Received: 2 May 2022 | Accepted: 15 August 2022

DOI: 10.1111/bjh.18432

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

Daratumumab plus lenalidomide, bortezomib and dexamethasone in newly diagnosed multiple myeloma: Analysis of vascular thrombotic events in the GRIFFIN study

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Funding information
Janssen Oncology

Summary

Patients with multiple myeloma are at increased risk of vascular thromboembolic events (VTEs). This post hoc analysis evaluated VTEs in the randomised phase 2 GRIFFIN study (ClinicalTrials.gov Identifier: NCT02874742) that investigated lenalidomide/bortezomib/dexamethasone (RVd) ± daratumumab (D). Patients with newly diagnosed multiple myeloma who were eligible for autologous stem cell transplantation (ASCT) received D-RVd/RVd induction, high-dose therapy and ASCT, D-RVd/

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RVd consolidation and up to 2 years of lenalidomide maintenance therapy ± D. VTE prophylaxis was recommended (at least aspirin, ≥162 mg daily) in accordance with International Myeloma Working Group guidelines. In the safety population (D-RVd, $n = 99$; RVd, $n = 102$), VTEs occurred in 10.1% of D-RVd patients and 15.7% of RVd patients; grade 2–4 VTEs occurred in 9.1% and 14.7%, respectively. Median time to the first onset of VTE was longer for D-RVd versus RVd patients (305 days vs 119 days). Anti-thrombosis prophylaxis use was similar between arms (D-RVd, 84.8% vs RVd, 83.3%); among patients with VTEs, prophylaxis use at time of first VTE onset was 60.0% for D-RVd and 68.8% for RVd. In summary, the addition of daratumumab to RVd did not increase the incidence of VTEs, but the cumulative VTE incidence was relatively high in this cohort and anti-thrombotic prophylaxis use was suboptimal.

KEYWORDS
daratumumab, GRIFFIN, newly diagnosed multiple myeloma, prophylaxis, vascular thromboembolic events, VTEs

INTRODUCTION

Patients with multiple myeloma (MM) have an increased risk of vascular thromboembolic events (VTEs), with estimates suggesting at least a seven-fold increased risk of developing VTEs.[1,2] In the newly diagnosed setting, VTEs mostly occur within the first year after diagnosis and during the first six months of therapy, regardless of treatment regimen.[3] Although the reason for this increased VTE risk is not entirely understood, some likely contributing factors include immobilisation, surgery, infections, central venous catheters, erythropoietin use, treatment agents, and acquired and inherited hypercoagulable states.[1] Although the introduction of oral immunomodulatory drugs (IMiDs) has improved the clinical management of MM, these agents are not without limitations and VTEs are a known complication of therapy, particularly with thalidomide or lenalidomide combined with dexamethasone.[1,4] Current guidelines from the International Myeloma Working Group (IMWG) recommend using VTE prophylaxis for patients with MM, assuming no contraindication (e.g., renal failure, von Willebrand disease, severe thrombocytopenia); the prophylaxis approach is modified based on baseline VTE risk for a given therapy regimen, with the goal of choosing the safest and least cumbersome prophylaxis that reduces VTE risk to less than 10%.[2] Two risk assessment models, SAVED and IMPEDE, have been validated to stratify VTE risk in patients with newly diagnosed MM (NDMM) according to certain predictive risk factors,[5,6] but routine incorporation of these models in clinical decision making is limited.

Daratumumab, a human IgGκ monoclonal antibody targeting CD38 with a direct on-tumour[7–10] and immunomodulatory[11–13] mechanism of action, is approved across lines of therapy for patients with NDMM or previously treated MM.[14,15] The daratumumab clinical profile is well established by an expansive clinical trial programme; however, an association with VTE has not been closely examined. The randomised, phase 2 GRIFFIN study investigated safety and efficacy of daratumumab plus lenalidomide, bortezomib and dexamethasone (D-RVd) versus RVd alone in NDMM patients eligible for ASCT.[16] In GRIFFIN, the primary analysis (median follow-up, 13.5 months) showed that the rate of stringent complete response (sCR) at the end of post-ASCT consolidation was significantly higher among patients who received D-RVd versus those who received RVd [42.4% vs 32.0%; one-sided $p = 0.068$ (prespecified one-sided $\alpha = 0.10$)],[16] and follow-up analyses demonstrated responses continued to deepen through the end of maintenance therapy.[17] This post hoc GRIFFIN analysis aimed to evaluate VTE risk and incidence among patients who received D-RVd versus RVd, correlate the baseline risk of VTE per SAVED score with overall VTE incidence, and examine the degree to which anti-thrombosis prophylaxis was administered in accordance with IMWG guidelines, as outlined in the GRIFFIN study protocol.[2]

METHODS

Patients and study design

The full study design and primary results from GRIFFIN, a multicentre, randomised, open-label, phase 2 study, were reported previously (ClinicalTrials.gov Identifier: NCT02874742).[16] Briefly, enrolled patients were aged 18 to 70 years and had a new diagnosis of MM according to 2014 IMWG guidelines (SLiM-CRAB criteria),[18] had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 to 2, and were candidates for high-dose therapy and ASCT. The following lab values were required: absolute neutrophil count $\geq 1.0 \times 10^9$/L, haemoglobin >75 g/L, platelet count $\geq 75 \times 10^9$/L ($\geq 50 \times 10^9$/L if ≥50% of bone marrow was infiltrated with MM cells), alanine aminotransferase and aspartate aminotransferase levels <2.5 times the upper limit of

normal (ULN), total bilirubin level <1.5 times the ULN, creatinine clearance ≥30 ml/min, and corrected serum calcium ≤14.0 mg/dl or free ionised calcium ≤6.5 mg/dl. Patients were randomised (1:1) to receive D-RVd or RVd; stratification factors were International Staging System (ISS) disease stage (I vs II vs III) and creatinine clearance (30–50 ml/min vs >50 ml/min).

