Thalidomide *versus* dexamethasone for the treatment of relapsed and/or refractory multiple myeloma: results from OPTIMUM, a randomized trial

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ABSTRACT

Background
Thalidomide has potent antimyeloma activity, but no prospective, randomized controlled trial has evaluated thalidomide monotherapy in patients with relapsed/refractory multiple myeloma.

Design and Methods
We conducted an international, randomized, open-label, four-arm, phase III trial to compare three different doses of thalidomide (100, 200, or 400 mg/day) with standard dexamethasone in patients who had received one to three prior therapies. The primary end-point was time to progression.

Results
In the intent-to-treat population (N=499), the median time to progression was 6.1, 7.0, 7.6, and 9.1 months in patients treated with dexamethasone, and thalidomide 100, 200, and 400 mg/day, respectively; the difference between treatment groups was not statistically significant. In the per-protocol population (n=465), the median time to progression was 6.0, 7.0, 8.0, and 9.1 months, respectively. In patients who had received two or three prior therapies, thalidomide significantly prolonged the time to progression at all dose levels compared to the result achieved with dexamethasone. Response rates and median survival were similar in all treatment groups, but the median duration of response was significantly longer in all thalidomide groups than in the dexamethasone group. Adverse events reported in the thalidomide groups, such as fatigue, constipation and neuropathy, confirmed the known safety profile of thalidomide.

Conclusions
Although thalidomide was not superior to dexamethasone in this randomized trial, thalidomide monotherapy may be considered an effective salvage therapy option for patients with relapsed/refractory multiple myeloma, particularly those with a good prognosis and those who have received two or three prior therapies. The recommended starting dose of thalidomide monotherapy is 400 mg/day, which can be rapidly reduced for patients who do not tolerate this treatment. *(Clinical trial registration number: NCT00452569)*

Key words: thalidomide, dexamethasone, multiple myeloma, prior therapy, time to progression.

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Introduction

Current treatments for multiple myeloma (MM) offer patients periods of remission in response to therapy, followed by relapse. Patients typically require multiple lines of therapy which are separated by progressively shorter periods of response.[1,2] Nevertheless, survival rates in MM patients have improved in recent years, due in part to the introduction of novel therapies, such as thalidomide, lenalidomide, and bortezomib.[3]

To date, no randomized controlled trial has evaluated thalidomide monotherapy in patients with relapsed and/or refractory MM. However, two systematic literature reviews have summarized the findings from phase II studies evaluating thalidomide in this setting.[4,5] Glasmacher *et al.* reviewed the results from 42 clinical trials involving a total of 1674 patients; the dose of thalidomide used in these studies varied from 50 to 800 mg/day.[4] Overall, thalidomide monotherapy produced a response rate of 29.4%, including a modest complete response rate of 1.6%. Median survival was 14 months (range, 5-58 months) and 1-year survival was 60%. Similar results were reported by Prince *et al.*, who assessed a more restricted subset of nine large published trials involving a total of 712 patients.[5] They found a response rate of 29.8%, including a complete response rate of 1.6%. Reported 1-year overall survival rates ranged from 49% to 86%. These results are generally comparable to those achieved with dexamethasone monotherapy,[6,7] which is considered a standard treatment option for patients with relapsed and/or refractory MM and has been used as a control arm in several recent randomized trials.[8-10]

The optimal dose of thalidomide when used as monotherapy in this setting is unknown. In the studies included in the analyses mentioned above, doses of thalidomide ranged from 50 mg/day to 800 mg/day. In 2005, based on a request from the European Union (EU) regulatory authorities, we initiated the first prospective, randomized controlled trial to compare the efficacy and safety of thalidomide, at three different doses, with dexamethasone in patients with relapsed and/or refractory MM who had received one to three prior therapies.

