10−5]), and PFS. In GRIFFIN, response to study treatment and PFS were evaluated using a validated computer algorithm in alignment with IMWG criteria [[21](https://www.nature.com/articles/s41408-024-01030-w#ref-CR21), [22](https://www.nature.com/articles/s41408-024-01030-w#ref-CR22)]. Patients were considered MRD positive if the MRD assessment was positive, indeterminate, or unavailable. Best response on study for MASTER was also evaluated using IMWG criteria.

The objective of this post hoc analysis was to evaluate the clinical efficacy of the daratumumab-based quadruplet therapies D-KRd (from MASTER) and D-RVd (from GRIFFIN) in patients with NDMM with HRCAs, defined as having ≥1 of the following genetic abnormalities: del(17p), t(4;14), t(14;16), t(14;20), and/or gain/amp(1q21) (≥3 copies of chromosome 1q21). Cytogenetic abnormalities (fluorescence in situ hybridization [FISH]) were assessed by the local labs, normally accessed at the study sites, on bone marrow aspirates in both MASTER and GRIFFIN. Patients with evaluable data were grouped into standard risk, high risk, or ultra-high risk based on the presence of 0, 1, or ≥2 HRCAs, respectively. In addition, MRD-negativity rates were also presented for patients achieving ≥CR in each cytogenetic subgroup. This study descriptively presents the results for the D-KRd and D-RVd groups side by side, and thus no statistical or treatment comparisons between the 2 groups were performed. Kaplan–Meier plots and estimates of PFS were provided for each HRCA group in each study.

**Results**

Patient characteristics

A total of 123 patients with NDMM were enrolled in the MASTER study; most patients had ≥1 HRCA (1 HRCA, 37.4%, *n* = 46; ≥2 HRCAs, 19.5%, *n* = 24) and the remainder had 0 HRCA (43.1%, *n* = 53). There was no difference in the median duration of study treatment for D-KRd induction, ASCT, and consolidation among patients with NDMM with 0, 1, or ≥2 HRCAs, which was 11.5, 11.5, and 11.7 months, respectively (Table [1](https://www.nature.com/articles/s41408-024-01030-w#Tab1)). Among 120 patients with NDMM in GRIFFIN who received D-RVd therapy (*n* = 104 randomized phase and *n* = 16 safety run-in), most had 0 HRCA (55.8%, *n* = 67) or 1 HRCA (28.3%, *n* = 34), and a smaller number of patients had ≥2 HRCAs (10.8%, *n* = 13). Six (5.0%) GRIFFIN patients were not evaluable for cytogenetic abnormalities because cytogenetic testing was not done or data were not captured; therefore, these patients were not included in this analysis. The median duration of study treatment for D-RVd induction, ASCT, and consolidation was 8.1, 8.1, and 7.4 months among patients with NDMM with 0, 1, or ≥2 HRCAs, respectively, and the median duration of study maintenance therapy was 24.4, 24.2, and 23.9 months for patients with 0, 1, or ≥2 HRCAs, respectively (Table [2](https://www.nature.com/articles/s41408-024-01030-w#Tab2)). In both MASTER and GRIFFIN, the median age of patients was 60 years. Among patients with ≥2 HRCAs, a relatively high proportion had International Staging System stage III disease (45.8% [*n* = 11] of D-KRd patients and 30.8% [*n* = 4] of D-RVd patients) or extramedullary disease (7.7% [*n* = 1] of D-RVd; data on extramedullary disease were not available in MASTER).

**Table 1 Baseline characteristics for patients who received D-KRd in MASTER.**

[**Full size table**](https://www.nature.com/articles/s41408-024-01030-w/tables/1)

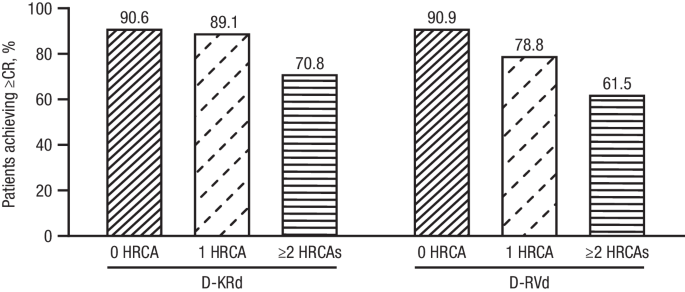
**Table 2 Baseline characteristics for patients who received D-RVd in GRIFFIN.**

[**Full size table**](https://www.nature.com/articles/s41408-024-01030-w/tables/2)

Efficacy

In an analysis of best response at any time point during the study, rates of ≥CR were highest for patients with 0 or 1 HRCA in both GRIFFIN and MASTER (Fig. [1](https://www.nature.com/articles/s41408-024-01030-w#Fig1)). In MASTER, rates of ≥CR among D-KRd patients were 90.6%, 89.1%, and 70.8% for 0, 1, or ≥2 HRCAs, respectively. In GRIFFIN, rates of ≥CR among D-RVd patients were 90.9%, 78.8%, and 61.5% for 0, 1, or ≥2 HRCAs.