All patients received four induction cycles and two post-ASCT consolidation cycles (all 21 days) of oral lenalidomide (25 mg daily; Days 1–14), subcutaneous bortezomib (1.3 mg/m^2; Days 1, 4, 8 and 11), and oral dexamethasone (20 mg; Days 1, 2, 8, 9, 15 and 16). Patients with a creatinine clearance of 30 ml/min to 50 ml/min could receive a reduced lenalidomide dose (10 mg every 24 h), and patients with severe renal impairment or end-stage renal disease were eligible for dose adjustments. The D-RVd group also received intravenous daratumumab (16 mg/kg) weekly during induction therapy (Cycles 1–4, Days 1, 8 and 15), then every three weeks during post-ASCT consolidation therapy (Cycles 5–6, Day 1). Pre-infusion medications included acetaminophen, diphenhydramine or equivalent, montelukast, and dexamethasone. Post-infusion medications included an anti-histamine (diphenhydramine or equivalent), a short-acting ß$_2$-adrenergic receptor agonist, and control medications for patients with lung disease. After completing induction (Cycle 4), patients underwent stem cell mobilisation, high-dose therapy (melphalan 200 mg/m^2), and ASCT, then two cycles of post-ASCT consolidation therapy (Cycles 5–6). Following consolidation therapy, all patients received maintenance therapy (Cycles 7+; 28-day cycles) of oral lenalidomide (10 mg daily, Days 1–21; increasing to 15 mg after three cycles, if tolerated) for up to two years or until disease progression. The D-RVd group also received intravenous daratumumab (16 mg/kg) on Day 1 every eight weeks during maintenance therapy. Alternatively, protocol amendments permitted patients the option to receive intravenous daratumumab (16 mg/kg) every four weeks during maintenance, instead of every eight weeks per the original protocol, or subcutaneous daratumumab (1800 mg) every four weeks. Following completion of study maintenance therapy (Cycle 32), patients could continue on lenalidomide maintenance monotherapy per local standard of care at physician discretion.

Adverse events (AEs) were monitored continuously from informed consent through 30 days after the last study treatment and graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03. Per study protocol, all patients were to receive VTE prophylaxis with at least aspirin ≥162 mg/day. Patients at increased VTE risk, based on their medical history, were to receive alternative prophylaxis of subcutaneous enoxaparin 40 mg/day or other low-molecular-weight heparin (LMWH; at equivalent dose and frequency for prophylaxis). Vitamin K antagonists, factor Xa inhibitors, or direct thrombin inhibitors may have been used at the treating physician's discretion. A medical review was performed on patient medical history data to identify relevant prior and ongoing cardiovascular comorbidities including hypertension, cardiac arrythmias, valvular disease and vascular ischaemic disease (stroke, coronary artery disease, ischaemic bowel, peripheral venous disease and cardiac congenital disorders).

All patients provided written informed consent; the study was conducted according to guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee).

Statistical approach

The prespecified primary end-point was sCR rate (per IMWG criteria[18,19]) by the end of post-ASCT consolidation, when all randomised patients had completed consolidation treatment or discontinued treatment, and the primary end-point was previously reported (median follow-up 13.5 months).[16] The present analysis occurred when all patients completed two years of maintenance therapy or discontinued treatment.

Responses were assessed using a validated computer algorithm according to IMWG criteria.[18,19] Thrombotic events were identified using a Standardised MedDRA Queries (SMQ) search for the term 'embolic and thrombotic events' which included: embolic and thrombotic events, arterial (SMQ); embolic and thrombotic events, venous (SMQ); and embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ). Response rates were compared between treatment groups. Baseline VTE risk was assessed using SAVED scores[5]: surgery within 90 days (S; +2), Asian race (A; −3), history of VTE (V; +3), eighty (age ≥80 years; E; +1), and dexamethasone dose (D; +2 for high, +1 for standard). In GRIFFIN, the VTE risk was not assessed using IMPEDE scores since not all variables required for derivation of IMPEDE were collected during the study. Exploratory comparisons between treatment groups were conducted using descriptive statistics and include no evaluation of statistical significance.

RESULTS

In total, 207 patients were randomised (D-RVd, n = 104; RVd, n = 103) and constituted the intent-to-treat (ITT) population; the safety analysis population included all randomised patients who received one or more doses of study treatment (D-RVd, n = 99; RVd, n = 102). At analysis (median follow-up, 38.6 months), VTEs had occurred in 10 (10.1%) patients in the D-RVd group and 16 (15.7%) patients in the RVd group. Patient demographics and baseline disease characteristics are summarised for each treatment group, by patients who did or did not experience VTEs (Table 1). The groups with VTEs had higher proportions of males than groups without VTEs, more patients with VTEs had an ECOG PS score of 1 or 2 than those without VTEs, and a higher proportion of patients without VTEs had ISS stage III disease compared to those who had VTEs [28 (15.5%) vs 0%, respectively]. Bone marrow involvement of ≥60% of plasma cells (by bone marrow biopsy/aspirate) was observed in five (50.0%) patients

TABLE 1 Demographic and baseline disease characteristics among patients who did or did not experience VTEs

