Elotuzumab, lenalidomide, bortezomib, dexamethasone, and autologous haematopoietic stem-cell transplantation for newly diagnosed multiple myeloma (GMMG-HD6): results from a randomised, phase 3 trial

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Summary

Background The aim of this trial was to investigate the addition of the anti-SLAMF7 monoclonal antibody elotuzumab to lenalidomide, bortezomib, and dexamethasone (RVd) in induction and consolidation therapy as well as to lenalidomide maintenance treatment in transplant-eligible patients with newly diagnosed multiple myeloma.

Methods GMMG-HD6 was a phase 3, randomised trial conducted at 43 main trial sites and 26 associated trial sites throughout Germany. Adult patients (aged 18–70 years) with previously untreated, symptomatic multiple myeloma, and a WHO performance status of 0–3, with 3 being allowed only if caused by myeloma disease and not by comorbid conditions, were randomly assigned 1:1:1:1 to four treatment groups. Induction therapy consisted of four 21-day cycles of RVd (lenalidomide 25 mg orally on days 1–14; bortezomib 1·3 mg/m² subcutaneously on days 1, 4, 8, and 11]; and dexamethasone 20 mg orally on days 1, 2, 4, 5, 8, 9, 11, 12, and 15 for cycles 1–2) or, RVd induction plus elotuzumab (10 mg/kg intravenously on days 1, 8, and 15 for cycles 1–2, and on days 1 and 11 for cycles 3–4; E-RVd). Autologous haematopoietic stem-cell transplantation was followed by two 21-day cycles of either RVd consolidation (lenalidomide 25 mg orally on days 1–14; bortezomib 1·3 mg/m² subcutaneously on days 1, 8, and 15; and dexamethasone 20 mg orally on days 1, 2, 8, 9, 15, and 16) or elotuzumab plus RVd consolidation (with elotuzumab 10 mg/kg intravenously on days 1, 8, and 15) followed by maintenance with either lenalidomide (10 mg orally on days 1–28 for cycles 1–3; thereafter, up to 15 mg orally on days 1–28; RVd/R or E-RVd/R group) or lenalidomide plus elotuzumab (10 mg/kg intravenously on days 1 and 15 for cycles 1–6, and on day 1 for cycles 7–26; RVd/E-R or E-RVd/E-R group) for 2 years. The primary endpoint was progression-free survival analysed in a modified intention-to-treat (ITT) population. Safety was analysed in all patients who received at least one dose of trial medication. This trial is registered with ClinicalTrials.gov, NCT02495922, and is completed.

Findings Between June 29, 2015, and on Sept 11, 2017, 564 patients were included in the trial. The modified ITT population comprised 559 (243 [43%] females and 316 [57%] males) patients and the safety population 555 patients. After a median follow-up of 49·8 months (IQR 43·7–55·5), there was no difference in progression-free survival between the four treatment groups (adjusted log-rank p value, p=0·86), and 3-year progression-free survival rates were 69% (95% CI 61–77), 69% (61–76), 66% (58–74), and 67% (59–75) for patients treated with RVd/R, RVd/E-R, E-RVd/R, and E-RVd/E-R, respectively. Infections (grade 3 or worse) were the most frequently observed adverse event in all treatment groups (28 [20%] of 137 for RVd/R; 32 [23%] of 138 for RVd/E-R; 35 [25%] of 138 for E-RVd/R; and 48 [34%] of 142 for E-RVd/E-R). Serious adverse events (grade 3 or worse) were observed in 68 (48%) of 142 participants in the E-RVd/E-R group, 53 (39%) of 137 in the RVd/R, 53 (38%) of 138 in the RVd/E-R, and 50 (36%) of 138 in the E-RVd/R (36%) group. There were nine treatment-related deaths during the study. Two deaths (one sepsis and one toxic colitis) in the RVd/R group were considered lenalidomide-related. One death in the RVd/E-R group due to meningoencephalitis was considered lenalidomide and elotuzumab-related. Four deaths (one pulmonary embolism, one septic shock, one atypical pneumonia, and one cardiovascular failure) in the E-RVd/R group and two deaths (one sepsis and one pneumonia and pulmonary fibrosis) in the E-RVd/E-R group were considered related to lenalidomide or elotuzumab, or both.

Interpretation Addition of elotuzumab to RVd induction or consolidation and lenalidomide maintenance in patients with transplant-eligible newly diagnosed multiple myeloma did not provide clinical benefit. Elotuzumab-containing therapies might be reserved for patients with relapsed or refractory multiple myeloma.

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Introduction

Monoclonal antibodies are now a cornerstone in multiple myeloma treatment, with their introduction to first-line treatment leading to improved rates of deep responses and prolonged progression-free survival.[1] Modern induction therapies for patients with untreated multiple myeloma, who are eligible for high-dose therapy and autologous hematopoietic stem-cell transplantation (HSCT), incorporate a monoclonal antibody (eg, daratumumab), an immunomodulatory agent (eg, lenalidomide or thalidomide), a proteasome inhibitor (eg, bortezomib or carfilzomib), and dexamethasone. Currently, approved induction and consolidation treatments in the EU and the USA include daratumumab, thalidomide, bortezomib, and dexamethasone.[2–4]

Elotuzumab is a humanised immunoglobulin G (IgG) monoclonal antibody that targets signalling lymphocytic activation molecule family member 7 (SLAMF7), a glycoprotein uniformly and highly expressed in multiple myeloma cells but not in healthy tissues. In addition, elotuzumab has several modes of action against multiple myeloma cells, including activation of natural killer cells, cell-mediated antibody-dependent cellular cytotoxicity, and macrophage-mediated antibody-dependent cellular phagocytosis.[5–8]

Based on the positive results of the ELOQUENT-2 (NCT01239797) and ELOQUENT-3 (NCT02654132) trials, elotuzumab was approved by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) for the treatment of patients with relapsed or refractory multiple myeloma, either in combination with lenalidomide and dexamethasone, or pomalidomide and dexamethasone.[9–12] In both trials, addition of elotuzumab resulted in a significantly reduced risk of progression or death (hazard ratio [HR]: in the ELOQUENT-2 trial 0·70, 95% CI 0·57–0·85; p<0·001, HR in the ELOQUENT-3 trial 0·54, 95% CI 0·34–0·86; p=0·008).[9,11]

Consequently, elotuzumab was evaluated as front-line treatment for patients with newly diagnosed multiple myeloma. The randomised phase 2 SWOG-1211 trial (NCT01668719) investigated the addition of elotuzumab to lenalidomide, bortezomib, and dexamethasone (RVd) in patients with newly diagnosed multiple myeloma harbouring high-risk disease features, such as high-risk by gene expression profiling, translocations t(14;16), t(14;20), deletion 17p, amplification 1q21, primary plasma cell leukaemia, or elevated serum lactate dehydrogenase. At a median follow-up of 53 months, no difference in progression-free survival was observed (median progression-free survival 33·6 months for RVd *vs* 31·5 months for elotuzumab with RVd HR 0·97 [80% CI 0·70–1·34]; one-sided p=0·45).[13]

Research in context

Evidence before this study

We searched PubMed for clinical trial reports published between Jan 1, 2007, and Dec 31, 2015, using the terms "multiple myeloma", "newly diagnosed", "elotuzumab", and/or "HuLuc63", without any language restrictions. At the time of study design, no clinical trials had been published on the addition of elotuzumab to an induction and consolidation therapy comprising lenalidomide, bortezomib, and dexamethasone (RVd). Similarly, no clinical study had been published examining the addition of elotuzumab to lenalidomide maintenance therapy in transplant-eligible patients with newly diagnosed multiple myeloma. Therefore, this study set out to evaluate the efficacy of adding elotuzumab to the first-line standard-of-care induction and consolidation treatment comprising RVd, and maintenance therapy with lenalidomide in transplant-eligible patients with newly diagnosed multiple myeloma.

Added value of this study

To our knowledge, the phase 3 GMMG-HD6 trial was the first to show that the addition of elotuzumab to the standard-of-care treatment does not improve progression-free survival or overall survival in patients with newly diagnosed multiple myeloma who were eligible for autologous hematopoietic stem-cell transplantation (HSCT). Likewise, patients in this trial did not benefit from any therapeutic sequence including elotuzumab, irrespective of their cytogenetic profile (standard or high-risk). In addition, no new safety signals were observed with elotuzumab in combination with RVd induction and consolidation or lenalidomide maintenance therapy.

Implications of all the available evidence

The results of the GMMG-HD6 trial complement existing evidence from both the SWOG1211 and ELOQUENT-1 trials, which evaluated the efficacy of elotuzumab in patients with newly diagnosed multiple myeloma. In the SWOG1211 trial, there was no significant improvement of progression-free survival or overall survival in patients with untreated, high-risk multiple myeloma. Similarly, in the ELOQUENT-1 trial, progression-free survival and overall survival did not improve with the addition of elotuzumab to lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma who were ineligible for autologous HSCT. In contrast, in patients diagnosed with relapsed or refractory multiple myeloma, the ELOQUENT-2 and ELOQUENT-3 trials showed a significant progression-free survival and overall survival benefit when adding elotuzumab to lenalidomide and dexamethasone, or pomalidomide and dexamethasone.

