Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial

Sarah A. Holstein, *University of Nebraska Medical Center*
Sin-Ho Jung, *Duke University*
Paul G. Richardson, *Dana-Farber Partners CancerCare*
Craig Hofmeister, *Emory University*
David D. Hurd, *Wake Forest Baptist Medical Center*
Hani Hassoun, *Memorial Sloan Kettering Cancer Center*
Sergio Giralt, *Memorial Sloan Kettering Cancer Center*
Daniel J. Weisdorf, *University of Wisconsin*
Ravi Vij, *Washington University*
Jan S. Moreb, *University of Florida*

*Only first 10 authors above; see publication for full author list.*

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Summary

Background In the CALGB (Alliance) 100104 study, lenalidomide versus placebo after autologous stem-cell transplantation (ASCT) was investigated for patients with newly diagnosed myeloma. That study showed improved time to progression and overall survival and an increase in second primary malignancies for lenalidomide at a median follow-up of 34 months. Here we report an updated intention-to-treat analysis of CALGB (Alliance) 100104 at a median follow-up of 91 months.

Methods Patients were eligible for this randomised, double-blind, placebo-controlled, phase 3 trial if they had symptomatic disease requiring treatment; had received, at most, two induction regimens; and had achieved stable disease or better in the first 100 days after ASCT. We randomly assigned patients to either lenalidomide or placebo groups using permuted block randomisation, with a fixed block size of six. Randomisation was stratified by three factors: normal or elevated β2 microglobulin concentration at registration (≤2·5 mg/L vs >2·5 mg/L), previous use or non-use of thalidomide during induction therapy, and previous use or non-use of lenalidomide during induction therapy. The starting dose was two capsules (10 mg) per day, escalated to three capsules (15 mg) per day after 3 months. The primary endpoint was time to progression (time of progressive disease or death from any cause), with intention-to-treat analysis. This study is registered with ClinicalTrials.gov, identifier NCT00114101. New patients are no longer being recruited, but some patients remain on treatment and in follow-up.

Findings Between April 14, 2005, and July 2, 2009, 460 patients were randomly assigned to receive either lenalidomide (n=231) or placebo (n=229). After three interim analyses, the study was unblinded at a median follow-up of 18 months, at which point 86 (67%) of 128 patients without progressive disease in the placebo group chose to cross over to the lenalidomide group. The median follow-up for the updated survival analysis, as of Oct 19, 2016, was 91 months (IQR 83·6–103·1). The median time to progression was 57·3 months (95% CI 44·2–73·3) for the lenalidomide group and 28·9 months (23·0–36·3) for the placebo group (hazard ratio 0·57, 95% CI 0·46–0·71; p<0·0001). The most common grade 3–4 adverse events were neutropenia (116 [50%] patients in the lenalidomide group and 41 [18%] patients in the placebo group) and thrombocytopenia (34 [15%] patients in the lenalidomide group and 12 [5%] patients in the placebo group) and thrombocytopenia (34 [15%] patients in the lenalidomide group and 12 [5%] patients in the placebo group). 18 (8%) haematological and 14 (6%) solid tumour second primary malignancies were diagnosed after randomisation and before disease progression in the lenalidomide group, compared with three (1%) haematological and nine (4%) solid tumour second primary malignancies in the placebo group. Three haematological and five solid tumour second primary malignancies in the placebo group were in the crossover subgroup.

Interpretation Despite an increase in haematological adverse events and second primary malignancies, lenalidomide maintenance therapy after ASCT significantly improved time to progression and could be considered a standard of care.

Funding The National Cancer Institute.

Introduction

Despite improvements in the survival of patients with newly diagnosed myeloma as a result of induction therapy with new drugs followed by consolidation with high-dose melphalan and autologous stem-cell transplantation (ASCT), most patients will have disease relapse or progression. There has been substantial interest in the use of maintenance therapy after ASCT to delay disease relapse or progression and prolong survival. Several randomised studies have investigated the use of maintenance therapy with thalidomide, a first-generation immunomodulatory drug, after ASCT. Although an overall benefit in progression-free survival has been observed with thalidomide maintenance, a consistent...
benefit in overall survival has not been shown, and prolonged therapy with thalidomide has been restricted by this drug's side-effect profile.1 Lenalidomide, a second-generation immunomodulatory drug, has a more favourable side-effect profile than thalidomide and, therefore, has been studied in the context of maintenance therapy after ASCT.