	Patients who experienced VTEs			Patients who did not experience VTEs		
Characteristic	**Total (*n* = 26)**	**D-RVd (*n* = 10)**	**RVd (*n* = 16)**	**Total (*n* = 181)**	**D-RVd (*n* = 94)**	**RVd (*n* = 87)**
Age, years						
Median (range)	57.5 (35–70)	54.0 (35–70)	59.5 (47–70)	60.0 (29–70)	59.5 (29–70)	61.0 (40–70)
<65, *n* (%)	17 (65.4)	7 (70.0)	10 (62.5)	134 (74.0)	69 (73.4)	65 (74.7)
≥65, *n* (%)	9 (34.6)	3 (30.0)	6 (37.5)	47 (26.0)	25 (26.6)	22 (25.3)
Male, *n* (%)	19 (73.1)	8 (80.0)	11 (68.8)	99 (54.7)	50 (53.2)	49 (56.3)
Weight, kg	*n* = 26	*n* = 10	*n* = 16	*n* = 179	*n* = 92	*n* = 87
Median (range)	87.1 (62.0–148.5)	81.9 (63.6–141.5)	88.2 (62.0–148.5)	80.4 (37.4–158.6)	78.9 (48.8–158.6)	82.7 (37.4–150.1)
ECOG PS score, *n* (%)	*n* = 26	*n* = 10	*n* = 16	*n* = 177	*n* = 91	*n* = 86
0	3 (11.5)	1 (10.0)	2 (12.5)	76 (42.9)	38 (41.8)	38 (44.2)
1	17 (65.4)	7 (70.0)	10 (62.5)	86 (48.6)	44 (48.4)	42 (48.8)
2	6 (23.1)	2 (20.0)	4 (25.0)	15 (8.5)	9 (9.9)	6 (7.0)
ISS disease stage, *n* (%)[a]						
I	13 (50.0)	6 (60.0)	7 (43.8)	86 (47.5)	43 (45.7)	43 (49.4)
II	13 (50.0)	4 (40.0)	9 (56.3)	64 (35.4)	36 (38.3)	28 (32.2)
III	0	0	0	28 (15.5)	14 (14.9)	14 (16.1)
Missing	0	0	0	3 (1.7)	1 (1.1)	2 (2.3)
Type of measurable disease, *n* (%)[b]						
Serum and urine	4 (15.4)	1 (10.0)	3 (18.8)	33 (18.2)	22 (23.4)	11 (12.6)
Free light chain	3 (11.5)	2 (20.0)	1 (6.3)	23 (12.7)	13 (13.8)	10 (11.5)
Serum only	14 (53.8)	4 (40.0)	10 (62.5)	99 (54.7)	49 (52.1)	50 (57.5)
Urine only	5 (19.2)	3 (30.0)	2 (12.5)	22 (12.2)	9 (9.6)	13 (14.9)
Not evaluable	0	0	0	4 (2.2)	1 (1.1)	3 (3.4)
Bone marrow involvement (% plasma cells, bone marrow biopsy/ aspirate), *n* (%)[c]						
<10	3 (11.5)	1 (10.0)	2 (12.5)	13 (7.2)	9 (9.6)	4 (4.6)
10–59	9 (34.6)	4 (40.0)	5 (31.3)	88 (48.6)	42 (44.7)	46 (52.9)
≥60	14 (53.8)	5 (50.0)	9 (56.3)	73 (40.3)	40 (42.6)	33 (37.9)
Missing	0	0	0	7 (3.9)	3 (3.2)	4 (4.6)
Time from MM diagnosis to randomisation	*n* = 26	*n* = 10	*n* = 16	*n* = 179	*n* = 93	*n* = 86
Median (range), months	0.8 (0–3)	0.4 (0–3)	0.9 (0–2)	0.8 (0–61)	0.7 (0–12)	0.9 (0–61)
Cytogenetic profile, *n* (%)[d]	*n* = 25	*n* = 10	*n* = 15	*n* = 170	*n* = 88	*n* = 82
Standard risk, *n* (%)	21 (84.0)	8 (80.0)	13 (86.7)	144 (84.7)	74 (84.1)	70 (85.4)
High risk, *n* (%)	4 (16.0)	2 (20.0)	2 (13.3)	26 (15.3)	14 (15.9)	12 (14.6)
del17p	4 (16.0)	2 (20.0)	2 (13.3)	10 (5.9)	6 (6.8)	4 (4.9)
t(4;14)	1 (4.0)	0	1 (6.7)	13 (7.6)	8 (9.1)	5 (6.1)
t(14;16)	0	0	0	4 (2.4)	1 (1.1)	3 (3.7)

Abbreviations: D-RVd, daratumumab plus lenalidomide/bortezomib/dexamethasone; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; MM, multiple myeloma; RVd, lenalidomide/bortezomib/dexamethasone; VTEs, vascular thrombotic events.

[a]Based on the combination of serum β_2-microglobulin and albumin.

[b]Includes immunoglobulin D, immunoglobulin M, immunoglobulin E, and biclonal.

[c]Highest value by biopsy or aspirate.

[d]Cytogenetic risk was based on local fluorescence in situ hybridisation or karyotype analysis. Patients with high-risk cytogenetics had a del17p, t(4;14) or t(14;16) abnormality; a patient could be counted in more than one subcategory. Patients with standard-risk cytogenetic abnormalities had an absence of high-risk cytogenetic abnormalities.

receiving D-RVd and nine (56.3%) patients receiving RVd with VTEs, versus 40 (42.6%) and 33 (37.9%) patients receiving D-RVd and RVd, respectively, without VTEs. Among patients with VTEs, the median total number of treatment cycles was 32.0 (range, 20–32) in the D-RVd group and 30.5 (range, 4–32) in the RVd group.

Summary of VTE incidence and time to VTEs

VTEs occurred in 10 (10.1%) D-RVd patients and 16 (15.7%) RVd patients (Table 2). Grade 2–4 VTEs occurred in nine (9.1%) D-RVd patients and 15 (14.7%) RVd patients. No grade 5 VTEs occurred in either treatment group. The most common any-grade VTEs were deep-vein thrombosis [D-RVd, $n = 2$ (2.0%); RVd, $n = 7$ (6.9%)], pulmonary embolism [$n = 2$ (2.0%); $n = 4$ (3.9%)], and embolism classified as unspecified vessel type and mixed arterial and venous [$n = 2$ (2.0%); $n = 3$ (2.9%)]. Grade 2–4 pulmonary embolism occurred in two (2.0%) D-RVd patients and four (3.9%) RVd patients.

The median time to first onset of VTE was 305 (range, 6–810) days for D-RVd patients versus 119 (range, 21–822) days for RVd patients (Figure 1). Across both groups, the VTE incidence increased most rapidly during induction therapy, in which nearly half of VTEs occurred (Table 3). During induction (Cycles 1–4), overall VTE incidence was 5.1% ($n = 5$) for D-RVd and 8.8% ($n = 9$) for RVd. During consolidation therapy, no D-RVd patients had a VTE of first onset and one (1.4%) RVd patient experienced a VTE. Additional VTEs of first onset contiued to occur during the first year of maintenance therapy [Cycles 7–18: D-RVd, 2.2% ($n = 2$); RVd, 7.0% ($n = 5$)] and thereafter [Cycle 18+: D-RVd, 3.6% ($n = 3$); RVd, 1.7% ($n = 1$)]. The median dose of lenalidomide on or prior to the first onset date of VTE was 17.5 (range, 10–25) mg for the D-RVd group and 25.0 (range, 10–25) mg for the RVd group.