In the randomised phase 3 ELOQUENT-1 (NCT01335399) trial, elotuzumab was added to lenalidomide and dexamethasone in patients with newly diagnosed multiple myeloma who were not eligible for autologous HSCT. At a median follow-up of 70·6 months, progression-free survival was 29·5 months with lenalidomide and dexamethasone versus 31·4 months with elotuzumab, lenalidomide, and dexamethasone (HR 0·93 [95% CI 0·77–1·12]; stratified log-rank p=0·44).[14]

Data on elotuzumab in transplantation-eligible patients with newly diagnosed multiple myeloma are not available; therefore, the phase 3, four group, randomised German-speaking Myeloma Multicenter Group (GMMG)-HD6 trial (NCT02495922) investigated the addition of elotuzumab to RVd induction and consolidation, and lenalidomide maintenance therapy in patients with newly diagnosed multiple myeloma who are eligible for high-dose therapy and autologous HSCT. Herein, we report the results from the primary analysis of the GMMG-HD6 trial.

Methods

Study design and participants

GMMG-HD6 was a phase 3, open-label, randomised, active-controlled trial conducted at 43 main trial sites and 26 associated trial sites throughout Germany (appendix pp 2–3). The study protocol is available in the appendix (pp 12–113).

Eligible patients were aged 18 to 70 years, and had a confirmed diagnosis of untreated multiple myeloma requiring systemic treatment according to International Myeloma Working Group (IMWG) diagnostic criteria[15] (appendix p 101) and measurable disease based on the IMWG response criteria (appendix pp 102–04).[16] Patients were required to have a WHO performance status of 0–3, with 3 being allowed only if caused by myeloma disease and not by comorbid conditions; a platelet count of at least 75×10^9 platelets/L, or in case of a bone marrow plasma cell infiltration of 50% or more, a platelet count of at least 30×10^9 cells/L; a haemoglobin concentration greater than 8·0g/dL, unless myeloma-related; an absolute neutrophil count of at least $1·0\times10^9$ cells/L, unless myeloma-related. Patients with comorbidities such as severe cardiac or hepatic dysfunction, or both, and renal insufficiency requiring hemodialysis were excluded from the trial. Full inclusion and exclusion criteria are provided in the study protocol (appendix pp 47–48). Due to the teratogenicity of lenalidomide, pregnant and lactating patients were not eligible. The trial was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki principles, and local legal and regulatory requirements. The trial was approved by ethics committees at all study sites and all patients provided written informed consent.

Randomisation and masking

Eligible patients were randomly assigned (1:1:1:1) before the start of treatment. In the RVd/R group, patients were assigned to RVd induction and consolidation followed by lenalidomide maintenance. Patients in the RVd/E-R group were assigned to RVd induction, elotuzumab plus RVd consolidation followed by elotuzumab–lenalidomide maintenance therapy. Patients in the E-RVd/R group were assigned to elotuzumab with RVd induction, RVd consolidation followed by lenalidomide maintenance. In the E-RVd/E-R group, patients were assigned to elotuzumab with RVd induction and consolidation followed by elotuzumab–lenalidomide maintenance. Patients were randomised using block randomisation (block size of eight; not available to investigators) stratified by International Staging System (ISS; I *vs* II *vs* III). Treatment was not blinded to participants, investigators, or study personnel.

Procedures

Patients received four 21-day cycles of RVd (lenalidomide 25 mg orally on days 1–14; bortezomib 1·3 mg/m² subcutaneously on days 1, 4, 8, and 11; and dexamethasone 20 mg orally [or intravenously as part of premedication for elotuzumab] on days 1, 2, 4, 5, 8, 9, 11, and 12 and additionally on day 15 during cycles 1 and 2) as induction therapy. In the E-RVd/R and E-RVd/E-R groups, patients additionally received elotuzumab (10 mg/kg intravenously on days 1, 8, and 15 during cycles 1 and 2, and on days 1 and 11 during cycles 3 and 4) during induction therapy. Patients continued treatment with cyclophosphamide and G-CSF-based mobilisation of autologous haematopoietic stem-cells according to local institutional guidelines. Subsequently, patients were treated with high-dose melphalan (200 mg/m²) followed by autologous HSCT. Patients with high-risk cytogenetics or less than complete response could opt for a second course of high-dose melphalan followed by autologous HSCT.

Consolidation therapy consisted of two 21-day cycles of RVd (lenalidomide 25 mg orally on days 1–14; bortezomib 1·3 mg/m² subcutaneously on days 1, 8, and 15; and dexamethasone 20 mg orally [or intravenously as part of premedication for elotuzumab] on days 1, 2, 8, 9, 15, and 16). Maintenance therapy consisted of 26 28-day cycles (lenalidomide 10 mg orally on days 1–28 during cycles 1–3; thereafter, up to 15 mg orally on days 1–28) and dexamethasone (12 mg orally [or intravenously as part of premedication for elotuzumab]; days 1 and 15 during cycles 1–6, and on day 1 during cycles 7–26). In the RVd/E-R and E-RVd/E-R groups, elotuzumab was added for consolidation (10 mg/kg intravenously on days 1, 8, and 15) and maintenance (10 mg/kg intravenously; days 1 and 15 during cycles 1–6, and on day 1 during cycles 7–26). Details on permitted dose reductions and interruptions for lenalidomide and elotuzumab; premedication for elotuzumab treatment;

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See Online for appendix

and medication used for antiviral, antibacterial and thromboembolic prophylaxis are listed in the appendix (pp 56–58, 69–72). Criteria for patient withdrawal from the study are detailed in the appendix (pp 49–50) and included confirmed progressive disease, unacceptable toxicity, major protocol violations, pregnancy, and patient non-compliance.

Cytogenetic analyses from CD138-purified bone marrow plasma cells were performed centrally (Institute of Human Genetics, Heidelberg University, Heidelberg, Germany). In accordance with the IMWG consensus statement, high-risk cytogenetics were defined as the presence of at least one of the following abnormalities in at least 10% of purified cells: del(17)(p13), t(4;14)(p16;q32), or t(14;16)(q32;q23).[17] Elevated serum lactate dehydrogenase was defined as a concentration greater than the upper limit of normal (>ULN). Renal impairment was defined as either estimated creatinine clearance of less than 40 mL/min or serum creatinine of greater than 177 µmol/L.

Response assessments were conducted after each subsequent section of the trial (eg, after induction), every three months during maintenance therapy or during follow-up and at unscheduled time-points (eg, suspected disease progression). Response rates were assessed locally and reviewed centrally by the GMMG trial office (Heidelberg, Germany; appendix pp 102–04) according to IMWG response criteria.[16] Bone marrow punctures were required at baseline, to confirm suspected complete response, and at the end of study. Serum monoclonal protein assessment has not been corrected for interference with elotuzumab.

Adverse events were recorded at the trial sites during patient visits and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0). All adverse events grade 3 or worse and specific adverse events grade 2 or worse, namely system organ class cardiac disorders and infections and infestations, and specific terms (polyneuropathy and thromboembolic events) were recorded during each trial phase (induction, consolidation, and maintenance therapy, except intensification). Intensification (stem cell mobilisation, high-dose therapy, and autologous HSCT) was performed according to routine care, and only serious adverse events were recorded and are not reported here. Serious adverse events were recorded independently of CTCAE grade. In case of multiple occurrences of adverse events, maximum severity was recorded regardless of seriousness. Safety data were coded using MedDRA software (version 21.1).[18]

