**Long-Term Follow-Up of MRC Myeloma IX Trial: Survival Outcomes with Bisphosphonate and Thalidomide Treatment**

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**Translational Relevance**

Myeloma is a heterogeneous disease. Understanding its various distinct biological subtypes may help design of optimal treatments for individual patients. The MRC Myeloma IX trial employed a factorial design to evaluate bisphosphonate and thalidomide therapy in patients with newly diagnosed multiple myeloma. Results confirmed the beneficial effects of zoledronic acid and thalidomide-based therapy, and highlighted important issues regarding clinical trial design in multiple myeloma. Specifically, cytogenetic profiling can identify subgroups with distinct biological characteristics. Early analyses highlight treatment differences in patients with adverse biological characteristics, whereas later analyses show the impact of therapy in patients with more indolent clinical courses. Therefore, long-term follow-up is necessary in multiple myeloma trials.

**Abstract**

**Purpose:** MRC Myeloma IX was a phase III trial evaluating bisphosphonate and thalidomide-based therapy for newly diagnosed multiple myeloma. Results were reported previously after a median follow-up of 3.7 years (Current Controlled Trials number: ISRCTN68454111). Survival outcomes were re-analyzed after an extended follow-up (median: 5.9 years).

**Experimental Design:** At first randomization, patients ($N$ = 1,970) were assigned to bisphosphonate (clodronic acid or zoledronic acid) and induction therapies (cyclophosphamide-vincristine-doxorubicin-dexamethasone [CVAD] or cyclophosphamide-thalidomide-dexamethasone [CTD] followed by high-dose therapy plus autologous stem cell transplantation for younger/fitter patients [intensive pathway], and melphalan-prednisone (MP) or attenuated CTD [CTDa] for older/less fit patients [non-intensive pathway]). At second randomization, patients were assigned to thalidomide maintenance therapy or no maintenance. Interphase FISH (iFISH) was used to analyze cytogenics.

**Results:** Zoledronic acid significantly improved progression-free survival (PFS; hazard ratio [HR], 0.89; $P$ = 0.02) and overall survival (OS; HR, 0.86; $P$ = 0.01) compared with clodronic acid. In the intensive pathway, CTD demonstrated non-inferior PFS and OS compared with CVAD, with a trend toward improved OS in patients with favorable cytogenics ($P$ = 0.068). In the non-intensive pathway, CTDa significantly improved PFS (HR, 0.81; $P$ = 0.007) compared with MP and there was an emergent survival benefit after 18–24 months. Thalidomide maintenance improved PFS (HR, 1.44; $P$ < 0.0001) but not OS (HR, 0.96; $P$ = 0.70), and was associated with shorter OS in patients with adverse cytogenics ($P$ = 0.01).

**Conclusions:** Long-term follow-up is essential to identify clinically meaningful treatment effects in myeloma subgroups based on cytogenetics.

**Introduction**

Although substantial advances in myeloma treatment have prolonged survival times (1, 2),

myeloma still remains incurable. Myeloma is also a heterogeneous disease, and an

understanding of subtypes with different biological behavior may help identify the best approach

for individual patients. The MRC Myeloma IX trial employed a factorial design to evaluate the

effects of bisphosphonate therapy and thalidomide-based regimens in the context of: (a)

induction therapy for patients suitable for high-dose therapy with autologous stem cell

transplantation (HDT-ASCT), regardless of age; (b) initial therapy for older, less fit patients; and

(c) maintenance therapy following either intensive (i.e. HDT-ASCT) or non-intensive treatment.