Response rates among patients with VTEs

Among patients who experienced VTEs, clinical responses deepened over time and response rates were higher in the D-RVd group versus the RVd group after two years of maintenance (Figure 2A). By the end of post-ASCT consolidation, complete response or better (≥CR) was achieved in 50.0% of D-RVd patients with VTEs versus 31.3% of RVd patients with VTEs. Response rates continued to deepen during maintenance therapy and improved for D-RVd versus RVd; after two years of maintenance therapy, the rate of ≥CR among patients with VTEs rose to 90.0% for D-RVd and 68.8% for RVd.

At the time of first onset of VTEs, a best response of CR or better occurred in 50.0% of D-RVd patients with VTEs versus 31.3% of RVd patients with VTEs (Figure 2B).

SAVED scores and cardiovascular comorbidities

VTE risk was assessed using the SAVED score, which was calculated based on patient-specific parameters and stratified into low (<2 points) and high risk (≥2 points). Generally, a higher SAVED score indicates higher VTE risk. The median SAVED score in the ITT population was 0 (range, 0–3) in the D-RVd group and 0 (range, −3 to 4) in the RVd group.

TABLE 2 Summary of total VTE incidence in the safety analysis population[a]

	D-RVd ($n = 99$)			RVd ($n = 102$)		
Patients with ≥1 VTE, *n* (%)	**Grade 1**	**Grade 2–4**	**Total**	**Grade 1**	**Grade 2–4**	**Total**
Total number with ≥1 VTE	1 (1.0)	9 (9.1)	10 (10.1)	1 (1.0)	15 (14.7)	16 (15.7)
Embolic and thrombotic events	2 (2.0)	3 (3.0)	5 (5.1)	1 (1.0)	10 (9.8)	11 (10.8)
Deep vein thrombosis	1 (1.0)	1 (1.0)	2 (2.0)	0	7 (6.9)	7 (6.9)
Pulmonary embolism	0	2 (2.0)	2 (2.0)	0	4 (3.9)	4 (3.9)
Embolism venous	0	0	0	1 (1.0)	0	1 (1.0)
Jugular vein thrombosis	0	1 (1.0)	1 (1.0)	0	1 (1.0)	1 (1.0)
Subclavian vein thrombosis	0	1 (1.0)	1 (1.0)	0	0	0
Thrombophlebitis superficial	1 (1.0)	1 (1.0)	2 (2.0)	0	0	0
Unspecified and mixed arterial and venous	0	6 (6.1)	6 (6.1)	1 (1.0)	5 (4.9)	6 (5.9)
Embolism	0	2 (2.0)	2 (2.0)	1 (1.0)	2 (2.0)	3 (2.9)
Cerebral congestion	0	2 (2.0)	2 (2.0)	0	1 (1.0)	1 (1.0)
Cerebrovascular accident	0	0	0	0	1 (1.0)	1 (1.0)
Hemiparesis	0	0	0	0	1 (1.0)	1 (1.0)
Intestinal infarction	0	1 (1.0)	1 (1.0)	0	0	0
Vascular access site thrombosis	0	1 (1.0)	1 (1.0)	0	0	0

Abbreviations: D-RVd, daratumumab plus lenalidomide/bortezomib/dexamethasone; RVd, lenalidomide/bortezomib/dexamethasone; VTE, vascular thrombotic event.

[a]No grade 5 VTEs were reported in either treatment group.

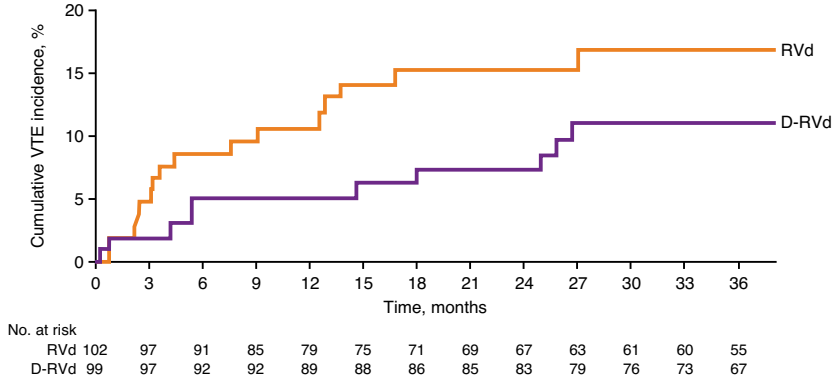

FIGURE 1 Cumulative incidence of VTEs in the safety analysis population. D-RVd, daratumumab plus lenalidomide/bortezomib/dexamethasone; RVd, lenalidomide/bortezomib/dexamethasone; VTE, vascular thrombotic event. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Summary of patients with ≥1 VTE by treatment phase in the safety analysis population