Outcomes

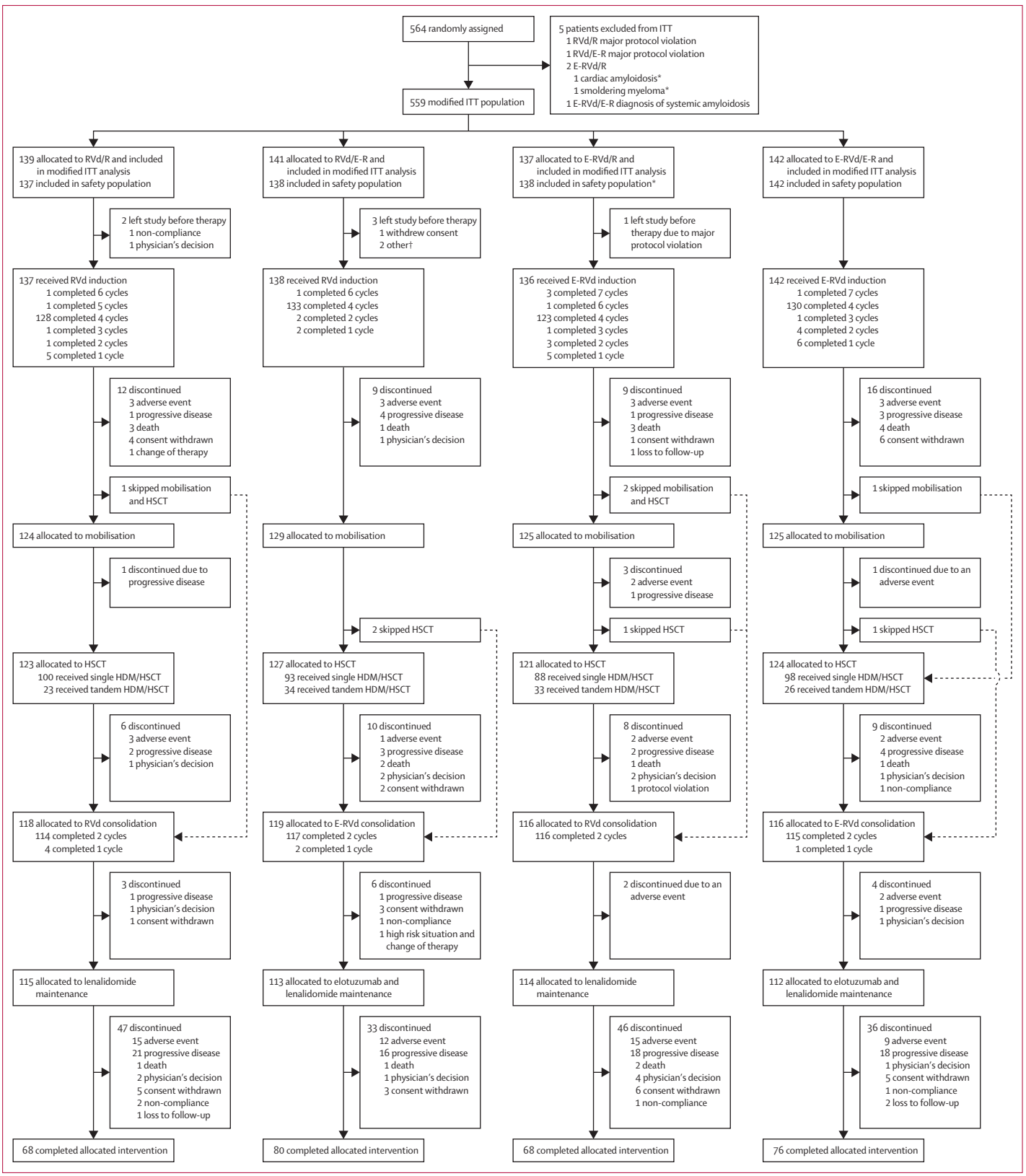
The primary endpoint was centrally reviewed progression-free survival, defined as time from randomisation to progression or death from any cause, whichever occurred first. Patients without progression and still alive at the end of the study were censored at the date of the last response assessment. Patients without any response assessment after randomisation were censored at the date of randomisation. Secondary endpoints were: overall survival, defined as time from randomisation to time of death from any cause; rates of complete response after induction and consolidation therapy, respectively, and best response to treatment during the study, according to the IMWG response criteria[16]; time to progression, defined as time from randomisation to time of first disease progression; duration of response, defined as time from first observation of partial response or better to the date of first observation of disease progression; and quality-of-life assessment of patients at baseline, during induction treatment, consolidation and maintenance treatment via patient self-report questionnaires (appendix p 25). Quality-of-life assessment is currently being analysed and will be reported separately. For time to progression and duration of response, death without preceding progression or relapse (non-relapse mortality) was considered a competing event.

Statistical analysis

Efficacy analyses were performed using a modified ITT population comprising all randomly assigned patients with signed informed consent, except patients who withdrew consent before the start of study treatment or with major violations of the inclusion or exclusion criteria (appendix pp 47–48, 90). Patients were analysed according to the treatment group assigned at randomisation. The analysis of the primary endpoint was confirmatory at a two-sided significance level of 0·05. All other analyses were exploratory and carried out at a two-sided significance level of 0·05, unless noted otherwise.

The sample size was calculated regarding progression-free survival. Initially, the required sample size was calculated as 516 patients. Inclusion of 516 patients considering 3 years of recruitment, 3 years minimal follow-up time, a total of 10% dropouts and 5% high-risk patients leaving the study prematurely after induction therapy allows for rejecting the global null hypothesis of no difference between the four treatment groups; ie, $H_0^{1\text{-}2\text{-}3\text{-}4}{:}\lambda_{A1}(t)=\lambda_{A2}(t)=\lambda_{B1}(t)=\lambda_{B2}(t)$ *vs* $H_A^{1\text{-}2\text{-}3\text{-}4}{:}\lambda_i(t)=\theta\lambda_j(t)$ for at least one pair (i,j) of groups $i,j \quad \{A1,A2,B1,B2\}$, with hazard rate $\lambda_i(t)$ for group i and a HR $\theta \neq 1$, at the two-sided significance level of 5·0% with a power of 91%, assuming progression-free survival rates of 60%, 70%, 70%, and 80% after 3 years (corresponding to HRs relative to the control

Figure 1: **CONSORT diagram of the GMMG-HD6 trial**
RVd/R=RVd induction and consolidation with lenalidomide maintenance. RVd/E-R=RVd induction, elotuzumab plus RVd consolidation with elotuzumab–lenalidomide maintenance. E-RVd/R=elotuzumab plus RVd induction, RVd consolidation with lenalidomide maintenance. E-RVd/E-R=elotuzumab plus RVd induction and consolidation with elotuzumab–lenalidomide maintenance. HSCT=autologous haematopoietic stem cell transplantation. HDM=high dose melphalan. ITT=intention-to-treat population. *Patient received at least one dose of the treatment and was thus included in the safety analysis. †External hospitalisation and a high-risk situation.


564 randomly assigned
5 patients excluded from ITT
1 RVd/R major protocol violation
1 RVd/E-R major protocol violation
2 E-RVd/R
1 cardiac amyloidosis*
1 smoldering myeloma*
1 E-RVd/E-R diagnosis of systemic amyloidosis
559 modified ITT population
139 allocated to RVd/R and included in modified ITT analysis
137 included in safety population
141 allocated to RVd/E-R and included in modified ITT analysis
138 included in safety population
137 allocated to E-RVd/R and included in modified ITT analysis
138 included in safety population*
142 allocated to E-RVd/E-R and included in modified ITT analysis
142 included in safety population
2 left study before therapy
1 non-compliance
1 physician's decision
3 left study before therapy
1 withdrew consent
2 other†
1 left study before therapy due to major protocol violation
137 received RVd induction
1 completed 6 cycles
1 completed 5 cycles
128 completed 4 cycles
1 completed 3 cycles
1 completed 2 cycles
5 completed 1 cycle
138 received RVd induction
1 completed 6 cycles
133 completed 4 cycles
2 completed 2 cycles
2 completed 1 cycle
136 received E-RVd induction
3 completed 7 cycles
1 completed 6 cycles
123 completed 4 cycles
1 completed 3 cycles
3 completed 2 cycles
5 completed 1 cycle
142 received E-RVd induction
1 completed 7 cycles
130 completed 4 cycles
1 completed 3 cycles
4 completed 2 cycles
6 completed 1 cycle
12 discontinued
3 adverse event
1 progressive disease
3 death
4 consent withdrawn
1 change of therapy
9 discontinued
3 adverse event
4 progressive disease
1 death
1 physician's decision
9 discontinued
3 adverse event
1 progressive disease
3 death
1 consent withdrawn
1 loss to follow-up
16 discontinued
3 adverse event
3 progressive disease
4 death
6 consent withdrawn
1 skipped mobilisation and HSCT
2 skipped mobilisation and HSCT
1 skipped mobilisation
124 allocated to mobilisation
129 allocated to mobilisation
125 allocated to mobilisation
125 allocated to mobilisation
1 discontinued due to progressive disease
3 discontinued
2 adverse event
1 progressive disease
1 discontinued due to an adverse event
2 skipped HSCT
1 skipped HSCT
1 skipped HSCT
123 allocated to HSCT
100 received single HDM/HSCT
23 received tandem HDM/HSCT
127 allocated to HSCT
93 received single HDM/HSCT
34 received tandem HDM/HSCT
121 allocated to HSCT
88 received single HDM/HSCT
33 received tandem HDM/HSCT
124 allocated to HSCT
98 received single HDM/HSCT
26 received tandem HDM/HSCT
6 discontinued
3 adverse event
2 progressive disease
1 physician's decision
10 discontinued
1 adverse event
3 progressive disease
2 death
2 physician's decision
2 consent withdrawn
8 discontinued
2 adverse event
2 progressive disease
1 death
2 physician's decision
1 protocol violation
9 discontinued
2 adverse event
4 progressive disease
1 death
1 physician's decision
1 non-compliance
118 allocated to RVd consolidation
114 completed 2 cycles
4 completed 1 cycle
119 allocated to E-RVd consolidation
117 completed 2 cycles
2 completed 1 cycle
116 allocated to RVd consolidation
116 completed 2 cycles
116 allocated to E-RVd consolidation
115 completed 2 cycles
1 completed 1 cycle
3 discontinued
1 progressive disease
1 physician's decision
1 consent withdrawn
6 discontinued
1 progressive disease
3 consent withdrawn
1 non-compliance
1 high risk situation and change of therapy
2 discontinued due to an adverse event
4 discontinued
2 adverse event
1 progressive disease
1 physician's decision
115 allocated to lenalidomide maintenance
113 allocated to elotuzumab and lenalidomide maintenance
114 allocated to lenalidomide maintenance
112 allocated to elotuzumab and lenalidomide maintenance
47 discontinued
15 adverse event
21 progressive disease
1 death
2 physician's decision
5 consent withdrawn
2 non-compliance
1 loss to follow-up
33 discontinued
12 adverse event
16 progressive disease
1 death
1 physician's decision
3 consent withdrawn
46 discontinued
15 adverse event
18 progressive disease
2 death
4 physician's decision
6 consent withdrawn
1 non-compliance
36 discontinued
9 adverse event
18 progressive disease
1 physician's decision
5 consent withdrawn
1 non-compliance
2 loss to follow-up
68 completed allocated intervention
80 completed allocated intervention
68 completed allocated intervention
76 completed allocated intervention

group of 0·698, 0·698, and 0·437). The intermediate progression-free survival rates are conservatively chosen representing the least favourable distribution of rates with respect to power. Further comparisons between treatment groups were realised within a closed testing procedure. Assuming RVd/R as standard group, the power for the comparison of the standard group against the best treatment group result as 88%. Sample size calculation was performed using the ART program for multigroup survival trials in Stata.[19,20]

Given a faster actual enrolment into the study (22 months instead of 36 months) and therefore resulting shorter overall study duration, the sample size was increased to 564 patients on May 3, 2017, by an approved amendment to the study protocol.