Cancer and Leukemia Group B (CALGB) 100104, in collaboration with the Blood and Marrow Transplant Clinical Trials Network and the Eastern Cooperative Oncology Group (ECOG), randomly assigned 460 patients with myeloma in the USA to lenalidomide (n=231) or placebo (n=229) maintenance after ASCT. CALGB is now part of the Alliance for Clinical Trials in Oncology. The first publication1 showed that lenalidomide maintenance was associated with significantly longer time to disease progression than placebo (median of 46 months for the lenalidomide group and 27 months for the placebo group; hazard ratio [HR] 0·48, 95% CI 0·36–0·63; p<0·0001) and significant improvement in overall survival at a median follow-up of 34 months.2 18 (8%) patients in the lenalidomide group developed second primary malignancies before disease progression compared with six (3%) patients in the placebo group. Three other large randomised studies (IFM 2005-02, GIMEMA RV-209, and Myeloma XI) have assessed the role of lenalidomide maintenance after ASCT.3 4 5 Whereas both IFM 2005-02 and GIMEMA RV-209 reported significant improvements in progression-free survival with lenalidomide, no significant improvement was seen in overall survival. The survival data for the Myeloma XI trial1 have not yet been reported. The incidence of second primary malignancies (excluding non-invasive skin cancers) with lenalidomide maintenance was 7·5% in IFM 2005-023 and 2·8% in GIMEMA RV-209.4 A meta-analysis that included CALGB 100104, IFM 2005-02, and GIMEMA RV-209 found that lenalidomide maintenance significantly improved overall survival.4 Here, we present a post-hoc analysis of CALGB (Alliance) 100104 to provide long-term follow-up data with respect to time to progression, overall survival, and incidence of second primary malignancies.

Methods

Study design and participants

For this randomised, double-blind, placebo-controlled, phase 3 trial, adults aged 18–70 years were enrolled from 47 centres across the USA (appendix p 36). Patients were eligible if they had active myeloma; an ECOG performance status score of 0 or 1; symptomatic disease requiring treatment; had received no more than 12 months of any previous therapy; were within 12 months of initiation of induction therapy; and had received, at most, two induction regimens. Patients were excluded if they had disease progression during induction therapy or had previously undergone a peripheral blood, bone marrow, or solid organ transplant. Patients with stable disease or better (marginal, partial, or complete response) in the first 100 days after ASCT were eligible. Additional details regarding inclusion and exclusion criteria can be found in the appendix (p 6). Each participant signed a protocol-specific consent form approved by the institutional review board, in accordance with federal and institutional guidelines. The study was

Added value of this study

We report the long-term follow-up of the randomised, phase 3 CALGB (Alliance) 100104 study investigating lenalidomide versus placebo maintenance therapy after single ASCT. This analysis confirms the benefit in time to progression and overall survival with lenalidomide maintenance, regardless of the response achieved after ASCT. This analysis also provides a detailed update of the incidence of second primary malignancies in this study population and confirms that, although lenalidomide maintenance is associated with an increased risk of both haematological and solid-tumour second primary malignancies, the risk is offset by the magnitude of the benefits in time to progression and overall survival.

Implications of all the available evidence

This updated analysis, together with the available literature, confirms that continuous lenalidomide maintenance after ASCT until disease progression provides a significant benefit in time to progression and overall survival, and can therefore be considered a standard of care.
approved by the adult Central Institutional Review Board for the National Cancer Institute (NCI).

Randomisation and masking
Patients were randomly assigned (1:1), in a double-blinded manner, to lenalidomide or placebo maintenance groups between 90 days and 100 days after ASCT. Randomisation was stratified by three factors: normal or elevated β2 microglobulin concentration at registration (≤2·5 mg/L vs >2·5 mg/L), previous use or non-use of thalidomide during induction therapy, and previous use or non-use of lenalidomide during induction therapy. For each stratum, we used permuted block randomisation, with a block size of six and equal allocation between the two groups. The study was unblinded on Dec 17, 2009, after the third interim analysis. A detailed description of the randomisation, unblinding, and interim analyses is included in the appendix (pp 2–6). Of the 128 eligible patients without progressive disease in the placebo group, 86 chose to cross over to lenalidomide therapy.

Procedures
All patients with stable disease or better were scheduled to start therapy between 100 days and 110 days after ASCT. All patients were started on two capsules (10 mg of lenalidomide or placebo) per day, which were administered orally. After 3 months, the dose could be escalated to three capsules (15 mg) per day for reasons described in the appendix (p 7). Response and progression were initially defined with the European Blood and Marrow Transplant Group criteria,7 but were subsequently defined with the International Myeloma Working Group (IMWG) criteria.8 Criteria for continued treatment were defined with the IMWG criteria.8 Criteria for continued treatment were decided by the local centres. Disease progression (see appendix p 2 for definition); death; and responses at 100 days, 1 year, 2 years, and 3 years after ASCT were determined at the treatment centre and centrally reviewed according to the IMWG criteria, with the exception that stringent complete response was not used as a response category because most patients did not undergo free light-chain testing. The central review was done in a blinded manner by four authors (SAH, PLM, SG, and EAS).

Outcomes
The primary endpoint was time to progression, defined as the time to progressive disease or death from any cause after transplantation. Secondary objectives included overall survival (defined as the length of time from ASCT to death from any cause), assessment of complete response, and determination of the feasibility of long-term administration of lenalidomide. The assessment of second primary malignancies was an exploratory objective not specified in the protocol. Reporting of adverse events was mandated by the protocol. Sites submitted all adverse events to the Alliance Statistics and Data Center using the NCI Common Terminology Criteria for Adverse Events.9 All reactions deemed necessary to be reported in an expedited manner and new malignancies were reported using the NCI Adverse Event Expedited Reporting System.10

Statistical analysis
We planned to randomly assign 462 patients to either lenalidomide or placebo in a period of 33 months. Accounting for a dropout of 15%, this sample size would require 554 patients to be registered in this period. Under an equal allocation scheme (ie, 231 patients per group), a planned accrual period of 33 months, and a follow-up of 30 months, this sample size would have a power of at least 0·9 for the log-rank test to compare a median time to progression of 2 years for the control group with 2·8 years for the experimental group (HR 1·4), with a one-sided α value of 0·05.