Results from a median follow-up of 3.7 years have been published previously: zoledronic acid

improves overall survival (OS) compared with clodronic acid (3); pre-HDT-ASCT induction

therapy with CTD (cyclophosphamide-thalidomide-dexamethasone) improves response rates

and is associated with non-inferior progression-free survival (PFS) and OS compared with

CVAD (cyclophosphamide-vincristine-doxorubicin-dexamethasone) (4); use of an attenuated

CTD regimen (CTDa) in patients ineligible for HDT-ASCT is associated with significantly better

response, although there was no difference in OS when compared with standard MP

(melphalan-prednisone) (5); and thalidomide maintenance therapy improves PFS but not OS,

with the benefit being seen in those with favorable interphase FISH (iFISH) cytogenic profiles

(6). The current analysis reports data from MRC Myeloma IX following an extended follow-up of

approximately 6 years.

**Patients and Methods**

The MRC Myeloma IX study was a multicenter, randomized, open-label, phase III, factorial-

design trial conducted in the UK (Current Controlled Trials number: ISRCTN68454111). Study

protocol details have been published previously (3–6). A multicenter research ethics committee

and local ethics committees approved the protocol and all patients gave written informed

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consent. Briefly, patients with newly diagnosed multiple myeloma were assigned to one of two treatment pathways: younger, fitter patients eligible for HDT-ASCT entered the intensive treatment pathway, whereas older, less fit patients entered the non-intensive pathway. At study entry, all patients were randomized to receive bisphosphonate therapy with zoledronic acid (4 mg every 3 to 4 weeks) or clodronic acid (1,600 mg/d) until disease progression. Patients in the intensive pathway were randomized to induction therapy with CTD or CVAD for a maximum of 6 cycles (21-d each) before proceeding to HDT-ASCT (melphalan 200 mg/m$^2$). Patients in the non-intensive pathway were randomized to CTDa or MP for 6 to 9 cycles. After initial therapy, all eligible patients underwent a second randomization to no maintenance or low-dose thalidomide maintenance therapy given until disease progression (50 mg/d for 4 weeks, increasing thereafter to 100 mg/d if well tolerated). A total of 1,600 patients (750 in the intensive pathway and 850 in the non-intensive pathway) were expected to enroll during a 5-year period. Due to rapid recruitment, the protocol was amended to increase the trial sample size in the intensive pathway to 1,080 patients, which allowed for adequately powered non-inferiority comparisons for PFS and OS. The overall target recruitment was increased to 1,930 patients.

Measures were taken to reduce the risk of osteonecrosis of the jaw (ONJ) (7). All suspected cases of ONJ were referred to a dental professional for diagnosis and management, with reports centrally reviewed by an investigator.

*Efficacy and safety endpoints.* The primary endpoints were PFS and OS. PFS was calculated as the time from randomization (bisphosphonate/induction therapy randomization or maintenance randomization) to the time of progression or death. Progression was defined as relapse from complete response if the patient achieved complete response, or progressive disease according to European Group for Blood and Marrow Transplantation (EBMT) criteria (8). Response to therapy was measured by central laboratory analysis performed in

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Birmingham, UK, and defined according to modified EBMT criteria (8). For intensive pathway patients, response was assessed after induction therapy and 100 d after HDT-ASCT. OS was defined as the time from randomization to the time of death. Follow-up assessments were performed by local investigators every 3 or 4 weeks during initial therapy and every 3 months during the maintenance phase. Treatment-related adverse events were recorded. Thromboembolic events and acute renal failure were required to be reported if they occurred during the study period, or until death or disease progression.

***iFISH cytogenic profiling.*** Bone marrow aspirates were collected at study entry in order to determine the cytogenetic profiles of patients using iFISH on CD138-purified plasma cells (Miltenyi Biotec GmbH, Bergisch Gladbach, Germany). Patients were classified as having a "favorable" or "adverse" cytogenetic profile. An adverse cytogenetic profile was defined as gain(1q), t(4;14), t(14;16), t(14;20), and del(17p); del(1p32) was considered adverse in the intensive pathway patients only. A favorable profile was defined as the absence of the previously listed abnormalities, as well as the absence of t(11;14), t(6;14), and hyperdiploidy.