With respect to the primary endpoint progression-free survival, the four treatment groups were compared within a closed testing procedure using a hierarchical step-down approach.[21] This approach controls the family-wise error rate in a multi-comparison setting, since all null hypotheses are tested in a predefined hierarchical order at the same significance level. The closure principle was followed by calculating the adjusted p value for every hypothesis as the maximum of the p values of all hypotheses implying that hypothesis. All null hypotheses were tested confirmatory at the two-sided 5% significance level using the log-rank test stratified by ISS stage at randomisation. Significant different progression-free survival of a treatment group with respect to a comparator group would be concluded if the adjusted p value of the elementary hypothesis were below 0·05.

An interim analysis with respect to progression-free survival was planned to be conducted at 2·5 years after start of recruitment to rule out lack of efficacy. The observed effect between the best and the worst treatment group was used to recommend a stop for futility based on the conditional power as proposed by Lachin.[22] The nonbinding recommendation to stop the study for futility was at a conditional power of 20% or less.

For single time-to-event endpoints (progression-free survival, overall survival), Kaplan-Meier estimates were calculated along with 95% CIs. For survival curve comparisons, the log-rank test was used. In order to evaluate the robustness of the primary and secondary analyses of progression-free survival and overall survival, multivariable Cox regression, adjusting for the covariates sex, age, WHO performance status (0–1 *vs* >1), ISS (I *vs* II *vs* III), serum lactate dehydrogenase (≤ULN *vs* >ULN), high-risk cytogenetics (no *vs* yes), renal insufficiency according to CRAB criteria (no *vs* yes), was done. Furthermore, predefined exploratory univariable subgroup analyses were performed. These include progression-free survival and overall survival analyses in the subgroups: sex (male *vs* female), age (≤60 *vs* 61–65 *vs* 66–70 years), WHO performance status (0–1 *vs* >1), ISS (stages I *vs* II *vs* III), renal insufficiency according to IMWG criteria (no *vs* yes), serum lactate dehydrogenase (≤ULN *vs* >ULN), and high-risk cytogenetics (no *vs* yes). Likelihood ratio tests were done to test a possible interaction between the covariate defining the respective subgroup and treatment using stratified Cox proportional hazards models.[23] In addition to the primary analysis, a secondary analysis was performed for progression-free survival based on the per protocol population, which includes all eligible patients who were randomly assigned and treated according to their assignment.

For competing event endpoints (time to progression and duration of response), incidence and survival curves were estimated by the Aalen-Johansen method.[24] For comparing cause-specific cumulative incidence curves, Gray's test was used.

IMWG response categories are reported after induction, after consolidation and as confirmed best response during the study. Response rates are tabulated along with two-sided 95% Pearson-Clopper CIs. Aggregated IMWG response rates were compared using Fisher's exact test. The Cochran-Armitage trend test was used for ordered response categories. Missing response assessments were counted as non-responders while responses denoted as not assessable were excluded for inferential comparisons.

All safety analyses were performed in all randomly assigned patients who received at least one dose of trial medication. Incidence rates of adverse events were descriptively summarised using MedDRA (version 4.0) system organ class and preferred term.[18] Incidence rates were compared by Fisher's exact test and the Cochran-Armitage test for ordinal adverse event grades. The statistical analysis plan of the trial is presented in the appendix (pp 114–29). All statistical analyses were conducted using R (version 4.2.1).[25] Data cutoff for the primary analysis was June 24, 2021, April 26, 2019, for the second interim analysis, and Dec 31, 2017, for the first interim analysis.

This trial is registered with ClinicalTrials.gov, NCT02495922, and is completed.

Role of the funding source

The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From June 29, 2015, to Sept 11, 2017, 564 patients were enrolled and randomly assigned. Five patients were excluded before start of the study treatment due to major violations of inclusion or exclusion criteria (figure 1). The modified ITT population consisted of 559 patients (139, 141, 137, and 142 patients in the RVd/R, RVd/E-R, E-RVd/R, and E-RVd/E-R groups, respectively). A total of 555 patients (137, 138, 138, and 142 patients in the RVd/R, RVd/E-R, E-RVd/R, and E-RVd/E-R group) received at least one dose of treatment.

Demographic and disease characteristics at baseline are shown in table 1. Median patient age at inclusion in the study was 59 years (range 27–70). Time from first

diagnosis of multiple myeloma requiring systemic therapy to start of therapy within the study was 30 days (IQR 13–54).

The futility interim analysis presented to the data safety monitoring board (DSMB) on Sept 17, 2018, resulted in a conditional power of 15·3%. After review of the safety and efficacy data, the recommendation of the DSMB was to continue the study as planned, but scheduled a further interim analysis after 6 months. This additional interim analysis of progression-free survival and overall survival was discussed confidentially by the DSMB on April 26, 2019. After review of the data provided, including updated safety profiles, the recommendation of the DSMB was to continue and complete the study as planned.

At data cutoff for this primary analysis, median follow-up was 49·8 months (IQR 43·7–55·5). A total of 221 progression-free survival and 78 overall survival events had occurred.

The primary efficacy analysis revealed no progression-free survival differences between the four treatment groups (stratified log-rank test p=0·86; figure 2A). Median progression-free survival was not reached (95% CI 45·5 months–not reached) in the in the RVd/R group, 60·8 months (50·3–not reached) in the RVd/E-R group, 56·6 months (50·0–not reached) in the E-RVd/R group, and not reached (45·6 months–not reached) in the E-RVd/E-R group. Progression-free survival at 3 years was 69% (95% CI 61–77) in the RVd/R group, 69% (61–76) in the RVd/E-R group, 66% (58–74) in the E-RVd/R group, and 67% (59–75) in the E-RVd/E-R group. Addition of elotuzumab to either induction or consolidation or maintenance treatment, or both, did not result in improved time to progression or prolonged duration of response as compared with RVd/R alone (stratified Gray's test p=0·79 for time to progression; p=0·77 for non-relapse mortality and p=0·64 for duration of response; p=0·45 non-relapse mortality; appendix p 4). A preplanned analysis on progression-free survival of the per-protocol population revealed a similar result (stratified log-rank test p=0·87; appendix p 5). Preplanned analysis of overall survival showed no significant differences among the four treatment groups (stratified log-rank p=0·43; figure 2B). Median overall survival was not reached in either treatment group. 3-year overall survival rate was 89% (95% CI 84–95) in the RVd/R group, 89% (84–94) in the RVd/E-R group, 93% (88–97) in the E-RVd/R group, and 90% (85–95) in the E-RVd/E-R group.

Prespecified, exploratory, univariable subgroup analyses revealed no consistent differences in progression-free survival and overall survival in any therapeutic sequence including elotuzumab, except for patients with elevated serum lactate dehydrogenase receiving elotuzumab during induction therapy (interaction p-value for progression-free survival p=0·0043 and overall survival p=0·088; HR 0·45, 95% CI 0·19–1·07, p=0·0704 in the E-RVd/R group and 0·36, 0·16–0·84, p=0·018 in the E-RVd/E-R group