We did the primary statistical analysis using the log-rank test and the secondary analysis using the Cox regression method. To assess the occurrence of second primary malignancies after randomisation, we considered the non-protocol endpoint of event-free survival (defined as time of first event, including a second primary malignancy, progressive disease, or death). Interim analyses were planned on a semi-annual basis to coincide with the semi-annual meetings of the CALGB Data and Safety Monitoring Board, starting from about 21 months after the start of the trial. We did superiority tests using a group sequential test designed by Emerson and Fleming,11 and we did futility tests to test whether the HR of time to disease progression between the two groups was less than 1·4, with a one-sided α value of 0·05. We estimated the survival functions using the Kaplan-Meier estimator.12

The Cox score statistic13 was used to test discrepancy between survival distributions, with adjustment for baseline patient characteristics. HRs were estimated with the Cox model under the implicit assumption of proportional hazards. To assess cause-specific (progression, death, and second primary malignancy) risk, cumulative incidence curves were estimated with Kaplan-Meier estimators14 and were compared with the log-rank test proposed by Gray.15 All analyses were right-censored and per protocol and were done with ASCT as the reference date, except for the event-free-survival analysis, which used the randomisation date. We compared the complete response at 1 year after transplantation for the lenalidomide and placebo groups with the χ² test.

The difference between the groups in the incidence of the most frequent grade 3 and worse adverse events (at least possibly treatment-related) was tested with Fisher’s exact test and estimated with a conditional maximum likelihood estimator of the odds ratio.16 The analyses were done by the Alliance Statistics and Data Center using the R statistical environment, including the survival and cmprsk extension packages, and SAS 9.4 for Windows.
A detailed description of the statistical considerations, including the design and analysis methods, has been provided in the appendix. All analyses were based on the study database as frozen on Oct 19, 2016.

This study is registered with ClinicalTrials.gov, identifier NCT00114101.

Role of the funding source
The NCI sponsored the study. Lenalidomide and placebo were provided by Celgene (Summit, NJ, USA) to the NCI, which in turn provided the study drugs to the investigators. Celgene was not involved in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had access to the data in the study through the Alliance Statistics and Data Center, which collected the data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Between April 14, 2005, and July 2, 2009, 460 of 568 enrolled patients were randomly assigned to receive either lenalidomide (n=231) or placebo (n=229). As reported previously,2 patients were evenly distributed by age, sex, disease stage, and β2 microglobulin concentration at registration (appendix p 20). The disposition of the patients, including reasons for ineligibility, is shown in figure 1 and the appendix (p 8). The reasons for treatment discontinuation are summarised in the appendix (p 22).

After three interim analyses, the study was unblinded at a median follow-up of 18 months (IQR 10·1–25·6), at which point 86 (67%) of 128 patients without progressive disease in the placebo group chose to cross over to the lenalidomide group.

The median duration of treatment was 31·0 months (95% CI 24·8–35·8) for the lenalidomide group compared with 18·1 months (17·1–22·6) for the placebo group (p<0·0001). Within the placebo group, the median duration of treatment was 30·7 months (27·3–36·1) for the crossover patients and 14·5 months (12·5–17·3) for the non-crossover patients. Treatment-free intervals were not determined. The median dose for the duration of treatment for the lenalidomide group was 6·8 mg per day (IQR 4·6–9·5).

The median follow-up for the updated survival analysis, as of Oct 19, 2016, was 91 months (IQR 83·6–103·1). 146 (63%) of the 231 patients in the lenalidomide group had progressive disease or had died at this timepoint, compared with 176 (77%) of the 229 patients in the placebo group (figure 2). The median time to disease progression was 57·3 months (95% CI 44·2–73·3) for the lenalidomide group and 28·9 months (23·0–36·3) for the placebo group (HR 0·57, 95% CI 0·46–0·71; p<0·0001). Time-to-progression analyses comparing Alliance (European Medicines Agency) and US Food and Drug Administration censoring rules are shown in the appendix (p 23). 88 (38%) of the 231 patients in the lenalidomide group had died compared with 120 (52%) of the 229 patients in the placebo group (figure 2). The median overall survival was 113·8 months (95% CI 100·4–not reached) for the lenalidomide group and 84·1 months (73·8–106·0) for the placebo group (HR 0·61, 95% CI 0·46–0·77; p<0·0001). Time-to-progression analyses comparing Alliance (European Medicines Agency) and US Food and Drug Administration censoring rules are shown in the appendix (p 23). Overall survival at 5 years was 76% (95% CI 70–81) for the lenalidomide group and 64% (58–70) for the placebo group.