***Statistical analysis.*** The cutoff date for the current analysis was January 5, 2012. The intent-to-treat (ITT) population included all randomized patients. The per-protocol population (for the non-inferiority comparison in the intensive pathway) included all randomized patients, but excluded those with major protocol violations. Patients who did not provide written informed consent or withdrew their consent were excluded from the ITT and per-protocol populations.

The statistical methods used were as previously described (3–6). Briefly, Cox proportional hazards models were used to compare treatment groups while adjusting for the minimization factors (creatinine, calcium, platelets, hemoglobin, and treatment center) and differences in bisphosphonate and/or induction therapy assignment. Non-inferiority of CTD compared with

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CVAD was concluded if the upper limit of the 95% confidence interval (CI) was no higher than 1.20. The other comparisons were for superiority, with $P < 0.05$ considered statistically significant. All hypothesis tests were 2-sided. Analysis according to iFISH cytogenic profiles was performed using the log-rank test.

**Results**

A total of 1,970 patients were enrolled from 121 treatment centers: 1,114 entered the intensive pathway and 856 entered the non-intensive pathway. Patient characteristics for each treatment group have been reported previously and were well balanced (3–6). Results from cytogenetic profiling of each treatment group are listed in Table 1. The median follow-up was 71 months (5.9 years).

*Bisphosphonate therapy.* Overall, 979 patients were randomized to clodronic acid and 981 to zoledronic acid. Survival analysis accounted for randomized chemotherapy (CVAD, CTD, MP, or CTDa), bisphosphonate therapy, and minimization factors (creatinine, calcium, platelets, hemoglobin, and treatment center). Kaplan-Meier estimates of PFS and OS demonstrated that median PFS was significantly longer in patients randomized to zoledronic acid than those randomized to clodronic acid (19 versus 18 months; hazard ratio [HR], 0.89; 95% CI, 0.80–0.98; $P = 0.02$; Figure 1A). Median OS was also significantly longer with zoledronic acid (52 versus 46 months; HR, 0.86; 95% CI, 0.77–0.97; $P = 0.01$; Figure 1B). Long-term rates of ONJ were higher with zoledronic acid compared with clodronic acid (3.7% versus 0.5%; $P < 0.0001$), but most events were manageable and of low grade.

*Intensive pathway.* A total of 540 patients started treatment with CVAD and 553 started treatment with CTD (per-protocol population: $n = 1,093$). Survival analyses were adjusted for chemotherapy regimen and bisphosphonate therapy (no interaction between these factors [$P =$

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0.55 for the ITT population]), and minimization factors. Median PFS in the CVAD and CTD groups was 24 and 26 months, respectively (HR, 0.98; 95% CI, 0.85–1.12; $P$ = 0.73; Figure 2A). Median OS was 63 months with CVAD and 71 months with CTD (HR, 0.90; 95% CI, 0.76–1.07; $P$ = 0.23; Figure 2B). These data demonstrate that induction therapy with CTD was non-inferior to CVAD in terms of survival outcomes. Among patients with a favorable iFISH profile ($n$ = 333), there was a trend toward improved median OS with CTD (98 versus 81 months; $P$ = 0.068; Figure 2C). Among those with an adverse iFISH profile ($n$ = 293), median OS was similar between CVAD and CTD (43 versus 49 months; $P$ = 0.39; Figure 2D). However, a possible survival benefit for CTD began to emerge after approximately 5 years, which would have been missed in earlier analyses.

*Non-intensive pathway.* Of the 856 patients assigned to the non-intensive pathway, 423 were assigned to MP and 426 were assigned to CTDa (ITT population). Survival analyses accounted for bisphosphonate therapy and minimization factors. Median PFS was significantly longer in the CTDa group than the MP group (13 versus 12 months; HR, 0.81; 95% CI, 0.69–0.94; $P$ = 0.007; Figure 3A). Median OS was similar between the two groups (34 versus 32 months; HR, 0.91; 95% CI, 0.77–1.07; $P$ = 0.24, Cox model; $P$ = 0.24, log-rank test; Figure 3B). The Kaplan-Meier curves of OS suggested an early benefit for MP, but they crossed after 18 to 24 months and remained separated thereafter in favor of CTDa. No significant differences in median PFS and median OS were observed when comparing MP and CTDa in the subgroups with favorable (Figure 3C) or adverse iFISH profiles (Figure 3D). However, there was some indication of a late survival benefit emerging in patients with an unfavorable iFISH profile (Figure 3D).