	D-RVd (*n*=99)					RVd (*n*=102)				
Patients with ≥1 VTE, *n* (%)	**C 1–4[a]** *n* = 99	**C 5–6[b]** *n* = 91	**C 7–18[c]** *n* = 89	**C 18+[c]** *n* = 84	**Total** *n* = 99	**C 1–4[a]** *n* = 102	**C 5–6[b]** *n* = 74	**C 7–18[c]** *n* = 71	**C 18+[c]** *n* = 58	**Total** *n* = 102
Total	5 (5.1)	0	2 (2.2)	3 (3.6)	10 (10.1)	9 (8.8)	1 (1.4)	5 (7.0)	1 (1.7)	16 (15.7)
Cerebral congestion	0	0	1 (1.1)	1 (1.2)	2 (2.0)	0	0	1 (1.4)	0	1 (1.0)
Deep vein thrombosis	2 (2.0)	0	0	0	2 (2.0)	3 (2.9)	1 (1.4)	3 (4.2)	0	7 (6.9)
Embolism	1 (1.0)	0	0	1 (1.2)	2 (2.0)	1 (1.0)	1 (1.4)	0	1 (1.7)	3 (2.9)
Pulmonary embolism	1 (1.0)	0	0	1 (1.2)	2 (2.0)	2 (2.0)	1 (1.4)	1 (1.4)	0	4 (3.9)
Thrombophlebitis superficial	0	0	2 (2.2)	0	2 (2.0)	0	0	0	0	0
Intestinal infarction	1 (1.0)	0	0	0	1 (1.0)	0	0	0	0	0
Jugular vein thrombosis	0	0	0	1 (1.2)	1 (1.0)	1 (1.0)	0	0	0	1 (1.0)
Subclavian vein thrombosis	0	0	0	1 (1.2)	1 (1.0)	0	0	0	0	0
Vascular access site thrombosis	1 (1.0)	0	0	0	1 (1.0)	0	0	0	0	0
Cerebrovascular accident	0	0	0	0	0	0	0	1 (1.4)	0	1 (1.0)
Embolism venous	0	0	0	0	0	1 (1.0)	0	0	0	1 (1.0)
Hemiparesis	0	0	0	0	0	1 (1.0)	0	0	0	1 (1.0)

Abbreviations: C, cycle; D-RVd, daratumumab plus lenalidomide/bortezomib/dexamethasone; RVd, lenalidomide/bortezomib/dexamethasone; VTE, vascular thrombotic event.

[a]Cycles 1–4 (21-day cycles) correspond to D-RVd or RVd induction therapy.

[b]Cycles 5–6 (21-day cycles) correspond to D-RVd or RVd post-ASCT consolidation therapy.

[c]Cycles 7–32 (28-day cycles) comprised study treatment maintenance therapy of D-R or R. Following completion of study maintenance therapy (Cycle 32), patients could continue R maintenance monotherapy per local standard of care.

Among patients who experienced VTEs, the median SAVED score was slightly higher for RVd patients than for D-RVd patients [D-RVd: 0 (range, 0–3); RVd: 0.5 (range, 0–4); Table 4]; slightly higher individual scores were observed in the RVd versus D-RVd groups.

In an analysis of comorbidities, the median number of cardiovascular comorbidities was one for patients in the overall population as well as among patients who experienced VTEs. The proportion of patients without any cardiovascular comorbidities was 48.1% (50/104) for D-RVd patients and 24.3% (25/103) for RVd patients in the overall population compared with 30.0% (3/10) and 12.5% (2/16), respectively, for patients who experienced VTEs. The proportions of patients with one cardiovascular comorbidity were similar for the overall population [D-RVd, 41.3% (43/104); RVd, 57.3% (59/103)] and patients who experienced VTEs [D-RVd, 40.0% (4/10); RVd, 62.5% (10/16)], while the proportion of patients with two cardiovascular comorbidities was lower in the

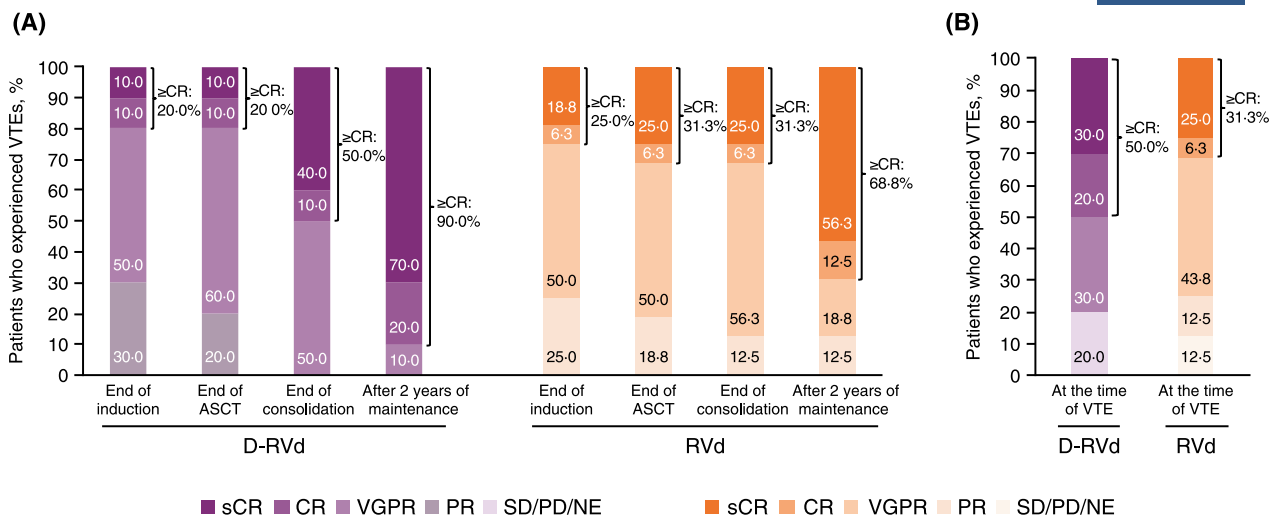

FIGURE 2 Summary of response rates over time among patients who experienced VTEs (A) and response rates among these patients at first onset of VTE (B). ASCT, autologous stem cell transplant; CR, complete response; D-RVd, daratumumab plus lenalidomide/bortezomib/dexamethasone; PR, partial response; RVd, lenalidomide/bortezomib/dexamethasone; sCR, stringent complete response; SD/PD/NE, stable disease/progressive disease/not evaluable; VGPR, very good partial response; VTEs, vascular thrombotic events. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 4 VTE risk according to SAVED scores[a] among the ITT population and patients who experienced VTEs

	ITT population		Patients who experienced VTEs	
SAVED score	D-RVd (*n* = 104)	RVd (*n* = 103)	D-RVd (*n* = 10)	RVd (*n* = 16)
Median (range)	0 (0–3)	0 (−3 to 4)	0 (0–3)	0.5 (0–4)
Mean (SD)	0.3 (0.88)	0.7 (1.07)	0.7 (1.16)	0.8 (1.06)

Abbreviations: D-RVd, daratumumab plus lenalidomide/bortezomib/dexamethasone; ITT, intent-to-treat; RVd, lenalidomide/bortezomib/dexamethasone; SD, standard deviation; VTE, vascular thrombotic event.