The median time to crossover to lenalidomide for patients in the placebo group who chose to cross over at the time of study unblinding was 11 months.
The HRs for time to progression and overall survival were similar for the original lenalidomide group and for the lenalidomide group including patients in the placebo group who had crossed over to lenalidomide within 6 months or 12 months of randomisation (appendix p 9).

For patients who had disease progression, the median survival time after progression was similar for the two treatment groups: 42·6 months (95% CI 36·4–60·5) for lenalidomide and 39·2 months (31·2–45·0) for placebo (HR 0·83, 95% CI 0·61–1·13; p=0·23; figure 3). Similarly, we did not observe differences in survival time after progression when patients in the placebo group who crossed over within 6 months or 12 months of randomisation were included in the lenalidomide group (appendix p 10).

The time to second objective disease progression could not be calculated as neither the date of second progression nor the start of third-line therapy was routinely collected from the sites.

Patients were stratified by previous lenalidomide or thalidomide therapy and β2 microglobulin concentration (elevated vs normal). Figure 4 shows forest plots comparing the relative effects of these stratification factors, as well as centrally adjudicated response at randomisation (very good partial response [VGPR] or complete response vs no VGPR or complete response), on time to disease progression and overall survival. Lenalidomide maintenance was associated with a benefit in time to disease progression across all stratification groups (figure 4A). Patients who received lenalidomide induction and maintenance (n=84) had a median time to disease progression of 71·6 months (95% CI 57·3–97·8), compared with 46·0 months (37·2–73·1; HR 0·80, 95% CI 0·57–1·13; p=0·21) for those who received lenalidomide maintenance in the absence of previous lenalidomide induction (n=147; appendix p 11). Lenalidomide maintenance benefited overall survival regardless of whether or not patients had received previous lenalidomide induction (figure 4B). The median overall survival did not differ significantly between patients who received lenalidomide maintenance with previous lenalidomide induction (104·7 months, 95% CI 97·8–not reached) and those who received lenalidomide maintenance without previous lenalidomide induction (113·8 months, 90·5–not reached; HR 0·66, 95% CI 0·41–1·05; p=0·078; appendix p 11). For patients in the placebo group, the presence or absence of lenalidomide induction did not affect the median time to disease progression (HR 0·84, 95% CI 0·62–1·15) or overall survival (0·97, 0·67–1·42; appendix p 11).

The median time to disease progression for patients in the placebo group who were not in VGPR or complete response at the time of randomisation (n=60) was 19·8 months (95% CI 14·6–36·8) compared with 33·0 months (23·6–40·6) for patients in VGPR or complete response (n=153; HR 0·71, 95% CI 0·51–1·00; p=0·37; appendix p 12). For the lenalidomide group, the median time to disease progression for patients not in VGPR or complete response at the time of randomisation (n=86) was 37·2 months (28·9–60·1) compared with 66·7 months (50·6–94·3) for patients in VGPR or complete response (n=128, 0·59, 0·42–0·83; p=0·0018). For patients who did not have a VGPR or complete response, the median overall survival was 90·6 months (72·5–not reached) for the placebo group and 97·8 months (75·0–not reached) for the lenalidomide group. For patients who did have a VGPR or complete response, the median overall survival was 80·6 months (68·9–not reached) for the placebo group and was not reached (100·4–not reached) for the lenalidomide group (appendix p 12).

A centralised review was done to assess response (per IMWG criteria) at the time of randomisation and at
1 year, 2 years, and 3 years after ASCT (table 1). We observed similar proportion of patients achieving a complete response in the placebo and lenalidomide groups at 1 year after ASCT (p=0.78). However, after 3 years, most patients who remained in complete response or who had a VGPR were either in the lenalidomide group or the crossover group. There were no reliable data regarding the number of patients in biochemical relapse at each timepoint.

We reviewed reported salvage therapies and compiled the confirmed initial salvage therapies (appendix pp 24, 25). Of patients with confirmed initial salvage regimens, more patients had received lenalidomide or a lenalidomide-containing regimen at the time of relapse in the placebo group (73 [70%] of 104 patients) than in the lenalidomide group (32 [32%] of 101 patients) or crossover group (18 [43%] of 42 patients). 35 patients were reported to have received a second ASCT, seven patients had undergone allogeneic transplant, and one patient had received a second ASCT and an allogeneic transplant from a haploidentical donor.

Grade 3 or worse haematological and non-haematological adverse events that occurred after randomisation were previously reported for the lenalidomide and placebo groups.1 With longer follow-up, a small number of additional adverse events were reported (table 2; appendix p 26). The most common grade 3–4 adverse events were neutropenia (116 [50%] patients in the lenalidomide group and 41 [18%] patients in the placebo group) and thrombocytopenia (34 [15%] patients in the lenalidomide group and 12 [5%] patients in the placebo group). The adverse events in the placebo group were further categorised into the crossover subgroup and the non-crossover subgroup. Almost all haematological adverse events in the placebo group were in patients who had crossed over to receive lenalidomide. A total of three grade 5 adverse events were reported: two (infection and vascular event) in the lenalidomide group and one (cardiac arrhythmia) in the placebo non-crossover group.