*Maintenance therapy.* A total of 820 patients were randomized to thalidomide maintenance or no maintenance therapy. Two patients withdrew consent, forming an ITT population of 818 patients (492 from the intensive pathway and 326 from the non-intensive pathway). Survival

analyses were adjusted for treatment center and previous combined chemotherapy and bisphosphonate therapy (clodronic acid + CVAD, clodronic acid + CTD, zoledronic acid + CVAD, zoledronic acid + CTD, clodronic acid + MP, clodronic acid + CTDa, zoledronic acid + MP, or zoledronic acid + CTDa). Median PFS was significantly longer in the 408 patients randomized to thalidomide maintenance compared with the 410 patients randomized to no maintenance therapy (22 versus 15 months; HR, 1.44; 95% CI, 1.22–1.70; $P$ < 0.0001; Figure 4A). Median OS was similar in both groups (60 months in both groups; HR, 0.96; 95% CI, 0.79–1.17; $P$ = 0.70; Figure 4B). The benefit in median PFS with thalidomide maintenance was only seen in the 255 patients with favorable iFISH profiles (29 versus 18 months; $P$ = 0.01). However, thalidomide maintenance had no impact on median OS in patients with favorable iFISH profiles (Figure 4C), and appeared to have a negative effect on OS in the 197 patients with adverse iFISH profiles (35 versus 47 months; $P$ = 0.01; Figure 4D).

**Discussion**

With an extended follow-up of 5.9 years, this analysis confirms the positive effects of zoledronic acid and thalidomide-based therapy in the treatment of multiple myeloma. The benefit in OS observed with zoledronic acid emerged early and was maintained over the long term. The combined early anticancer benefits of zoledronic acid and its ability to reduce skeletal-related events (9) justifies its use as a standard therapy in newly diagnosed multiple myeloma patients.

For patients suitable for HDT-ASCT, induction therapy with CTD improved response rates both pre- and post-ASCT (4). In our study, however, CTD only provided non-inferior median PFS and median OS compared with CVAD. For patients ineligible for HDT-ASCT, the use of CTDa improved median PFS compared with MP but resulted in similar median OS. In the overall analysis, maintenance therapy with thalidomide had a positive, clinically significant impact on median PFS, but did not significantly enhance median OS. It is important to note that the OS

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results may have been confounded by use of effective salvage therapy, particularly with novel agents like bortezomib or lenalidomide, as their availability and pattern of use changed during the course of the trial.

We also show that patients with a favorable cytogenetic profile were generally more likely to benefit from thalidomide-based therapy than those with an unfavorable cytogenetic profile. The genetic characterization of specific disease subgroups with distinct biological profiles can reveal unexpected heterogeneity of outcomes within an apparently homogeneous disease state. This is particularly well illustrated in the current analysis, in which thalidomide maintenance therapy had no impact on OS overall, but had a significant effect on PFS and potential OS benefit in patients with a favorable cytogenetic profile. This was counterbalanced by a negative influence on survival in patients with an adverse cytogenetic profile. The difference in outcomes between patients with favorable and adverse cytogenetics could be explained by the intraclonal heterogeneity at the myeloma-propagating cell level, in which certain genetic abnormalities acquire clonal advantage, expand, and evolve (10). In this scenario, the clonal advantage of the adverse phenotype and the selective pressure by thalidomide may account for increased malignancy, acquired drug resistance, and poor survival following relapse during thalidomide maintenance in patients with adverse cytogenetics. In this context, it has been observed that high-risk patients acquire greater levels of genetic changes at relapse (11). It should be noted, however, that the cytogenetic subgroups within each treatment group were relatively small, and the study was not formally powered to compare outcomes among these groups. Furthermore, the number of patients with specific cytogenetic abnormalities was also too few to determine the contribution of each individual abnormality. Therefore, larger studies should be conducted before cytogenetics can be used to guide clinical practice.