Design and Methods

In order to determine the optimal dose of thalidomide monotherapy in patients with relapsed and/or refractory MM, as requested by EU regulatory authorities, we conducted a randomized, open-label, parallel-group, active-controlled, four-arm, phase III trial. The primary objective was to compare the time to progression (TTP) in patients with relapsed and/or refractory MM treated with three different doses of thalidomide (100, 200, or 400 mg/day) with the TTP in patients treated with dexamethasone, and to select the optimum dose of thalidomide in terms of time to progression and toxicity. Secondary objectives were to compare each dose of thalidomide with dexamethasone in terms of the following outcomes: response rate, progression-free survival, and overall survival. The safety of thalidomide and dexamethasone were also assessed; particular attention was paid to the evaluation of neuropathy in patients treated with thalidomide. The final protocol was approved by independent ethics committees at each participating center, and the trial was designed and monitored in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient prior to entering the study.

Patients

Eligible patients were aged 18 years or more, had received one to three prior lines of therapy for MM, and required additional therapy due to disease progression. Patients with secretory MM and measurable monoclonal protein (M-protein) in serum (>10 g/L of immunoglobulin [Ig] G M-protein and >5 g/L IgA M-protein) or urine (≥200 mg/24 h) were eligible. Patients with the rare subclasses of IgD, IgE, or IgM were allowed to participate if the level of M-protein was >5 g/L in the serum or ≥200 mg/24 h in the urine; patients with Waldenström's macroglobulinemia were excluded. Other inclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status scores of 0, 1, or 2; and life expectancy of more than 3 months. Patients had to be willing and able to adhere to the study visit schedule and other protocol requirements, and provide written informed consent. For 4 weeks before starting treatment, during treatment, and 4 weeks after the last dose, women of child-bearing potential had to agree to use two methods of contraception: one effective (i.e. hormone therapy, tubal ligation) and one barrier (i.e. latex condom, diaphragm). Men had to agree to use barrier contraception (latex condom) when engaging in sexual activity during treatment and for 4 weeks after the last dose.

Exclusion criteria included: serum creatinine levels of >3.0 mg/dL; severe cardiac dysfunction (New York Heart Association class III or IV); grade 2 or higher peripheral neuropathy; or prior treatment with thalidomide or lenalidomide.

Study design and treatment

Screening tests for eligibility were performed no more than 28 days before the first day of treatment for invasive tests (i.e. electrocardiogram, nerve conduction studies, skeletal survey, and bone marrow collection) or 14 days for laboratory evaluations. Patients were stratified according to the number of prior therapies received (1 *versus* 2-3), prior autologous stem-cell transplantation (yes *versus* no), and disease stage based on the International Staging System (ISS; stage I or II *versus* III). Patients were randomized in a 1:1:1:1 fashion to dexamethasone (DEX) or thalidomide given at a dose of 100 mg/day (THAL 100), 200 mg/day (THAL 200), or 400 mg/day (THAL 400) for twelve 28-day cycles. All study medication consisted of capsules or tablets to be taken orally by patients at home. Treatment was administered in an open-label fashion. Dexamethasone was given at a dose of 40 mg/day on days 1-4, 9-12, and 17-20 of each 28-day cycle for the first four cycles, and then on days 1-4 only for the subsequent eight cycles. Thalidomide was given daily at the appropriate dose for 12 cycles. Treatment beyond 12 cycles was left to the investigator's discretion.

Patients were assessed at baseline and every 4 weeks thereafter until week 48. A visit to confirm disease progression was conducted within 1-4 weeks after the first evidence of disease progression. A final visit was scheduled 30-33 days after the last dose had been administered, and the follow-up period began immediately after this visit. During follow-up, patients were assessed every 6 weeks until disease progression and every 12 weeks after disease progression was observed. All patients who discontinued treatment for any reason other than disease progression or death — including patients who completed the planned 12 cycles of therapy — were followed for disease progression and/or survival until study closure. To minimize bias in this open-label study, response and TTP were also assessed by an independent review committee that was blinded to the type of treatment each patient received. Study closure was triggered when progression had occurred in 160 patients in the DEX and THAL 400 groups, as documented by the independent review committee, and the last patient's end-of-treatment visit was completed.