[a]SAVED scores were calculated using patient-specific parameters: surgery within 90 days (S; +2), Asian race (A; −3), history of VTE (V; +3), eighty (age≥80years; E; +1), and dexamethasone dose (D; +2 for high, +1 for standard).

overall population [D-RVd, 7.7% (8/104); RVd, 13.6% (14/103)] compared with those who experienced VTEs [D-RVd, 30.0% (3/10); RVd, 25.0% (4/16)].

VTE prophylaxis use

In the overall safety analysis population, anti-thrombosis prophylaxis medication at any time was received by 84 (84.8%) D-RVd patients and 85 (83.3%) RVd patients (Table 5). Overall, 48 (48.5%) D-RVd patients and 31 (30.4%) RVd patients were already receiving anti-thrombosis prophylaxis before the first dose of study drug and continued prophylaxis during the study. The most frequently used drugs for anti-thrombosis prophylaxis overall were salicylic acid and derivatives, used in approximately 80% of all patients. Among patients who received salicylic acid and derivatives, the median daily dose for D-RVd patients (*n* = 77) was 110.8 mg (range, 80.0–650.0 mg) and for RVd patients (*n* = 82) was 81.0 mg (range, 81.0–650.0 mg). Heparins were used in approximately 15% of patients, including low-molecular-weight and standard heparin. Other drugs used included direct factor Xa inhibitors (5%–8%), platelet aggregation inhibitors (≤1%), vitamin K antagonists (≤1%), and direct thrombin inhibitors (≤1%).

Among patients who developed VTEs, anti-thrombosis prophylaxis was used in eight (80.0%) patients in the D-RVd group and 15 (93.8%) patients in the RVd group at any time. However, only six (60.0%) D-RVd patients and 11 (68.8%) RVd patients were receiving anti-thrombosis prophylaxis medication at time of first onset of VTE. This included aspirin in four (40.0%) D-RVd patients and 10 (62.5%) RVd patients, as well as LMWH in one (10.0%) and two (12.5%) patients, respectively. One (10.0%) D-RVd patient received rivaroxaban (at a daily full dose of 20 mg). In the RVd group, one (6.3%) patient received prasugrel and one (6.3%) patient received warfarin. The protocol-recommended aspirin dose was ≥162 mg/day; among patients who experienced a VTE (at any time) and received anti-thrombosis prophylaxis, the median daily dose of salicylic acid and derivatives was 162.0 mg (range, 80.0–325.0 mg) for D-RVd (*n* = 5) and 81.0 mg (range, 81.0–325.0 mg) for RVd (*n* = 14).

DISCUSSION

Patients with MM have an increased risk of VTEs, which is further exacerbated by oral IMiD treatment.[1,4] In this post hoc analysis of the GRIFFIN study, the addition of daratumumab to RVd for induction/consolidation therapy for transplant-eligible patients with NDMM did not appear to increase VTE incidence. VTEs occurred in 10.1% of D-RVd patients (grade 2–4, 9.1%) and 15.7% of RVd patients (grade 2–4, 14.7%). The overall VTE rates in GRIFFIN,

TABLE 5 Summary of anti-thrombosis prophylaxis medication use[a]

	Overall safety analysis population		Patients who experienced VTEs			
	Total anti-thrombosis prophylaxis use		Total anti-thrombosis prophylaxis use		Anti-thrombosis use at the first onset time of VTE	
	D-RVd (*n* = 99)	RVd (*n* = 102)	D-RVd (*n* = 10)	RVd (*n* = 16)	D-RVd (*n* = 10)	RVd (*n* = 16)
Total number of patients with ≥1 anti-thrombosis prophylaxis concomitant medication, *n* (%)	84 (84.8)	85 (83.3)	8 (80.0)	15 (93.8)	6 (60.0)	11 (68.8)
Anti-thrombotic agents, *n* (%)	20 (20.2)	21 (20.6)	4 (40.0)	7 (43.8)	2 (20.0)	3 (18.8)
Heparin group	14 (14.1)	17 (16.7)	3 (30.0)	4 (25.0)	1 (10.0)	2 (12.5)
Enoxaparin	9 (9.1)	11 (10.8)	1 (10.0)	3 (18.8)	0	0
Lovenox	4 (4.0)	5 (4.9)	2 (20.0)	2 (12.5)	1 (10.0)	2 (12.5)
Heparin	1 (1.0)	2 (2.0)	0	0	0	0
Dalteparin	1 (1.0)	1 (1.0)	0	0	0	0
Enoxaparin sodium	1 (1.0)	0	0	0	0	0
Direct factor Xa inhibitors, *n* (%)	8 (8.1)	5 (4.9)	2 (20.0)	3 (18.8)	1 (10.0)	0
Xarelto	3 (3.0)	3 (2.9)	1 (10.0)	1 (6.3)	1 (10.0)	0
Apixaban	2 (2.0)	1 (1.0)	1 (10.0)	1 (6.3)	0	0
Rivaroxaban	2 (2.0)	1 (1.0)	0	1 (6.3)	0	0
Eliquis	1 (1.0)	0	0	0	0	0
Anti-platelet medications (excluding heparin), *n* (%)	0	1 (1.0)	0	1 (6.3)	0	1 (6.3)
Prasugrel	0	1 (1.0)	0	1 (6.3)	0	1 (6.3)
Salicylic acid and derivatives[b]	77 (77.8)	82 (80.4)	5 (50.0)	14 (87.5)	4 (40.0)	10 (62.5)
Vitamin K antagonists, *n* (%)	0	1 (1.0)	0	1 (6.3)	0	1 (6.3)
Warfarin	0	1 (1.0)	0	1 (6.3)	0	1 (6.3)
Direct thrombin inhibitors, *n* (%)	1 (1.0)	0	0	0	0	0
Pradaxa	1 (1.0)	0	0	0	0	0

Abbreviations: D-RVd, daratumumab plus lenalidomide/bortezomib/dexamethasone; RVd, lenalidomide/bortezomib/dexamethasone; VTEs, vascular thrombotic events.