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An alternative approach to assessing the impact of therapy in disease subtypes with different biological profiles is to perform analysis at short- and long-term follow-up. In the non-intensive pathway, there was a possible emergence of a late survival benefit favoring CTDa over MP. In the intensive pathway, there was a trend toward improved OS with CTD over CVAD after approximately 5 years of follow-up only in patients with an adverse cytogenetic profile. This benefit is consistent with the earlier, sustained benefit among patients with a favorable cytogenetic profile, but a clearer picture emerged approximately 5 years after the initiation of induction therapy. The fuller picture would have been missed in analyses with shorter follow-up.

Several studies have evaluated thalidomide maintenance therapy and a survival advantage has not been demonstrated consistently (6, 12–15), although it became apparent in a meta-analysis of these trials (6). Our results indicate that thalidomide maintenance therapy exerts a clinically meaningful effect by significantly improving median PFS, although median OS was not affected. The varying effects of thalidomide maintenance therapy in patients with favorable and adverse cytogenetics are supported by previous observations (16–18) and emphasize the importance of stratifying patients by cytogenetic profile at baseline in future maintenance studies. The median duration of thalidomide maintenance therapy was short (7 months; range: 0–50), primarily due to the poor tolerability of long-term thalidomide therapy (6). Among those who discontinued thalidomide maintenance before disease progression, more than 50% did so due to treatment-related adverse events. The poor tolerability of long-term thalidomide suggests it may be best used as short-term consolidation therapy rather than for maintenance (19, 20).

Lenalidomide is an immunomodulatory drug with an improved tolerability profile compared with thalidomide (21), which makes it  particularly well-suited for long-term maintenance therapy. Studies evaluating lenalidomide maintenance after HDT-ASCT (22, 23) or following initial therapy for older/less fit patients ineligible for HDT-ASCT (24) are encouraging. Indeed,

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lenalidomide-based maintenance regimens are replacing thalidomide-based maintenance regimens, particularly in the USA. As multiple myeloma is increasingly considered a chronic disease requiring a long-term approach to care, continuous therapy strategies involving maintenance treatment will undoubtedly play an increasingly important role in the management of this disease.

The treatment landscape for multiple myeloma is constantly changing. Since this study was designed, data on new triple-combination induction therapies and novel emerging treatments have been published. For example, at least four new bortezomib-based triple combinations: bortezomib-thalidomide-dexamethasone (VTD), bortezomib-lenalidomide-dexamethasone (RVD), bortezomib-doxorubicin-dexamethasone (PAD), and cyclophosphamide-bortezomib-dexamethasone (CyBorD) have been described (25–30). In terms of novel emerging treatments, phase I/II trials have investigated induction-maintenance regimens including the two new proteasome inhibitors carfilzomib (carfilzomib-lenalidomide-dexamethasone induction with lenalidomide maintenance, and carfilzomib-cyclophosphamide-dexamethasone with carfilzomib maintenance) and ixazomib (ixazomib-lenalidomide-dexamethasone induction with ixazomib maintenance), and the histone deacetylase inhibitor vorinostat (RVD-vorinostat with lenalidomide ± bortezomib maintenance) (31–34). Future trials should investigate these emerging induction combination strategies, particularly in patients with different cytogenetic profiles.