Assessment and statistical analysis

The primary end-point was TTP, defined as the time from randomization to the date of first documentation of progressive disease, according to the European Group for Blood and Marrow Transplantation (EBMT) criteria,[11] as determined by the independent review committee. Patients without documented progression during the treatment or follow-up periods were considered a censored observation and were censored at the date of their last documented progression-free disease assessment. Secondary end-points included response rate (complete response plus partial response), progression-free survival, overall survival, and duration of response. Response was assessed using EBMT criteria at each cycle and confirmed at 8 weeks.[11] Progression-free survival was defined as the time from randomization to the time of first documentation of disease progression or death, and overall survival was defined as the time from randomization to the time of death from any cause.

The average daily dose was calculated as the total dose received during the treatment period divided by the number of days that the patient was scheduled to receive a dose. Adverse events were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0. Neuropathy was assessed using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity questionnaire and nerve conduction studies.

Additional exploratory analyses were performed for TTP within the following subgroups: number of prior therapies (1 *versus* 2-3); prior autologous stem cell transplantation (yes *versus* no); ISS stage (I or II *versus* III); age (<65 *versus* ≥65 years); ECOG performance status (0 *versus* 1 *versus* 2); geographic region (EU *versus* non-EU); chromosome 13 deletion (yes *versus* no); gender (male *versus* female); baseline serum β_2-microglobulin (≤3.5 *versus* >3.5 mg/L); and cytogenetic risk (standard *versus* high risk). High risk was defined by the presence of chromosome 17 deletion and/or translocation t(4;14). Cytogenetic profiles were determined in a central laboratory based on samples collected during screening.

The target accrual was 496 patients (124 in each treatment arm). The primary analysis consisted of three ordered comparisons of TTP with a stratified log-rank test, each conducted at a two-sided alpha level of 0.05. Stratification was based on the three factors used to stratify the randomization (number of prior therapies, prior autologous stem cell transplantation, and ISS stage). The first comparison was between the DEX and THAL 400 groups. If this comparison was *not* statistically significant, then the analysis was to be stopped and the conclusion would be that none of the three thalidomide doses provided superior TTP compared with dexamethasone at an alpha level of 0.05. If this first comparison *was* statistically significant, then the second comparison (DEX *versus* THAL 200) was to be conducted. If this comparison was not statistically significant then the analysis was to be stopped and the conclusion would be that TTP differed significantly at the overall 0.05 alpha level between DEX and THAL 400 only. If the second comparison was statistically significant, then the third comparison (DEX *versus* THAL 100) was to be conducted. If only one thalidomide group demonstrated significantly superior TTP compared with dexamethasone, it would be considered the optimum thalidomide dose. If two or more thalidomide doses provided superior TTP compared with dexamethasone and were considered equally efficacious (difference in median TTP <6 weeks), then the dose with the lowest toxicity proportion (defined by the proportion of patients with a dose reduction, interruption, or discontinuation) was to be selected as the optimum dose. If two or more thalidomide doses were considered equally toxic (toxicity proportion within 15% of the lowest toxicity proportion achieved), the lowest dose was to be selected as the optimum dose.

Results

Patients' characteristics

Between March 2006 and January 2009, 499 patients were randomized (intent-to-treat population) from 67 sites in Europe, India, Philippines, and South Africa. A total of 497 patients received at least one dose of study medication (safety population), and 465 had no major deviations from protocol (per-protocol population). The most common deviation from protocol was lack of valid assessment by the independent review committee (n=20; THAL 100 n=3, THAL 200 n=5, THAL 400 n=5, and DEX n=7). Other deviations included administration of study treatment as first-line therapy (n=3; n=1 each in the THAL 100, THAL 400, and DEX groups) or to patients who had received ≥3 prior therapies (n=3; THAL 100 n=1 and THAL 200 n=2); no study treatment given (DEX n=2); administration of the incorrect dose of thalidomide (THAL 400 n=2); lack of serum M-protein assessment within 28 days prior to randomization (THAL 400 n=2 and DEX n=1); inclusion of patients refractory to dexamethasone (THAL 100 n=1); use of prohibited antimyeloma treatment during the study period (THAL 400 n=1); and the inclusion of patients who had received dexamethasone (THAL 400 n=1) or corticosteroids (DEX n=1) within 4 weeks prior to randomization.