[a]All concomitant medications were coded according to the WHODrug dictionary. The coded terms are displayed. Because of this, several products with the same active ingredient are listed separately by brand name or generic name.

[b]Coded terms for the ASA derivatives included aspirin/00002701/, aspirin Ec, acetylsalicylic acid, asa, aspirin enteric coated K.P., aspirin or ecotrin.

including those with the first occurrence during induction therapy (D-RVd, 5.1%; RVd, 8.8%), were higher than previously reported for patients with NDMM without a high VTE risk while on lenalidomide-induction therapy (2.3% with aspirin prophylaxis and 1.2% with LMWH group prophylaxis).[20] The anti-thrombotic prophylaxis recommendations in the GRIFFIN study protocol were aligned with IMWG guidance stating that aspirin prophylaxis should be used for any myeloma patient with at most one VTE risk factor and LMWH (or full-dose warfarin) prophylaxis should be used for patients with more than one VTE risk factor.[2] Despite this, only 84.8% and 83.3% of D-RVd and RVd patients, respectively, received VTE prophylaxis. Among patients with VTEs, 80.0% of D-RVd patients and 93.8% of RVd patients received anti-thrombosis prophylaxis, but only 60.0% and 68.8%, respectively, were receiving anti-thrombosis prophylaxis medication at the onset of first VTE. These data indicate suboptimal use of anti-thrombotic prophylaxis, even in academic centres. The relatively high VTE incidence in GRIFFIN may be due to suboptimal use of anti-thrombosis prophylaxis, and prophylaxis use should be strongly encouraged or required even during maintenance therapy, as VTEs occur well beyond the induction phase. Additionally, these data also reflect that aspirin (salicylic acid and derivatives) may not be sufficient prophylaxis for myeloma patients treated with RVd. These data indicate that revisiting the IMWG guidance may be warranted for this patient population.

The median time to first onset of VTE was longer for D-RVd than RVd patients (305 days vs 119 days). Across both study groups, the VTE incidence increased most rapidly during induction therapy, yet VTEs continued to occur during maintenance therapy at a lower rate. The median time to onset of VTE for the D-RVd group was 305 days, notably longer than for the RVd group and other reports of VTE incidence among NDMM patients[3]; however, the longer median may be skewed by the relatively small number of

D-RVd patients with VTEs during induction and consolidation. Regardless of the small number of patients with VTEs, the finding that VTEs continued to occur during consolidation and maintenance suggests that it is important to continue VTE prophylaxis beyond induction. As expected, the patients in the RVd arm were exposed to a higher median dose of lenalidomide, which may have contributed to the higher incidence of VTEs in the RVd arm. While this analysis was not powered to evaluate efficacy, responses among patients with VTEs were consistent with the primary findings of the GRIFFIN study[16] and demonstrate that despite VTEs, patients still benefited from D-RVd therapy. D-RVd was associated with higher rates of ≥CR compared to RVd; by the end of post-ASCT consolidation, rates of ≥CR among patients with VTEs were 50.0% for D-RVd versus 31.3% for RVd, mirroring improved rates of ≥CR for D-RVd across all patients. Patients who developed VTEs were also able to continue therapy and experienced deepening of response; after two years of maintenance treatment, rates of ≥CR for patients who experienced VTEs were 90.0% for D-RVd and 68.8% for RVd. Thus, development of VTEs did not prevent patients from completing planned therapy or achieving maximal depth of response.

Risk assessment tools, such as calculated SAVED scores, may help identify patients at high risk for VTE. Relatively high rates of VTE (incidence ≥10%) were recorded in both groups, despite retrospective SAVED scores suggesting a low risk of VTEs (median score well below 2 points). Mean SAVED scores were less than 1 in the ITT population and among those who developed VTEs. This analysis shows that lower-risk patient populations (based on SAVED score) are also at risk of developing VTEs while on IMiD-based combination regimens and implies the need for more precise tools to predict VTE risk. Use of the IMPEDE score may have possibly improved risk assessment in the present study; however, its use with our analysis was not possible as not all variables required for derivation of the IMPEDE score were collected during the study. Another observation is that the proportion of patients with two cardiovascular comorbidities was lower in the overall population compared with those who experienced VTEs. This suggests that a high cardiovascular disease burden should be considered when assessing a patient's VTE risk; however, it is important to note that these results could be confounded by small patient numbers. Nevertheless, it is noteworthy that more than 15% of patients in both arms had no recorded use of VTE prophylaxis, and 30%–40% of patients in both arms were not receiving antithrombotic prophylaxis at the time of VTE. These observations are consistent with the notion that existing VTE risk stratification tools are somewhat limited in their ability to capture all relevant aspects of coagulation in MM patients, and that we need improved algorithms that take account of disease-specific, patient-specific, and treatment-specific characteristics.[21,22] Importantly, this analysis also suggests a need to better understand VTE pathogenesis in MM, and to improve and optimise adherence to anti-thrombosis prophylaxis, even in patients considered at low risk.

Two recent reports have assessed VTE incidence in patients with MM receiving daratumumab.[23,24] A systematic review and meta-analysis of pooled data from six clinical trials reported that the addition of daratumumab to established backbone regimens did not increase the risk for VTEs.[23] Similarly, a post hoc analysis of the phase 3 CASTOR, POLLUX, and MAIA clinical trials data revealed that VTE incidences were similar in patients receiving daratumumab-containing regimens and non-daratumumab regimens (hazard ratio 0.80; 95% confidence interval, 0.57–1.13; $p = 0.17$), with risk factors for VTEs similar in both populations.[24] Our results from GRIFFIN are consistent with these previous findings that daratumumab was not associated with increased VTE incidence.