Second primary malignancies that were diagnosed after the time of randomisation and before the time of myeloma progression and receipt of salvage therapy are shown in table 3. 18 (8%) haematological, 14 (6%) solid tumour, and 11 (5%) non-invasive second primary malignancies were diagnosed in the lenalidomide group, compared with three (1%) haematological, nine (4%) solid tumour, and six (3%) non-invasive second primary malignancies in the placebo group. Three (100%) haematological, five (56%) solid tumour, and five (83%) non-invasive second primary malignancies in the placebo group were in the crossover subgroup. Of the 21 patients with haematological second primary malignancies, nine received a thalidomide-containing induction regimen, six received a lenalidomide-containing regimen, and six received an anthracycline-containing induction regimen (appendix p 32). Details of the solid tumour second primary malignancies are shown in the appendix (p 33). Almost all of the solid tumour second primary malignancies were reported within the first 3 years after randomisation but, with longer follow-up, haematological
Second primary malignancies continued to develop (appendix p 13). The median times to haematological or solid tumour second primary malignancies were similar for both treatment groups: 60·8 months (95% CI 36·1–not reached) to haematological and 27·0 months (18·1–not reached) to solid tumour second primary malignancies in the placebo group compared with 49·8 months (35·7–83·5) to haematological (p=0·86) and 21·7 months (16·6–not reached; p=0·45) to solid tumour second primary malignancies in the lenalidomide group (appendix p 14). Second primary malignancies were also reported after myeloma progression and initiation of salvage therapy, including one haematological, four solid tumour, and two non-invasive second primary malignancies in the lenalidomide group, and five haematological, two solid tumour, and two noninvasive second primary malignancies in the placebo group (appendix p 34). Of the second primary malignancies in the placebo group that occurred after myeloma progression and initiation of salvage therapy, one haematological and one non-invasive second primary malignancy occurred in the crossover subgroup. Finally, one haematological, seven solid tumour, and two noninvasive second primary malignancies were reported in enrolled patients who were never randomised (appendix p 35).

We analysed the cumulative incidence risks (CIRs) of progressive disease, death, and second primary malignancies by treatment group. As shown in figure 5A, the CIR of progressive disease or death was higher with placebo than with lenalidomide (HR 0·57, 95% CI 0·45–0·72; p=0·0001), whereas the CIR of developing a second primary malignancy was higher with lenalidomide than with placebo (0·53, 0·39–0·71; p<0·0001; figure 5B). The CIR of death from any cause was higher with placebo than with lenalidomide (0·57, 0·45–0·72; p<0·0001; figure 5C). The CIR curves for haematological versus solid tumour second primary malignancies are shown in the appendix (p 15).

The CIRs of progressive disease or death and second primary malignancies were assessed for patients in the placebo group who did and did not cross over (appendix pp 16, 17). The risks of progressive disease, death, or a second primary malignancy were not significantly different between the lenalidomide and crossover groups. The median event-free survival (time to progressive disease, second primary malignancy, or death from any cause) was 27·0 months (95% CI 21·8–34·9) for the placebo group and 44·2 months (37·3–56·1) for the lenalidomide group (HR 0·63, 95% CI 0·51–0·78; p<0·0001; appendix p 18).

<table>
<thead>
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<th>Time of randomisation</th>
<th>Placebo (n=229)</th>
<th>Lenalidomide (n=231)</th>
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<tr>
<td></td>
<td>No crossover (n=143)</td>
<td>Crossover (n=86)</td>
</tr>
<tr>
<td>Complete response</td>
<td>33 (14%)</td>
<td>20 (9%)</td>
</tr>
<tr>
<td>VGPR</td>
<td>60 (26%)</td>
<td>40 (17%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>32 (14%)</td>
<td>20 (9%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (2%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Relapse or progressive disease</td>
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<tr>
<td>Not evaluable*</td>
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<td>5 (2%)</td>
</tr>
<tr>
<td>Off-study†</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>VGPR or complete response rate</td>
<td>41%</td>
<td>26%</td>
</tr>
</tbody>
</table>

| 1 year after ASCT     |               |                    |             |
| Complete response     | 26 (11%)       | 22 (10%)           | 48 (21%)    | 46 (20%) |
| VGPR                  | 32 (14%)       | 36 (16%)           | 68 (30%)    | 65 (28%) |
| Partial response      | 8 (3%)         | 13 (6%)            | 21 (9%)     | 36 (16%) |
| Stable disease        | 0 (0%)         | 0 (0%)             | 0 (0%)      | 2 (1%)   |
| Relapse or progressive disease | 15 (4%) | 6 (3%)             | 13 (6%)     | 19 (8%)  |
| Not evaluable*        | 26 (11%)       | 2 (1%)             | 28 (12%)    | 50 (22%) |
| Off-study†            | 36 (16%)       | 7 (3%)             | 43 (19%)    | 33 (16%) |
| VGPR or complete response rate | 25%        | 25%                 | 51%         | 48%      |