	RVd/R (n=139)	RVd/E-R (n=141)	E-RVd/R (n=137)	E-RVd/E-R (n=142)
Age at randomisation, years				
Median (IQR)	59 (52–64)	60 (53–63)	59 (52–64)	59 (52–65)
Sex				
Female	59 (42%)	66 (47%)	54 (39%)	64 (45%)
Male	80 (58%)	75 (53%)	83 (61%)	78 (55%)
WHO performance status				
0	90 (65%)	74 (52%)	73 (53%)	71 (50%)
1	39 (28%)	54 (38%)	45 (33%)	62 (44%)
2	6 (4%)	10 (7%)	16 (12%)	7 (5%)
3	3 (2%)	3 (2%)	3 (2%)	2 (1%)
Unknown	1 (<1%)	..	..	1 (<1%)
0–1	129 (93%)	128 (91%)	118 (86%)	133 (94%)
>1	9 (6%)	13 (9%)	19 (14%)	9 (6%)
Heavy chain type				
IgG	77 (55%)	105 (74%)	80 (58%)	85 (60%)
IgA	27 (19%)	20 (14%)	27 (20%)	20 (14%)
Light-chain only	35 (25%)	14 (10%)	28 (20%)	35 (25%)
Other*	..	2 (1%)	2 (1%)	2 (1%)
ISS disease stage				
I	56 (40%)	58 (41%)	58 (42%)	55 (39%)
II	55 (40%)	54 (38%)	51 (37%)	52 (37%)
III	28 (20%)	29 (21%)	28 (20%)	35 (25%)
High-risk cytogenetics				
No	86 (62%)	84 (60%)	80 (58%)	90 (63%)
Yes	37 (27%)	29 (21%)	29 (21%)	24 (17%)
Unknown	16 (12%)	28 (20%)	28 (20%)	28 (20%)
Deletion del(17)(p13)				
No	105 (76%)	103 (73%)	98 (72%)	107 (75%)
Yes	21 (15%)	16 (11%)	14 (10%)	8 (6%)
Unknown	13 (9%)	22 (16%)	25 (18%)	27 (19%)
Translocation t(4;14)(p16;q32)				
No	108 (78%)	103 (73%)	94 (69%)	103 (73%)
Yes	15 (11%)	11 (8%)	14 (10%)	11 (8%)
Unknown	16 (12%)	27 (19%)	29 (21%)	28 (20%)
Translocation t(14;16)(q32;q23)				
No	119 (86%)	112 (79%)	102 (74%)	109 (77%)
Yes	6 (4%)	5 (4%)	6 (4%)	5 (4%)
Unknown	14 (10%)	24 (17%)	29 (21%)	28 (20%)
Elevated lactate dehydrogenase				
No	120 (86%)	123 (87%)	112 (82%)	109 (77%)
Yes	18 (13%)	18 (13%)	24 (18%)	32 (23%)
Unknown	1 (1%)	..	1 (1%)	1 (1%)
Renal impairment				
No	126 (91%)	131 (93%)	126 (92%)	124 (87%)
Yes	13 (9%)	10 (7%)	10 (7%)	18 (13%)
Unknown	..	..	1 (1%)	..

Data are n (%) unless stated otherwise. Ethnicity and race data were not recorded. RVd=lenalidomide, bortezomib, and dexamethasone. RVd/R=RVd induction and consolidation with lenalidomide maintenance. RVd/E-R=RVd induction, elotuzumab plus RVd consolidation with elotuzumab and lenalidomide maintenance. E-RVd/R=elotuzumab plus RVd induction, RVd consolidation with lenalidomide maintenance. E-RVd/E-R=elotuzumab plus RVd induction and consolidation with elotuzumab and lenalidomide maintenance. ISS=International Staging System. *Includes IgD, IgE, and IgM.

Table 1: **Baseline demographics and patient characteristics, modified intention-to-treat population**

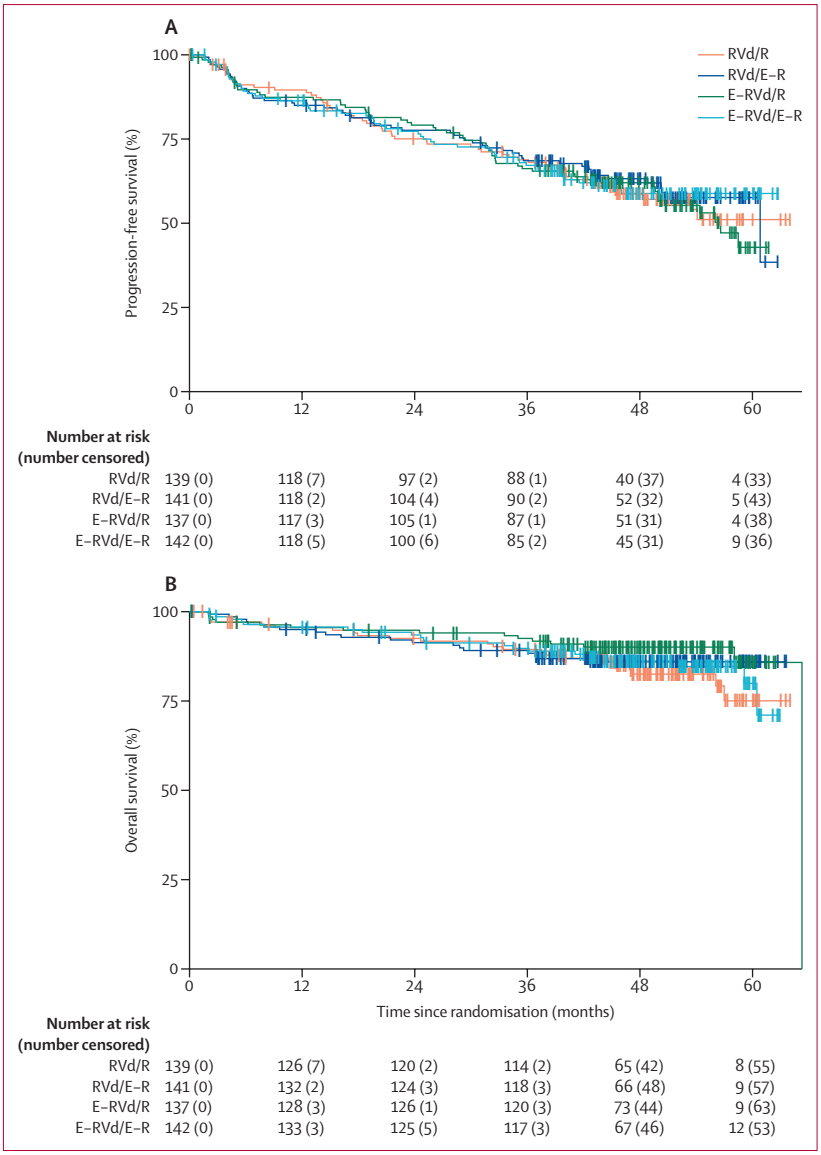


Figure 2: **Rates for progression-free survival and overall survival from time of randomisation**
(A) Progression-free survival and (B) overall survival, from time of randomisation. RVd/R=RVd induction and consolidation with lenalidomide maintenance. RVd/E-R=RVd induction, elotuzumab plus RVd consolidation with elotuzumab–lenalidomide maintenance. E-RVd/R=elotuzumab plus RVd induction, RVd consolidation with lenalidomide maintenance. E-RVd/E-R=elotuzumab plus RVd induction and consolidation with elotuzumab–lenalidomide maintenance.

for progression-free survival, and 0·21, 0·04–1·00, p=0·0501 in the E-RVd/R group and 0·61, 0·21–1·70, p=0·35 in the E-RVd/E-R group for overall survival) as compared with the RVd/R group (appendix pp 6–7).

In the preplanned multivariable analysis of progression-free survival, treatment with elotuzumab showed no statistically significant difference in any therapeutic sequence (RVd/E-R, E-RVd/R or E-RVd/E-R) as compared with standard treatment with RVd/R (table 2). ISS stage (III *vs* I: HR 2·04, 95% CI 1·36–3·07, p=0·0006) and high-risk cytogenetics (1·63, 1·19–2·25, p=0·0026) were the only factors with a significant prognostic impact on progression-free survival. Preplanned multivariable analysis of overall survival found no statistically significant difference for the addition of elotuzumab compared to standard treatment in any therapeutic sequence (table 2). WHO performance status (HR 3·38, 95% CI 1·74–6·56, p=0·0003), high-risk cytogenetics (2·58, 1·56–4·26, p=0·0002), and ISS stage (III *vs* I 1·95, 1·04–3·67, p=0·038) significantly impacted overall survival in the multivariable model.

Best response during the study period in the RVd/R, RVd/E-R, E-RVd/R, and E-RVd/E-R groups is listed in the appendix (p 8). Rates of very good partial response or better during the study period were 78% (95% CI 70–84) in the RVd/R group, 83% (76–89) in the RVd/E-R group, 84% (77–90) in the E-RVd/R group, and 76% (68–83) in the E-RVd/E-R group (p=0·29). Rates of very good partial response or better and complete response after induction therapy were similar when comparing RVd with E-RVd treatment (very good partial response or better 53%, 95% CI 47–59 and 59%, 53–65, p=0·14; complete response 3%, 2–6 and 3%, 2–6, p=1·0). After consolidation therapy, rates of very good partial response or better were 77% (95% CI 69–84) in the RVd/R group, 76% (68–83) in the RVd/E-R group, 84% (76–90) in the E-RVd/R, and 68% (60–76) in the E-RVd/E-R group (p=0·068). Rates of complete response after consolidation therapy were 46% (95% CI 37–55) in the RVd/R, 30% (23–39) in the RVd/E-R, 41% (32–50) in the E-RVd/R, and 33% (25–42) in the E-RVd/E-R group (p=0·0099).