**Fig. 1: Rates of ≥CR (best response on study) by cytogenetic risk status\* among patients who received D-KRd in MASTER† and D-RVd in GRIFFIN‡.**

[](https://www.nature.com/articles/s41408-024-01030-w/figures/1)

Rates of ≥CR were assessed based on International Uniform Response Criteria Consensus Recommendations, and percentages were calculated with the number of patients in the treatment group as the denominator. ≥CR complete response or better, D-KRd daratumumab plus carfilzomib/lenalidomide/dexamethasone, D-RVd daratumumab plus lenalidomide/bortezomib/dexamethasone, HRCA high-risk cytogenetic abnormality. \*HRCAs include any of the following genetic abnormalities: del(17p), t(4;14), t(14;16), t(14;20), and gain/amp(1q21) (≥3 copies of chromosome 1q21). Patients were grouped into categories: standard risk (0 HRCA), high risk (1 HRCA), or ultra-high risk (≥2 HRCAs). †Evaluable patients in MASTER included all enrolled patients (0 HRCA, *n* = 53; 1 HRCA, *n* = 46; ≥2 HRCAs, *n* = 24). ‡Evaluable patients in GRIFFIN were the response-evaluable population (0 HRCA, *n* = 66; 1 HRCA, *n* = 33; ≥2 HRCAs, *n* = 13).

[**Full size image**](https://www.nature.com/articles/s41408-024-01030-w/figures/1)

MRD-negativity (both 10–5 and 10–6) rates were generally similar for D-KRd across patients with 0, 1, or ≥2 HRCAs, but were highest for D-KRd in patients with 1 HRCA (Table [3](https://www.nature.com/articles/s41408-024-01030-w#Tab3)). In MASTER, MRD-negativity rates following D-KRd were 80.0%, 86.4%, and 83.3% at the 10–5 threshold for 0, 1, or ≥2 HRCAs, respectively, and 68.0%, 79.5%, and 66.7% at the 10–6 threshold. In D-KRd patients who achieved ≥CR, MRD-negativity (10–5) rates were 84.4%, 89.7%, and 94.1% for 0, 1, or ≥2 HRCAs, respectively. Rates of sustained MRD negativity (10–5) lasting ≥12 months were 64.0%, 72.7%, and 50.0% among D-KRd patients with 0, 1, or ≥2 HRCAs. Median time to MRD negativity (10–5) was similar across HRCA groups (0 HRCA, 7.5 months; 1 HRCA, 7.1 months; ≥2 HRCAs, 7.6 months). In GRIFFIN, MRD-negativity (10–5) rates in D-RVd patients were 76.1%, 55.9%, and 61.5% for 0, 1, or ≥2 HRCAs, respectively. MRD-negativity (10–6) rates were higher for D-RVd patients with 0 HRCA (44.8%) and 1 HRCA (26.5%) compared with ≥2 HRCAs (15.4%). In patients who achieved ≥CR, MRD-negativity (10–5) rates in D-RVd patients were 83.3%, 69.2%, and 87.5% among patients with 0, 1, or ≥2 HRCAs, respectively. Rates of sustained MRD negativity (10–5) lasting ≥12 months were 53.7%, 38.2%, and 30.8% among D-RVd patients with 0, 1, or ≥2 HRCAs. Median time to MRD negativity (10–5) was 8.5, 8.6, and 19.6 months among D-RVd patients with 0, 1, or ≥2 HRCAs.

**Table 3 MRD negativity by cytogenetic risk statusa among patients who received D-KRd in MASTER and D-RVd in GRIFFIN.**

[**Full size table**](https://www.nature.com/articles/s41408-024-01030-w/tables/3)

PFS rates in MASTER and GRIFFIN were superior for patients with 0 or 1 HRCA compared with ≥2 HRCAs (Fig. [2](https://www.nature.com/articles/s41408-024-01030-w#Fig2)). In MASTER, at a median follow-up of 31.1 months, estimated 24-month PFS rates for D-KRd patients were 92.4%, 95.7%, and 65.5% for 0, 1, or ≥2 HRCAs, respectively, and estimated 36-month rates were 89.9%, 86.2%, and 52.4%. In GRIFFIN, PFS analyses were conducted for D-RVd patients in a combined analysis of randomized patients (median follow-up at final analysis among all randomized patients, 49.6 months) and among patients from the safety run-in phase (median follow-up, 59.5 months). Estimated 36-month rates for all D-RVd patients were 96.7%, 90.5%, and 53.5% for 0, 1, or ≥2 HRCAs, respectively, and estimated 48-month PFS rates were 93.7%, 90.5%, and 53.5%.