| 2 years after ASCT    |               |                    |             |
| Complete response     | 16 (7%)        | 17 (7%)            | 33 (14%)    | 41 (18%) |
| VGPR                  | 8 (3%)         | 22 (10%)           | 30 (13%)    | 43 (19%) |
| Partial response      | 2 (1%)         | 13 (6%)            | 15 (7%)     | 19 (8%)  |
| Stable disease        | 0 (0%)         | 0 (0%)             | 0 (0%)      | 1 (1%)   |
| Relapse or progressive disease | 10 (4%) | 9 (4%)             | 12 (5%)     | 22 (10%) |
| Not evaluable*        | 29 (13%)       | 13 (6%)            | 42 (18%)    | 61 (26%) |
| Off-study†            | 78 (34%)       | 12 (5%)            | 90 (39%)    | 44 (19%) |
| VGPR or complete response rate | 10%        | 17%                 | 27%         | 36%      |

| 3 years after ASCT    |               |                    |             |
| Complete response     | 5 (2%)         | 8 (3%)             | 13 (6%)     | 30 (13%) |
| VGPR                  | 3 (1%)         | 19 (8%)            | 22 (10%)    | 24 (10%) |
| Partial response      | 1 (<1%)        | 4 (2%)             | 5 (2%)      | 8 (3%)   |
| Stable disease        | 0 (0%)         | 0 (0%)             | 0 (0%)      | 1 (<1%) |
| Relapse or progressive disease | 8 (3%) | 6 (3%)             | 9 (4%)      | 21 (9%)  |
| Not evaluable*        | 31 (14%)       | 27 (12%)           | 58 (25%)    | 84 (36%) |
| Off-study†            | 95 (41%)       | 22 (10%)           | 117 (51%)   | 63 (27%) |
| VGPR or complete response rate | 3%          | 12%                 | 15%         | 23%      |

Data are n (%) or %. VGPR=very good partial response. ASCT=autologous stem-cell transplantation. *Not evaluable because of missing data. †Off-study because of previous disease relapse or progression.

Table 1: Adjudicated response rates per central review

Discussion

This updated analysis of the phase 3 randomised CALGB (Alliance) 100104 trial investigating lenalidomide versus placebo maintenance after ASCT showed a persistent benefit in time to disease progression and overall survival for lenalidomide. This benefit was maintained despite the crossover of most of the eligible patients in the placebo group.
to lenalidomide treatment at the time of study unblinding. Survival after progression did not differ between the two treatment groups. The benefit derived from lenalidomide maintenance was independent of induction therapy and the VGPR or complete response status at the time of randomisation. However, lenalidomide maintenance was associated with an increased risk of haematological second primary malignancies. This study and several other randomised trials3–5,17,18 have shown benefit with prolonged lenalidomide therapy. A meta-analysis6 of the CALGB, IFM, and GIMEMA studies found that lenalidomide maintenance significantly improved overall survival at a median follow-up of 79.5 months (median overall survival was not reached for lenalidomide vs 86 months for the control; HR 0.75; p=0.001).

The study most directly comparable to CALGB (Alliance) 100104 is the IFM 2005-02 trial,3 which also assessed lenalidomide versus placebo maintenance therapy after ASCT. Although a benefit in progression-free survival with lenalidomide was observed in that study,3 no difference was seen in overall survival between the study groups. Multiple factors might contribute to the difference in survival outcomes between the studies, including the types of induction regimens, consolidation therapy, number of transplants, duration of lenalidomide maintenance, and available salvage therapies. Overall, the IFM 2005-02 study population was exposed to more

<table>
<thead>
<tr>
<th></th>
<th>Lenalidomide (n=231)</th>
<th>Placebo (n=143)</th>
<th>Crossover (n=86)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1</td>
<td>Grade 2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Haematological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>15 (6%)</td>
<td>6 (3%)</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>4 (2%)</td>
<td>5 (2%)</td>
<td>28 (12%)</td>
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<tr>
<td>Lymphopenia</td>
<td>2 (1%)</td>
<td>2 (1%)</td>
<td>20 (9%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14 (6%)</td>
<td>36 (16%)</td>
<td>82 (35%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>75 (32%)</td>
<td>33 (14%)</td>
<td>23 (10%)</td>
</tr>
<tr>
<td>Non-haematological</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conduction abnormality</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (4%)</td>
<td>9 (4%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Rash</td>
<td>22 (10%)</td>
<td>22 (10%)</td>
<td>9 (4%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>54 (23%)</td>
<td>36 (16%)</td>
<td>12 (5%)</td>
</tr>
<tr>
<td>Febrile neutropenia (fever of unknown origin)</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>14 (6%)</td>
</tr>
<tr>
<td>Infection (documented clinically or microbiologically)</td>
<td>1 (&lt;1%)</td>
<td>4 (2%)</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>Infection with normal absolute neutrophil count or grade 1 or 2 neutrophils</td>
<td>0 (0%)</td>
<td>6 (3%)</td>
<td>13 (6%)</td>
</tr>
<tr>
<td>Pain</td>
<td>7 (3%)</td>
<td>4 (2%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Vascular</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Data are n (%). Adverse events were those that occurred in at least 10% of patients for grades 1–2, at least 2% of patients for grades 3–4, or any patients for grade 5.