Safety data from each of the overall study treatment phases, induction, consolidation, and maintenance, are presented in table 3. Any adverse event of grade 3 or worse during study treatment occurred in 115 (84%) of 137 patients in the RVd/R group, 105 (76%) of 138 patients in the RVd/E-R group, 105 (76%) of 138 patients in the E-RVd/R group, and 115 (81%) of 142 patients in the E-RVd/E-R group. Infections (grade 3 or worse) occurred in 28 (29%), 32 (23%), 35 (25%) and 48 (34%) patients in the RVd/R, RVd/E-R, E-RVd/R, and E-RVd/E-R groups, respectively. The most common infections across all treatment groups were upper and lower respiratory tract infections (appendix p 9). Patients who experienced at least one serious adverse event (grade 3 or worse) were reported in the RVd/R (53 [39%]), RVd/E-R (53 [38%]), E-RVd/R (50 [36%]), and E-RVd/E-R (68 [48%]) groups. The frequency of thromboembolic events (grade 3 or worse) in each group was RVd/R (four [3%]), RVd/E-R (one [1%]), E-RVd/R (seven [5%]) and E-RVd/E-R (ten [7%]). Lymphopenia (grade 3 or worse) was observed in the groups receiving elotuzumab–lenalidomide maintenance (RVd/E-R 23 [17%] and E-RVd/E-R 23 [16%]), and in those receiving standard lenalidomide maintenance (RVd/R 19 [14%] and E-RVd/R nine [7%]). Peripheral neuropathy (grade 3 or worse) was reported in the RVd/R (13 [10%]), RVd/E-R (seven [5%]), E-RVd/R (eight [6%]), and

E-RVd/E-R (eight [6%]) groups. Elotuzumab infusion-related reactions were very rare with one (<1%) and three patients (<1%) experiencing a grade 2 infusion-related reaction in the E-RVd/R and E-RVd/E-R groups, respectively.

Dose reductions for each treatment group are listed in supplementary appendix (p 10). 70 patients discontinued study treatment due to drug-related toxicity: 16 (12%) of 137 patients in the RVd/R group (all lenalidomide-related), 15 (11%) of 138 patients in the RVd/E-R group (all lenalidomide-related), 22 (16%) of 138 patients in the E-RVd/R group (one [1%] elotuzumab-related, 17 [12%] lenalidomide-related, and four [3%] elotuzumab–lenalidomide-related), and 13 (9%) of 142 patients in the E-RVd/R group (one [1%] elotuzumab-related, eight [6%] lenalidomide-related, and four [3%] elotuzumab–lenalidomide-related).

21 deaths occurred during study and within 30 days after end of study. Of these, nine deaths were at least possibly related to study treatment (elotuzumab or lenalidomide, or both; appendix p 11). Two deaths (one sepsis and one toxic colitis) in the RVd/R group were considered lenalidomide-related. One death in the RVd/E-R group due to meningoencephalitis was considered lenalidomide and elotuzumab-related. Four deaths (one pulmonary embolism, one septic shock, one atypical pneumonia, and one cardiovascular failure) in the E-RVd/R group were considered related to lenalidomide or elotuzumab, or both. Two deaths (one sepsis and one pneumonia and pulmonary fibrosis) in the E-RVd/E-R group were considered related to lenalidomide or elotuzumab, or both.

	Progression-free survival			Overall survival		
	HR	95% CI	p value	HR	95% CI	p value
Treatment arm (RVd/E-R *vs* RVd/R)	0·91	0·60–1·38	0·67	0·86	0·45–1·55	0·66
Treatment arm (E-RVd/R *vs* RVd/R)	1·04	0·70–1·56	0·83	0·53	0·26–1·08	0·08
Treatment arm (E-RVd/E-R *vs* RVd/R)	0·89	0·58–1·35	0·58	0·82	0·43–1·57	0·56
Age (continuous, per 10 years)	1·11	0·92–1·35	0·28	1·26	0·91–1·75	0·16
Sex (female *vs* male)	0·74	0·55–1·01	0·058	0·82	0·50–1·36	0·44
WHO performance status (>1 *vs* 0–1)	1·38	0·85–2·24	0·19	3·38	1·74–6·56	0·0003
ISS stage (II *vs* I)	1·42	1·00–2·02	0·048	0·83	0·44–1·55	0·56
ISS stage (III *vs* I)	2·04	1·36–3·07	0·00057	1·95	1·04–3·67	0·038
High-risk cytogenetics (yes *vs* no)	1·63	1·19–2·25	0·0026	2·58	1·56–4·26	0·0002
Elevated LDH (yes *vs* no)	1·46	0·98–2·17	0·062	1·66	0·91–3·02	0·10
Renal impairment (yes *vs* no)	0·80	0·47–1·38	0·43	0·70	0·29–1·66	0·42

HR=hazard ratio. ISS=International Staging System. LDH=lactate dehydrogenase. RVd=lenalidomide, bortezomib, and dexamethasone. RVd/R=RVd induction and consolidation with lenalidomide maintenance. RVd/E-R=RVd induction, elotuzumab plus RVd consolidation with elotuzumab and lenalidomide maintenance. E-RVd/R=elotuzumab plus RVd induction, RVd consolidation with lenalidomide maintenance. E-RVd/E-R=elotuzumab plus RVd induction and consolidation with elotuzumab and lenalidomide maintenance.

Table 2: **Multivariable Cox model, modified intention-to-treat population**

Discussion

To our knowledge, the GMMG-HD6 trial was the first randomised phase 3 trial to assess the efficacy of elotuzumab in combination with RVd induction and consolidation treatment, and lenalidomide maintenance therapy in patients with newly diagnosed multiple myeloma who were eligible for high-dose therapy and autologous HSCT. Our study shows that addition of elotuzumab to induction, consolidation, and maintenance treatment does not provide a survival benefit in this patient population.

This finding is in line with observations from the ELOQUENT-1 and SWOG-1211 trials. The patient population in the ELOQUENT-1 trial comprised patients with newly diagnosed multiple myeloma who were not eligible for autologous HSCT, whereas patients in the SWOG-1211 trial could either be eligible or ineligible for autologous HSCT and had features of high-risk disease. However, autologous HSCT was only allowed at the time of disease progression or relapse, in contrast to the GMMG-HD6 trial, in which it was preplanned. High-risk disease was defined more broadly in the SWOG-1211 than in the GMMG-HD6 trial and comprised high-risk by gene expression profiling, translocations t(14;16), t(14;20), deletion 17p, amplification 1q21, primary plasma cell leukaemia, or elevated serum lactate dehydrogenase. In comparison, our trial defined high risk according to the IMWG consensus criteria, comprising cytogenetic abnormalities deletion 17p, t(4;14), and t(14;16).[17]

Univariable subgroup analyses from our study revealed that patients with elevated LDH (>ULN) at baseline benefitted from elotuzumab-containing induction (E-RVd/R and E-RVd/E-R groups) with regard to progression-free survival and overall survival. These results should be interpreted with caution, however, due to small patient numbers in these analyses and the limitation that this study was not powered to detect progression-free survival or overall survival differences in this subgroup. A similar effect has been observed in the ELOQUENT-1 study in patients with baseline LDH of at least 300U/L receiving elotuzumab, lenalidomide, and dexamethasone as compared with lenalidomide and dexamethasone with a HR of 0·70 (95% CI 0·48–1·04).[14] Further studies need to evaluate whether these results can be validated.

The results of ELOQUENT-1, SWOG-1211, and GMMG-HD6 contrast with the ELOQUENT-2 and ELOQUENT-3 trials. Both ELOQUENT-2 and ELOQUENT-3 showed a consistent progression-free survival and overall survival benefit with the addition of elotuzumab to either lenalidomide and dexamethasone, or pomalidomide and dexamethasone.[9–12] The reasons for the lack of benefit regarding outcomes from the addition of elotuzumab in combination with current treatment approaches such as RVd for newly diagnosed multiple myeloma remain elusive and are likely multifactorial. These factors include differences in patient immune system and microenvironment at first diagnosis compared with the time of relapse, tumour burden, and disease biology.