This long-term analysis highlights some important issues regarding clinical trial design in multiple myeloma. Firstly, multiple myeloma is a heterogeneous disease and comprehensive genetic/cytogenetic profiling is essential to identify subgroups with distinct biological characteristics and clinical outcomes. Only by conducting such analyses can the true clinical impact of novel treatments be assessed in the different disease subgroups. Secondly, early

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analyses with modest median follow-up may highlight differences in the impact of therapies on adverse biological subgroups, whereas longer-term analyses can show the impact of therapy in patient groups with more indolent clinical courses. Such observations provide a compelling argument for the performance of both early and late outcome analyses in current and future trials of multiple myeloma.

In summary, long-term follow-up may be essential in order to identify clinically relevant, beneficial effects of novel therapies in biologically different subgroups of multiple myeloma patients. Benefits in patients with a favorable cytogenetic profile, and the late emergence of possible survival benefits favoring thalidomide-based therapy, may have implications for the design of future trials evaluating thalidomide or lenalidomide therapy.

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Therapy for Patients with Multiple Myeloma (MM): Results of a Phase 1 Study. Blood

2012;120:Abstract 336.

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**Table 1.** Cytogenetic profiles determined by interphase FISH and according to treatment subgroup

| Subgroup | Cytogenetic profile | |
| --- | --- | --- |
| | Favorable, *n*/*N* (%) | Adverse, *n*/*N* (%) |
| Intensive pathway | | |
| CVAD (*n* = 556) | 166/307 (54) | 141/307 (46) |
| CTD (*n* = 555) | 167/319 (52) | 152/319 (48) |
| Non-intensive pathway | | |
| MP (*n* = 423) | 125/215 (58) | 90/215 (42) |
| CTDa (*n* = 426) | 129/225 (57) | 96/225 (43) |
| Maintenance | | |
| No thalidomide (*n* = 410) | 129/227 (57) | 98/227 (43) |
| Thalidomide (*n* = 408) | 126/225 (56) | 99/225 (44) |

Abbreviations: CTD, cyclophosphamide-thalidomide-dexamethasone; CTDa, attenuated CTD;

CVAD, cyclophosphamide-vincristine-doxorubicin-dexamethasone; MP, melphalan-prednisone.

**Figure legends**

**Figure 1.** Survival according to bisphosphonate therapy (intent-to-treat population): (A) progression-free survival; and (B) overall survival.

**Figure 2.** Survival according to induction therapy regimen in the intensive therapy pathway (per-protocol population): (A) progression-free survival; (B) overall survival; (C) overall survival in patients with favorable iFISH profiles; (D) overall survival in patients with adverse iFISH profiles. Abbreviations: CTD, cyclophosphamide-thalidomide-dexamethasone; CVAD, cyclophosphamide-vincristine-doxorubicin-dexamethasone.

**Figure 3.** Survival according to therapy regimen in the non-intensive therapy pathway (intent-to-treat population): (A) progression-free survival; (B) overall survival; (C) overall survival in patients with favorable iFISH profiles; (D) overall survival in patients with adverse iFISH profiles. Abbreviations: CTD, cyclophosphamide-thalidomide-dexamethasone; CTDa, attenuated CTD; CVAD, cyclophosphamide-vincristine-doxorubicin-dexamethasone; MP, melphalan-prednisone.