### Table 2: Adverse events

### Table 3: Second primary malignancies
traditional chemotherapy, whereas the CALGB (Alliance) 100104 study population was exposed to more novel drug-based therapy. The extent to which therapy before transplantation determines response to subsequent salvage therapies remains to be determined. However, our analysis showed that patients progressing on lenalidomide maintenance had a similar overall survival after progression to placebo patients after progression, which suggested that prolonged lenalidomide maintenance did not confer disease resistance.

The optimal dose, schedule, and duration of lenalidomide maintenance continue to be topics for discussion. This study, as well as the GIMEMA RV-209 and Myeloma XI studies, continued lenalidomide maintenance therapy until progression, whereas the IFM 2005-02 study discontinued lenalidomide maintenance after a median time of 2 years (range 1–3 years) because of concerns about the risk of second primary malignancies. The IFM 2009 study, which assessed the timing of ASCT, incorporated 1 year of lenalidomide maintenance, while the ongoing DETERMINATION trial (NCT01208662) in the USA is identical in design to the IFM 2009 study except that maintenance is continued until progression. Future comparison of survival outcomes and toxicities, including the incidence of second primary malignancies, between the IFM 2009 and DETERMINATION studies will provide important information about the effect of maintenance duration. Most studies done in the USA and France (eg, CALGB 100104, BMT CTN 0702, IFM 2005-02, and IFM 2009) have used continuous dosing of lenalidomide, whereas other studies done in Europe (eg, Myeloma XI, GIMEMA RV-209, RV-MM-EMN-441, and EMN02/H905) have used a 21 day out of 28 day schedule. In the absence of a prospective study comparing the two dosing schedules, conclusion of whether one schedule is better than the other from either a survival or toxicity perspective is difficult. However, the largest of the studies, CALGB 100104 and Myeloma XI, have found very similar median durations for time to disease progression or progression-free survival for the lenalidomide groups (57.3 months for this study and 60 months for Myeloma XI), despite their use of different dosing schedules. As ongoing and planned studies involving the addition of other drugs to lenalidomide maintenance progress (eg, NCT02874742, NCT01718743, NCT02495922, and NCT02203643), the optimal dosing, schedule, and duration of lenalidomide maintenance will probably continue to evolve.

Figure 5: Cumulative incidence risk of progressive disease, death, or SPM by treatment group

(A) The cumulative incidence risk of progressive disease or death from any cause was higher with placebo than with lenalidomide (p=0.0001), whereas the cumulative incidence risk of development of a SPM was higher with lenalidomide than with placebo (p=0.0013). (B) The cumulative incidence risk of death from any cause was higher with placebo than with lenalidomide (p=0.0001). (C) The cumulative incidence risk of death from myeloma was higher with placebo than with lenalidomide (p=0.0001), whereas the cumulative incidence risk of death from a SPM was higher with lenalidomide than with placebo (p=0.031). SPM=second primary malignancy. ASCT=autologous stem-cell transplantation.
A central review of the response data (table 1) showed that, despite substantial efforts by participating sites to provide follow-up data, data were missing at later timepoints (years 2 and 3). These data include those for bone marrow biopsies, 24 h urine quantitations, and incomplete serum and urine electrophoresis analyses. The independent review committee reviewed all available primary source data. Despite these limitations, this review did show that there was little difference in the rates of complete response or VGPR between the two groups at 1 year. However, most patients who had a complete response or a VGPR after 3 years were in either the lenalidomide group or the crossover subgroup of the placebo group.

This updated analysis of CALGB (Alliance) 100104 showed an increased risk of second primary malignancies associated with lenalidomide maintenance therapy, although the risks of progressive disease and death due to myeloma were substantially higher than the risk of second primary malignancies in both cohorts. The risk of second primary malignancies is associated with multiple factors, including the underlying disease, age of the patient, and type of myeloma therapy used. Several patients who were enrolled in the study but never randomised developed second primary malignancies (appendix p 36). This finding is consistent with the underlying risk of a second primary malignancy in this patient population. The risk of malignancy increases with advancing age, and age-related clonal haemopoiesis is associated with increased risk of haematological malignancies. Numerous studies have shown that monoclonal gammapathy of undetermined significance and myeloma, even in the absence of therapy, are associated with an increased risk of haematological malignancies. Numerous studies have shown that monoclonal gammapathy of undetermined significance and myeloma, even in the absence of therapy, are associated with an increased risk of haematological malignancies, particularly myelodysplastic syndrome and acute myeloid leukaemia. This finding implicates the presence of an intrinsic defect in the haemapoietic system of patients with plasma cell dyscrasias. An increased risk of solid tumours in patients with myeloma has also been reported. We did not find a predominant type of solid tumour second primary malignancy in this study. With respect to lenalidomide, a meta-analysis of 3254 newly diagnosed patients treated in seven randomised, phase 3 trials showed that the cumulative 5 year incidence of all second primary malignancies was 6-9% in patients who received lenalidomide compared with 4-8% in those who did not (p=0.037). An increase in haematological malignancies (3-1% vs 1-4%; p=0.029), but not solid tumours (3-8% vs 3-5%; p=0.72), was observed in that meta-analysis.