	RVd/R (n=137)				RVd/E-R (n=138)				E-RVd/R (n=138)				E-RVd/E-R (n=142)			
	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5
CTCAE (SOC categories)																
Any adverse event*	6 (4%)	92 (67%)	18 (13%)	5 (4%)	21 (15%)	85 (62%)	18 (13%)	2 (1%)	23 (17%)	76 (55%)	23 (17%)	6 (4%)	12 (8%)	89 (63%)	21 (15%)	5 (4%)
Infections and infestations	53 (39%)	24 (18%)	2 (1%)	2 (1%)	55 (40%)	29 (21%)	1 (1%)	2 (1%)	43 (31%)	30 (22%)	2 (1%)	3 (2%)	46 (32%)	44 (31%)	0	4 (3%)
Nervous system disorders	24 (18%)	23 (17%)	1 (1%)	0	35 (25%)	19 (14%)	0	0	30 (22%)	17 (12%)	1 (1%)	0	30 (21%)	14 (10%)	1 (1%)	0
Blood and lymphatic system disorders	0	27 (20%)	4 (3%)	0	0	27 (20%)	10 (7%)	0	0	25 (18%)	16 (12%)	0	0	39 (27%)	11 (8%)	0
Investigations†	1 (1%)	30 (22%)	7 (5%)	0	2 (1%)	30 (22%)	6 (4%)	0	1 (1%)	25 (18%)	2 (1%)	0	0	31 (22%)	7 (5%)	0
Gastrointestinal disorders	4 (3%)	8 (6%)	0	1 (1%)	5 (4%)	13 (9%)	1 (1%)	0	4 (3%)	7 (5%)	2 (1%)	0	3 (2%)	10 (7%)	0	0
General disorders and administration site conditions	1 (1%)	9 (7%)	1 (1%)	2 (1%)	5 (4%)	9 (7%)	0	0	1 (1%)	10 (7%)	0	1 (1%)	5 (4%)	14 (10%)	0	0
Metabolism and nutrition disorders	1 (1%)	8 (6%)	1 (1%)	0	3 (2%)	9 (7%)	1 (1%)	0	2 (1%)	10 (7%)	2 (1%)	0	2 (1%)	8 (6%)	3 (2%)	0
Skin and subcutaneous tissue disorders	0	18 (13%)	0	0	1 (1%)	6 (4%)	0	0	0	8 (6%)	0	0	0	13 (9%)	0	0
Vascular disorders	2 (1%)	7 (5%)	0	0	6 (4%)	2 (1%)	0	0	3 (2%)	5 (4%)	0	0	6 (4%)	7 (5%)	0	0
Cardiac disorders	3 (2%)	1 (1%)	2 (1%)	0	1 (1%)	4 (3%)	0	1 (1%)	5 (4%)	2 (1%)	1 (1%)	1 (1%)	4 (3%)	5 (4%)	3 (2%)	0
Musculoskeletal and connective tissue disorders	0	5 (4%)	0	0	1 (1%)	10 (7%)	0	0	3 (2%)	5 (4%)	0	0	1 (1%)	8 (6%)	0	0
Respiratory, thoracic, and mediastinal disorders	0	6 (4%)	0	0	2 (1%)	3 (2%)	0	0	1 (1%)	6 (4%)	1 (1%)	3 (2%)	1 (1%)	7 (5%)	3 (2%)	0
Renal and urinary disorders	1 (1%)	8 (6%)	1 (1%)	1 (1%)	1 (1%)	3 (2%)	0	0	2 (1%)	3 (2%)	0	1 (1%)	0	5 (4%)	1 (1%)	0
Injury, poisoning and procedural complications	2 (1%)	2 (1%)	0	0	1 (1%)	2 (1%)	0	0	1 (1%)	5 (4%)	0	0	0	9 (6%)	0	0
Psychiatric disorders	0	6 (4%)	0	0	0	6 (4%)	0	0	1 (1%)	5 (4%)	0	0	0	4 (3%)	0	0
Neoplasms benign, malignant, and unspecified	1 (1%)	4 (3%)	0	1 (1%)	0	3 (2%)	0	0	2 (1%)	1 (1%)	0	0	2 (1%)	2 (1%)	0	1 (1%)
Eye disorders	1 (1%)	2 (1%)	0	0	2 (1%)	1 (1%)	0	0	0	0	0	0	0	4 (3%)	0	0
Hepatobiliary disorders	0	0	0	0	0	3 (2%)	0	0	0	4 (3%)	0	0	0	3 (2%)	0	0
Immune system disorders	0	1 (1%)	0	0	0	0	1 (1%)	0	0	2 (1%)	0	0	0	1 (1%)	0	0
Surgical and medical procedures	0	0	0	0	0	1 (1%)	0	0	2 (1%)	1 (1%)	0	0	0	0	0	0
Ear and labyrinth disorders	0	0	0	0	0	0	0	0	1 (1%)	0	0	0	0	1 (1%)	0	0
Specific haematological adverse events																
Leukocytopenia	0	11 (8%)	0	0	0	15 (11%)	1 (1%)	0	1 (1%)	15 (11%)	2 (1%)	0	1 (1%)	15 (11%)	1 (1%)	0
Neutropenia	0	32 (23%)	5 (4%)	0	1 (1%)	23 (17%)	6 (4%)	0	2 (1%)	21 (15%)	9 (7%)	0	1 (1%)	21 (15%)	2 (1%)	0
Lymphopenia	0	14 (10%)	5 (4%)	0	0	18 (13%)	5 (4%)	0	0	5 (4%)	4 (3%)	0	0	14 (10%)	9 (6%)	0
Anaemia	2 (1%)	5 (4%)	0	0	1 (1%)	9 (7%)	0	0	0	7 (5%)	0	0	2 (1%)	9 (6%)	0	0
Thrombocytopenia	2 (1%)	12 (9%)	0	0	3 (2%)	13 (9%)	7 (5%)	0	3 (2%)	20 (14%)	3 (2%)	0	1 (1%)	20 (14%)	5 (4%)	0

(Table 3 continues on next page)

Daratumumab, an anti-CD38 monoclonal antibody, is approved in transplant-eligible and transplant-ineligible patients with newly diagnosed multiple myeloma. In the first part of the phase 3 CASSIOPEIA trial (NCT02541383), induction and consolidation therapy with daratumumab, bortezomib, thalidomide, and dexamethasone as compared to bortezomib, thalidomide, and dexamethasone improved stringent complete response rates (odds ratio 1·60 [95% CI 1·21–2·12]; p=0·0010) and progression-free survival (HR 0·47 [95% CI 0·33–0·67]; p<0·0001) in patients with newly diagnosed multiple myeloma who are eligible for an autologous HSCT.[4] Daratumumab, bortezomib, thalidomide, and dexamethasone resulted in rates of very good partial response or better of 65% and 85% after induction and consolidation therapy, respectively. The rate of complete response or better post consolidation in the CASSIOPEIA trial was 39% with daratumumab, bortezomib, thalidomide, and dexamethasone.[4] In patients with newly diagnosed multiple myeloma who are not eligible for an autologous HSCT, addition of daratumumab to lenalidomide and dexamethasone in the phase 3 MAIA trial (NCT02252172) or bortezomib, melphalan, and dexamethasone in the phase 3 ALCYONE trial (NCT02195479), resulted in rates of very good partial response or better of 79% and 71%, respectively.[26,27] Rates of very good partial response or better after induction therapy with RVd and E-RVd in our study were 53% and 59%. After consolidation therapy rates of very good partial response or better increased to 77%, 76%, 84%, and 68% in the RVd/R, RVd/E-R, E-RVd/R, and E-RVd/E-R groups. Our study did not correct for interference with elotuzumab in serum samples, therefore, underestimating rates of complete response. In line with this, rates of complete response after consolidation were lower in patients receiving elotuzumab during consolidation therapy (RVd/E-R 30% and E-RVd/E-R 33%) as compared with those who did not receive elotuzumab (RVd/R 46% and E-RVd/R 41%). Overall, the very good partial and complete response rates in both studies of patients with newly diagnosed multiple myeloma who are eligible for an autologous HSCT, CASSIOPEIA and GMMG-HD6, were high, though addition of elotuzumab in any treatment sequence did not significantly increase very good partial response rates or better in our study.

With the addition of elotuzumab to RVd induction and consolidation, and lenalidomide maintenance post-autologous HSCT, no new safety signals emerged. In line with the SWOG-1211 trial, infections were more common with the addition of elotuzumab to RVd induction and consolidation, and lenalidomide maintenance.[13] Lymphopenia was more common in patients receiving elotuzumab–lenalidomide maintenance in our study. Depletion of SLAMF7-positive immune cells, such as NK and T cells, by elotuzumab can contribute to increased rates of infection and therapeutic efficacy.[28] Similar to the SWOG-1211 and ELOQUENT-1 studies, neutropenia was

	RVd/R (n=137)				RVd/E-R (n=138)				E-RVd/R (n=138)				E-RVd/E-R (n=142)			
	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5	Grade 2	Grade 3	Grade 4	Grade 5
(Continued from previous page)																
Specific non-haematological adverse events																
Peripheral neuropathy	27 (20%)	12 (9%)	1 (1%)	0	36 (26%)	7 (5%)	0	0	27 (20%)	8 (6%)	0	0	30 (21%)	8 (6%)	0	0
Thromboembolic events	2 (1%)	4 (3%)	0	0	5 (4%)	1 (1%)	0	0	3 (2%)	6 (4%)	0	1 (1%)	7 (5%)	9 (6%)	1 (1%)	0
Infusion-related reactions	0	0	0	0	0	0	0	0	1 (1%)	0	0	0	3 (2%)	0	0	0
Any serious adverse event	12 (9%)	42 (31%)	6 (4%)	5 (4%)	21 (15%)	45 (33%)	6 (4%)	2 (1%)	23 (17%)	37 (27%)	7 (5%)	6 (4%)	14 (10%)	58 (41%)	5 (4%)	5 (4%)

Data are n (%). Multiple adverse events, including serious adverse events, are only counted once on a per-patient basis. All serious adverse events were recorded independent of grade; no grade 1 serious adverse events were recorded during the trial. RVd/R=RVd induction and consolidation with lenalidomide maintenance. RVd/E-R=RVd induction, elotuzumab plus RVd consolidation with elotuzumab and lenalidomide maintenance. E-RVd/R=elotuzumab plus RVd induction, RVd consolidation with lenalidomide maintenance. E-RVd/E-R=elotuzumab plus RVd induction and consolidation with elotuzumab and lenalidomide maintenance. CTCAE=Common Terminology Criteria for Adverse Events. SOC=System Organ Class. *According to the protocol, adverse events of grade 3 or higher were recorded using the National Cancer Institute CTCAE (version 4.0), despite the specific SOC categories (cardiac disorders, infections, and infestations) and specific adverse event terms (polyneuropathy and thromboembolic events) recorded already as grade 2. Grade 2 includes only adverse events CTC grade 2 for specific terms of interest: SOC cardiac disorders, SOC infections and infestations, as well as specific adverse event terms polyneuropathy and thromboembolic events or serious adverse events CTC grade 2. Specific haematologic and non-haematologic events of interest are presented by selection of multiple primary terms from MedDRA terminology independent of absolute frequency in the safety population. †SOC considered as investigations, as defined by the CTCAE to be a finding based on laboratory or other test results.