**Figure 4.** Survival according to thalidomide maintenance therapy regimen (intent-to-treat population): (A) progression-free survival; and (B) overall survival; (C) overall survival in patients with favorable iFISH profiles; (D) overall survival in patients with adverse iFISH profiles. Survival times reflect time since second randomization.
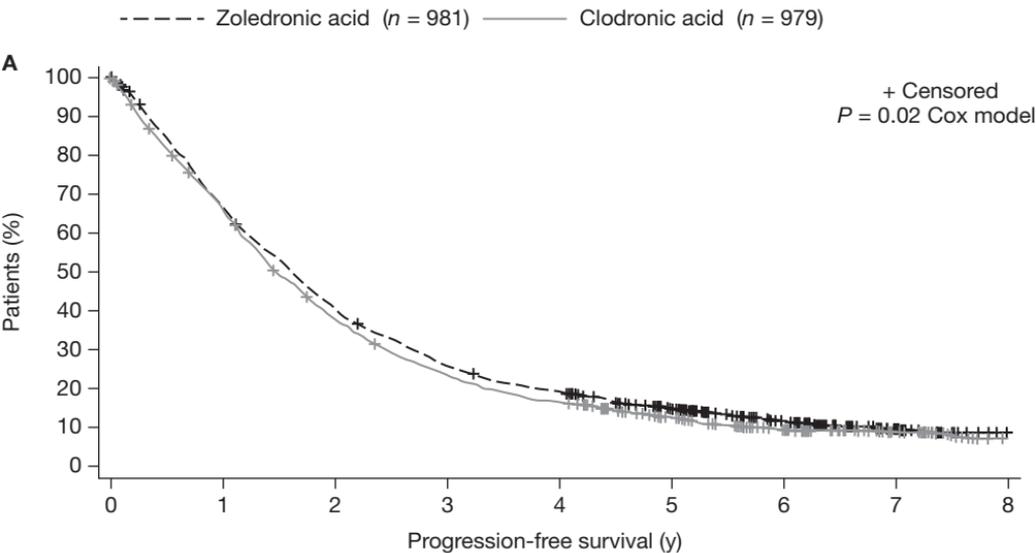
21