Since the time of first publication of CALGB 100104, four new solid tumour second primary malignancies and ten new haematological second primary malignancies were reported in the lenalidomide group. The risk of solid tumours appeared to be primarily incurred during the first several years of lenalidomide therapy after ASCT, with haematological malignancies continuing to be diagnosed at later follow-up (appendix pp 13,14).

However, given the overall small number of second primary malignancies, it was difficult to draw any definite conclusions regarding the temporal association between the type of second primary malignancy and lenalidomide exposure. Genetic analysis, particularly of the haematological second primary malignancies, is needed to better determine the mechanisms by which lenalidomide contributes to the pathogenesis of these malignancies. Although myelodysplastic syndrome and acute myeloid leukaemia have previously been associated with high-dose melphalan and myeloma therapy, the appearance of B-cell acute lymphoblastic leukaemia as a second primary malignancy has been somewhat unexpected. Further studies are needed to determine whether the effects of lenalidomide on IKZF1, a transcription factor that has been associated with B-cell acute lymphoblastic leukaemia, contribute to the development of acute lymphoblastic leukaemia as a second primary malignancy.

In conclusion, our study shows that lenalidomide maintenance therapy after ASCT confers significant benefit in time to disease progression and overall survival. The overall survival data (a median overall survival of 9-5 years from the time of ASCT with lenalidomide) provide a new benchmark for survival, particularly noteworthy because this study was done in an era when triplet regimens containing immunomodulatory drugs and proteasome inhibitors were not routinely used. Cytogenetic and fluorescence in-situ hybridisation testing of diagnostic samples was not available for most patients, thus the effect of lenalidomide maintenance on different cytogenetic risk groups could not be determined. Preliminary results from the Myeloma XI trial showed benefit for lenalidomide maintenance in patients with high-risk or low-risk cytogenetic abnormalities. This study showed that patients in complete response after ASCT benefited from lenalidomide maintenance; however, determination of a complete response was done by the numbers of bone-marrow plasma cells and immunofixation testing. The revised IMWG criteria now include minimal residual disease assessment, and multiple studies have shown superior outcomes for patients who achieve minimal residual disease negativity after ASCT. Thus, the extent to which lenalidomide maintenance improves survival outcomes for patients who are negative for minimal residual disease, compared with those who are positive for minimal residual disease, remains to be determined. One limitation of the study is that quality-of-life data were not prospectively collected. However, this study is among an increasing number of studies showing the feasibility of long-term maintenance therapy with lenalidomide. Lenalidomide maintenance until progression after ASCT might be considered a standard of care and should form the backbone of future maintenance studies incorporating novel drugs, such as monoclonal antibodies or vaccine-based approaches.
Contributors
SAH did the literature search, figure design and construction, data collection, data analysis, data interpretation, and writing. S-HJ contributed to the data analysis, data interpretation, and writing. PGR, CCH, DDH, HH, SG, EAS, DJW, RV, JSM, NSC, KB, TGG, LI, RTM, AB, HL, TM, MHQ, CR, BM, RLS, PH, MCF, and MHM contributed to the data interpretation and writing. SES contributed to the data analysis, VH and CJ contributed to the data analysis, data interpretation, figures, and writing. KO, TCS, SMD, CL, and KCA contributed to the study design, data interpretation, and writing. MB, CS, and MW contributed to the data collection and data analysis. PLM contributed to the literature search, study design, data collection, data analysis, data interpretation, and writing.

Declaration of interests
KCA reports personal fees from Celgene, Millennium Takeda, Gilead, and Bristol-Myers Squibb. SG reports research funding and personal fees from Celgene and Takeda, research funding from Sanofi, and personal fees from Jazz and Amgen. PH reports grants and personal fees from Celgene. HH reports grants from CALGB (Alliance) during the study and grants from Celgene outside of the study. CCH reports other support (local principal investigator for clinical trial using drug made by Celgene) from Celgene. SAH reports personal fees from Celgene, Takeda, and Amgen, and travel support and honoraria for response adjudication of this study by the Alliance for Clinical Trials in Oncology. HL reports grants from Celgene during the study and personal fees from Spectrum Pharmaceuticals, Prothena, Janssen, and Takeda. PGR reports research support and personal fees from Celgene, personal fees from Bristol-Myers Squibb, Karyopharm, Gamida Cell, Janssen, Sanofi, and The Binding Site; and travel support and honoraria for response adjudication of this study by the Alliance for Clinical Trials in Oncology. MCP reports personal fees from Atara Biotherapeutics, Pfizer, and Baxalta. PGR reports personal fees from Celgene. EAS reports personal fees from Celgene and Takeda. RV reports personal fees from Celgene, Bristol-Myers Squibb, Janssen, AbbVie, and Karyopharm, and research support and personal fees from Amgen and Takeda. TM reports grants from Sanofi and Amgen, outside of the study. DJW, MW, AB, MB, NSC, SMD, TGG, VH, MMH, DDH, LI, CJ, S-HJ, CL, RTM, BM, JSM, KO, MHQ, CR, RLS, CS, TCS, SES, and KB declare no competing interests.

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References