Table 3: **Most common adverse events during all treatment phases (induction, consolidation, and maintenance therapy) in the safety population**

less common with the addition of elotuzumab.[13,14] This might result from the intravenous application of dexamethasone up to 24 h before elotuzumab infusion as part of the premedication. Similar to the ELOQUENT-1 trial, peripheral neuropathy in the GMMG-HD6 trial was not increased with the use of elotuzumab.[14]

Our study had certain limitations. Patients were randomly assigned to a fixed induction, consolidation, and maintenance strategy before the start of induction therapy. This fixed allocation might have led to imbalances at the start of consolidation or maintenance, or both, treatments, which impacts the estimand of treatment effects. Thus, a double randomisation scheme (ie, first randomisation before induction and second randomisation before consolidation or maintenance) or two independent randomised trials, would have been preferable. The switch of therapeutic strategies before the start of consolidation (ie, addition of elotuzumab) is debatable. Induction and consolidation can be considered as one therapeutic sequence—eg, in accordance with the current approval for daratumumab, bortezomib, thalidomide, and dexamethasone from the CASSIOPEIA study.[4]

In conclusion, the GMMG-HD6 trial complements the existing evidence on the use of elotuzumab in patients with newly diagnosed multiple myeloma. Addition of elotuzumab to RVd induction and consolidation, and lenalidomide maintenance did not improve survival outcomes in patients with newly diagnosed multiple myeloma who are eligible for an autologous HSCT. Long-term follow up of the GMMG-HD6 trial is ongoing.

Contributors

EKM, HG, UB, JS, and AB designed the study. EKM, HG, BB, MHa, RF, MM, JD, IWB, AN, CS, RS, IM, AS, JT, PR, RF, UG, SK, UMM, ChristianK, MHe, KCW, MSR, HJS, and all investigators listed in the supplementary appendix (pp 2–3) included or treated patients within the trial. All authors contributed to study conduct, data processing, data analysis, data review, and data interpretation. EKM, HG, KM, and HJS wrote the manuscript. EKM, KM, CKu, JK, and AB were responsible for the statistical analysis. All authors participated in drafting and revising the manuscript, are accountable for all aspects of the work, and approved the final version before submission. EKM and HG had final responsibility for the decision to submit for publication. EKM, HG, UB, and KM have accessed and verified all the data in the study. The German-speaking Myeloma Multicenter Group (GMMG) initiated and designed the trial. Trial monitoring was performed by the Coordination Centre for Clinical Trials (KKS, Heidelberg, Germany). The GMMG and KKS collected, reviewed, and cleaned the trial data. The data were analysed, interpreted, and discussed and manuscript writing and revision were done by the GMMG. The corresponding author and GMMG study team had unrestricted access to all trial data, and had final responsibility for the decision to submit for publication.

Declaration of interests

EKM reports consulting or advisory role with Bristol Myers Squibb (BMS)/Celgene, GlaxoSmithKline, Janssen-Cilag, Sanofi Aventis, Stemline, and Takeda; honoraria from BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Sanofi Aventis, Stemline, and Takeda; research funding from Sanofi Aventis; and travel accommodation and expenses from BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Sanofi Aventis, Stemline, and Takeda. HG reports support for the present manuscript from BMS/Celgene, Chugai, and HD6 funding; consulting or advisory role with Amgen, BMS, Janssen, Sanofi, and Adaptive Biotechnology; honoraria from Amgen, BMS, Chugai, GlaxoSmithKline, Janssen, Novartis, Sanofi, and Pfizer; research funding from Amgen, BMS, Celgene, GlycoMimetics, GlaxoSmithKline, Heidelberg Pharma, Hoffmann-La Roche, Karyopharm, Janssen, Incyte Corporation, Millenium Pharmaceuticals, Molecular Partners, Merck Sharp and Dohme, MorphoSys, Pfizer, Sanofi, Takeda, and Novartis; travel accommodations and expenses from Amgen, BMS, GlaxoSmithKline, Janssen, Novartis, Sanofi, and Pfizer; and grants or provision of Investigational Medicinal Products from Amgen, Array Biopharma/Pfizer, BMS/Celgene, Chugai, Dietmar-Hopp-Foundation, Janssen, Johns Hopkins University, Mundipharma, and Sanofi. MHä reports consulting or advisory role with Novartis, BMS/Celgene, Gilead Sciences, Sanofi/Aventis, Roche, Amgen, SOBI, Janssen, Takeda, GlaxoSmithKline, Jazz Pharmaceuticals, Bayer Vital, and BMS. RF reports Honoraria from Amgen, BMS/Celgene, Janssen, Sanofi, and Takeda; and travel accommodations and expenses from BMS/Celgene, Janssen, and GSK. MM reports consulting or Advisory Role with Janssen, BMS, Abbvie, Sanofi, GlaxoSmithKline, Oncopeptides, Takeda, and Stemline; honoraria from Amgen, BMS, GlaxoSmithKline, Janssen, and Takeda; and travel accommodations and expenses from Amgen. JD reports honoraria from Sanofi, BMS, Janssen, AstraZeneca, Beigene; and travel accommodation and expenses from Amgen, BMS, Beigene, and Amgen. CM reports Consulting or Advisory Role from Celgene, BMS, and Janssen. CS reports consulting or advisory role from BMS, GlaxoSmithKline, Janssen, Pfizer, Roche, and Takeda; honoraria from Amgen, BMS/GlaxoSmithKline, Janssen, MSD, Novartis, Roche, Sanofi, and Takeda; research funding from Janssen, and Takeda; and travel accommodation and expenses from BMS, Janssen, Sanofi Aventis, and Takeda. RS reports consulting or advisory role with BMS/Celgene, GlaxoSmithKline, Janssen, Kite/Gilead, and Sanofi; and honoraria from Amgen, BMS/Celgene, GlaxoSmithKline, Janssen, Kite/Gilead, Sanofi, and Takeda. IvM reports consulting or advisory role with Sanofi, Amgen, Janssen, Takeda, Stemline, GSK, BMS, Oncopeptides, Pfizer, and AstraZeneca. PR reports honoraria from BMS and travel accommodation and expenses from BMS. UG reports consulting or advisory role with Amgen, Boehringer Ingelheim, BMS, Celtrion, Ipsen, Sanofi, and MSD; and honoraria from Amgen, AstraZeneca, and Novartis. SK reports travel accommodation and expenses from AbbVie. UMM reports consulting or advisory role with Sanofi-Aventis, BMS, Roche, GSK, Novartis, Pierre Fabre, MSD, and Guardant Health; and travel accommodation and expenses from Pierre Fabre, Ipsen, and Janssen. CK reports travel accommodation and expenses from European Hematology Association. KCW reports consulting or advisory role with Abbvie, Amgen, Adaptive Biotech, BMS/Celgene, BeiGene, Janssen, GlaxoSmithKline, Karyopharm, Oncopeptides, Pfizer, Roche Pharma, Sanofi, Takeda, and Menarini; honoraria from Abbvie, Amgen, Adaptive Biotech, Astra Zeneca, BMS/Celgene, BeiGene, Janssen, GlaxoSmithKline, Karyopharm, Novartis, Oncopeptides, Pfizer, Roche Pharma, Sanofi, Stemline, Takeda, and Menarini; and research funding from Abbvie, Amgen, BMS/Celgene, Janssen, GlaxoSmithKline, Sanofi, and Takeda. MSR reports consulting or advisory role with BMS, Amgen, GSK, Janssen, Sanofi, Pfizer, AbbVie, Novartis, and Roche; research funding from Sanofi; travel accommodation and expenses from BMS, AbbVie, Janssen, Sanofi, GSK; Honoraria from BMS, Janssen, GSK, AbbVie, and Sanofi; and receipt of equipment, materials, drugs, medical writing, gifts or other services from Novartis, Sanofi. HJS reports consulting or advisory role with Amgen, AstraZeneca, BMS/Celgene, Genzyme, GSK, Janssen Cilag, Oncopeptides, Pfizer, Sanofi, and Stemline; honoraria from Abbvie, Amgen, AstraZeneca, BMS/Celgene, Genzyme, GSK, Janssen Cilag, Oncopeptides, Pfizer, Roche, Sanofi, Stemline, and Takeda; and travel accommodation and expenses from Amgen, BMS/Celgene, Janssen Cilag, and Sanofi. All other authors declare no competing interests.

Data sharing

Data from published parts of the GMMG-HD6 trial can be made available upon request to and decision of the principal investigator (Hartmut Goldschmidt; hartmut.goldschmidt@med.uni-heidelberg.de) and the board of directors of the GMMG.

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