**Figure 1**
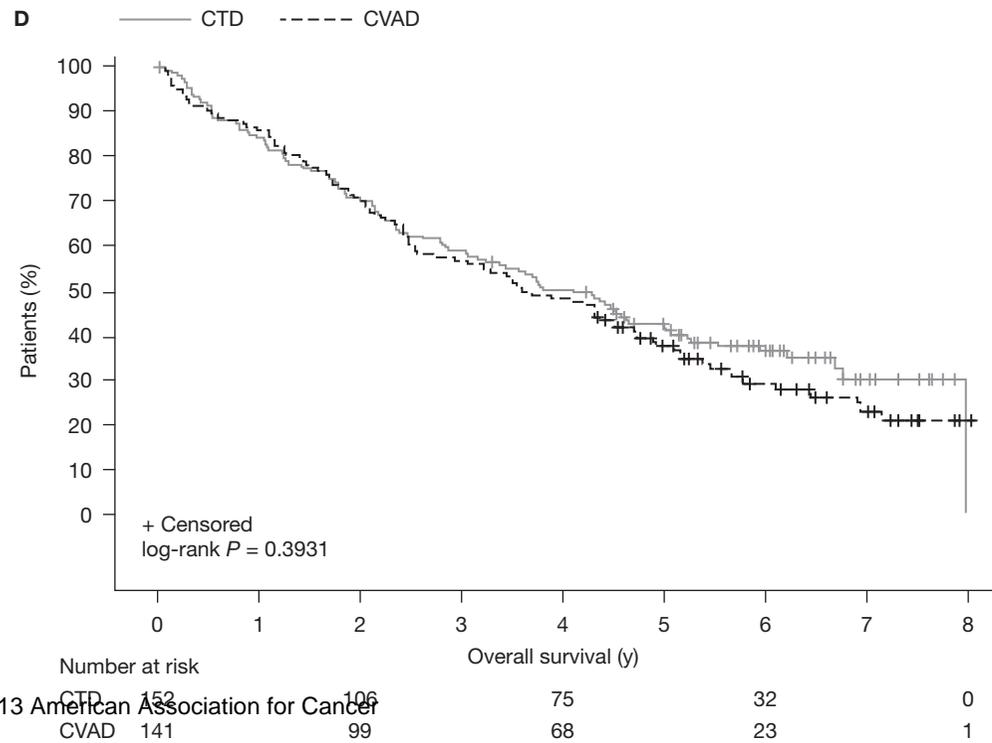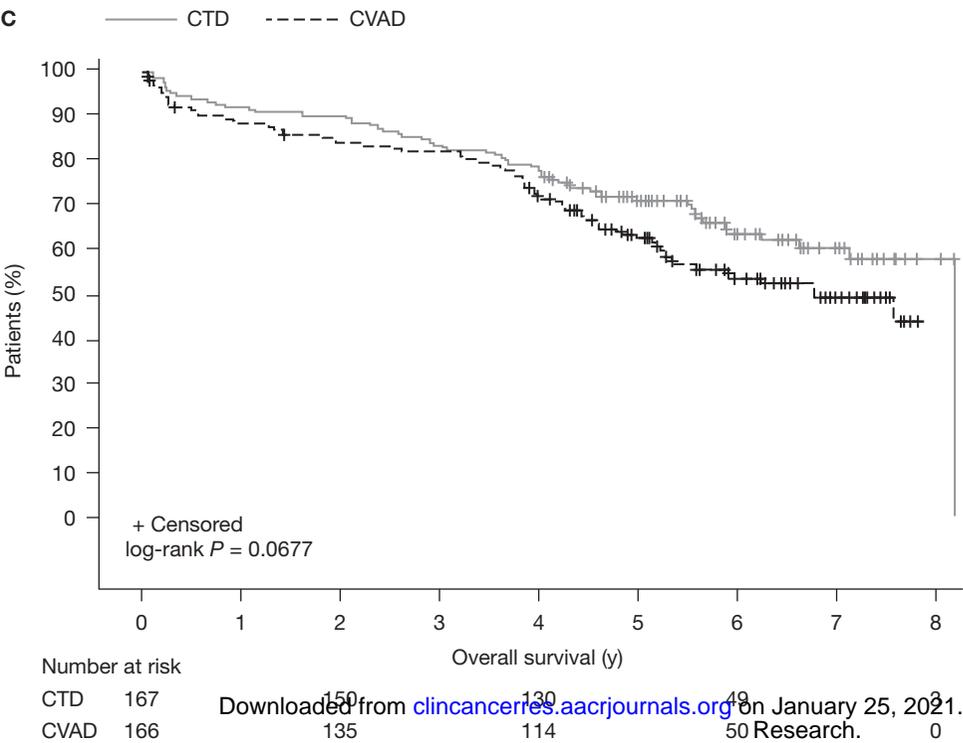
**Figure 2**

**Figure 3**

**Figure 4**

**A**  - - - - Maintenance  —— No maintenance

Patients (%)

*P* < 0.0001 Cox model

Progression-free survival (years from maintenance randomization)

Number at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Maintenance | 408 | 261 | 189 | 137 | 97 | 60 | 26 | 4 |
| No maintenance | 410 | 240 | 142 | 91 | 61 | 35 | 22 | 3 |

**B**  - - - - Maintenance  —— No maintenance

Patients (%)

*P* = 0.70 Cox model

Overall survival (years from maintenance randomization)

Number at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Maintenance | 408 | 369 | 320 | 276 | 215 | 133 | 61 | 11 |
| No maintenance | 410 | 369 | 332 | 283 | 222 | 136 | 67 | 12 |

**C**  - - - - Maintenance  —— No maintenance

Patients (%)

+ Censored
log-rank *P* = 0.5874

Overall survival (years from maintenance randomization)

Number at risk

| | | | | |
|---|---|---|---|---|
| Maintenance | 126 | 98 | 32 | |
| No maintenance | 129 | 103 | 37 | 0 |

**D**  - - - - Maintenance  —— No maintenance

Patients (%)

+ Censored
log-rank *P* = 0.0099

Overall survival (years from maintenance randomization)

Number at risk

| | | | | |
|---|---|---|---|---|
| Maintenance | 98 | 52 | 8 | 0 |
| No maintenance | 98 | 66 | 23 | 0 |

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# Clinical Cancer Research

## Long-Term Follow-Up of MRC Myeloma IX Trial: Survival Outcomes with Bisphosphonate and Thalidomide Treatment

Gareth J. Morgan, Faith E Davies, Walter M Gregory, et al.

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