In conclusion, in this post hoc analysis, the addition of daratumumab to RVd as therapy for transplant-eligible patients with NDMM did not appear to increase VTE incidence. Furthermore, our current data suggest that VTE prophylaxis use in this population was suboptimal, and VTE prophylactic therapy adherence may not be ideal in the United States, even at academic centres, which constituted the majority of study sites in this trial. Thus, these results suggest that an unmet need exists to improve and optimise adherence to anti-thrombosis prophylaxis in patients with NDMM, even among those who may be deemed at low risk for VTEs. Additional and larger prospective investigations are warranted to understand optimal VTE prophylaxis use in all patients with NDMM, guided by validated MM VTE prediction tools and even in those classified with lower VTE risk.

AUTHOR CONTRIBUTIONS

All authors participated in study design, or the acquisition of data, or the analysis or interpretation of data, and contributed to manuscript writing and reviewing. All authors approved the final version of the manuscript.

ACKNOWLEDGEMENTS

The authors thank the patients who volunteered to participate in this trial, their families, and the staff members at the trial sites who cared for them. This study (ClinicalTrials.gov Identifier: NCT02874742) was supported by Janssen Oncology and designed in partnership with Alliance Foundation Trials (https://acknowledgments.alliancefound.org). Writing and editorial support were provided by Charlotte Majerczyk, PhD, and Michelle Kwon, PhD, of Cello Health Communications/MedErgy, and were funded by Janssen Pharmaceuticals. This study (ClinicalTrials.gov Identifier: NCT02874742) was supported by research funding from Janssen Oncology.

CONFLICT OF INTERESTS

Douglas W. Sborov acted as an advisor/consultant for Janssen, Bristol Myers Squibb/Celgene, Sanofi, AbbVie, and GlaxoSmithKline. Muhamed Baljevic acted as a consultant for Bristol Myers Squibb/Celgene; participated in advisory committees for Oncopeptides, Janssen, Karyopharm, and

Bristol Myers Squibb/Celgene; and received research support from Amgen and Exelixis. Brandi Reeves acted as a consultant and received honoraria from Bristol Myers Squibb, Incyte, and Pharma Essentia. Jacob Laubach has nothing to disclose. Yvonne A. Efebera has received honoraria from Janssen, Takeda, GlaxoSmithKline, Oncopeptide and Sanofi; served on the speakers bureau and advisory board for Oncopeptide, Sanofi and GlaxoSmithKline; and has received research fund from Bristol Myers Squib. Cesar Rodriguez acted as an advisor and participated on speakers bureaus for Amgen, Bristol Myers Squibb, Takeda, Karyopharm, Oncopeptides, and Sanofi. Luciano J. Costa received research funding from Amgen and Janssen; and acted as a consultant for Amgen, Janssen, Bristol Myers Squibb, and Karyopharm. Ajai Chari participated in advisory committees for AbbVie, Amgen, Bristol Myers Squibb/Celgene, Genentech, GlaxoSmithKline, Janssen, Karyopharm, Oncopeptides, Sanofi, Seattle Genetics, Secura Bio, and Shattuck Labs; received research funding from Amgen, Bristol Myers Squibb/Celgene, Janssen, Seattle Genetics, and Takeda/Millennium; and acted as a consultant for Amgen, Antengene, Bristol Myers Squibb/Celgene, Janssen, Secura Bio, and Takeda/Millennium. Rebecca Silbermann acted as a consultant for Janssen and Sanofi Aventis; and received research funding from Sanofi Aventis. Sarah A. Holstein acted as a consultant for and received honoraria from Celgene, Genentech, GlaxoSmithKline, Janssen, Secura Bio, Sorrento, Takeda, and Oncopeptides; and received research funding from Oncopeptides. Larry D. Anderson participated in advisory committees and acted as a consultant for Amgen, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Karyopharm, Oncopeptides, AbbVie, and Prothena. Jonathan L. Kaufman participated in advisory committees for Incyte and TG Therapeutics; acted as a consultant for AbbVie, Bristol Myers Squibb, Janssen, Roche/Genentech, and Tecnopharma; received research funding from AbbVie, Amgen, Bristol Myers Squibb, Fortis Therapeutics, Heidelberg Pharma, Janssen, Novartis, Roche/Genentech, Sutro Biopharma, and Takeda; and received honoraria from AbbVie, Janssen, Roche/Genentech, and Tecnopharma. Nina Shah acted as a consultant for GlaxoSmithKline, Amgen, Indapta Therapeutics, Sanofi, Care Dx, Kite, Karyopharma, and Oncopeptides; and received research funding from Celgene/Bristol Myers Squibb, Janssen, Bluebird Bio, Sutro Biopharma, Teneobio, Poseida, and Nektar. Huiling Pei, Annelore Cortoos, J. Blake Bartlett and Jessica Vermeulen are current employees and stock shareholders of Janssen. Sharmila Patel is a current employee of Janssen. Thomas S. Lin is a current employee and stock shareholder of Janssen; and holds stock in GlaxoSmithKline. Peter M. Voorhees participated in advisory committees for AbbVie, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Karyopharm, Oncopeptides, Pfizer, and Sanofi; and acted as a consultant for Bristol Myers Squibb, Novartis, Oncopeptides, and Secura Bio. Paul G. Richardson received institutional research support from Oncopeptides, Celgene/Bristol Myers Squibb, Takeda, and Karyopharm; and received honoraria for his role as an advisory committee member from Karyopharm, Oncopeptides, Celgene/Bristol Myers Squibb, Takeda, Janssen, Sanofi, Secura Bio, GlaxoSmithKline, Regeneron, AstraZeneca, and Protocol Intelligence.

DATA AVAILABILITY STATEMENT

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 (YODA) Project site at http://yoda.yale.edu.

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How to cite this article: Sborov DW, Baljevic M, Reeves B, Laubach J, Efebera YA, Rodriguez C, et al. Daratumumab plus lenalidomide, bortezomib and dexamethasone in newly diagnosed multiple myeloma: Analysis of vascular thrombotic events in the GRIFFIN study. Br J Haematol. 2022;199(3):355–365. https://doi.org/10.1111/bjh.18432