Of the 499 randomized patients, 121 (24%) completed the planned 12 cycles of therapy; major reasons for discontinuation were disease progression (53%) and adverse events (10%). Other reasons included withdrawal of informed consent (8%), death (4%), or loss to follow-up (0.4%) (Figure 1).

The distribution of the patients' baseline characteristics was comparable among the four treatment groups (Table 1). Approximately 30% of patients were treated at centers outside of Europe. The median age was approximately 64 years, and most patients had ISS stage I or II disease. The median time since diagnosis was 2.5 years, and most patients had received one prior therapy for relapsed and/or refractory MM. The most common reason for change in last treatment was relapse or disease progression (72%) followed by resistance to current therapy (13%), which may explain the relatively short interval between diagnosis and randomization for some patients (Table 1). Approximately a third of patients had previously undergone autologous stem cell transplantation, and 15% had received prior treatment with bortezomib. Patients were distributed evenly across the 3.5 mg/L baseline β_2-microglobulin cut-off in each treatment group. Approximately 50% of patients were assessed for cytogenetic risk, the majority of whom had standard-risk profiles. In each arm, 10-12% of the patients had high-risk cytogenetics (5% in the THAL 200 arm).

Time to progression

In the intent-to-treat population (N=499), the median TTP in the DEX, and THAL 100, 200 and 400 groups was 6.1, 7.0, 7.6, and 9.1 months, respectively (Figure 2A). The difference between the DEX and THAL 400 groups was not statistically significant [hazard ratio (HR), 0.73; 95% confidence interval (95% CI) 0.53-1.00; *P*=0.055). The estimated proportion of patients without disease progression at 1 year in the THAL 400 group was nearly double that in the DEX group (41% *versus* 23%). In the per-protocol population (n=465), the median TTP was 6.0, 7.0, 8.0, and 9.1 months, respectively. The difference between the DEX and THAL 400 groups was statistically significant (stratified log-rank

P=0.049), in favor of THAL 400.

Exploratory analyses were performed to compare TTP between the THAL groups and DEX in various populations within the intent-to-treat population. Notably, thalidomide at all dose levels produced significantly longer TTP than dexamethasone in patients who had received two or three lines of therapy before entering the study (Table 2). An advantage for thalidomide was also seen in younger patients (aged <65 years) and those with ISS stage I or II disease, lower β_2-microglobulin levels, and favorable cytogenetics (no chromosome 17 deletion and no translocation t(4;14) – patients with a t(4;14) translocation and a chromosome 17 deletion are typically considered refractory to thalidomide) (Table 2). In general, the benefit of thalidomide over dexamethasone was evident in patients with favorable prognostic factors, although benefit was also observed in patients who had received more than one prior therapy.

Response and survival

The overall response rate determined by the independent review committee in the DEX, THAL 100, THAL 200, and THAL 400 groups was 25%, 21%, 18%, and 21%, respectively (Table 3). Complete responses were observed in 2%, 3%, 2% and 2% of patients, respectively. There were no significant differences between the DEX and individual THAL groups in terms of response at weeks 24 and 48. There were higher response rates in the DEX group at the beginning of treatment because patients were given a high-dose DEX regimen for the first four cycles. Response rates changed once the DEX patients received low-dose DEX at cycle 5.

A total of 27, 13, 11, and 17 patients in the DEX, THAL 100, THAL 200, and THAL 400 groups, respectively, had confirmed response followed by progression or death and were, therefore, eligible for duration of response analysis. Relatively low numbers were available because of the censoring rule applied in this analysis, according to which duration of response was censored in patients who were considered responders and who had completed treatment, or were ongoing at data cut-off, without any end criteria. The same rule applied to patients who had no end criteria at withdrawal and in those who did not respond (response duration zero). The median duration of response was signif-

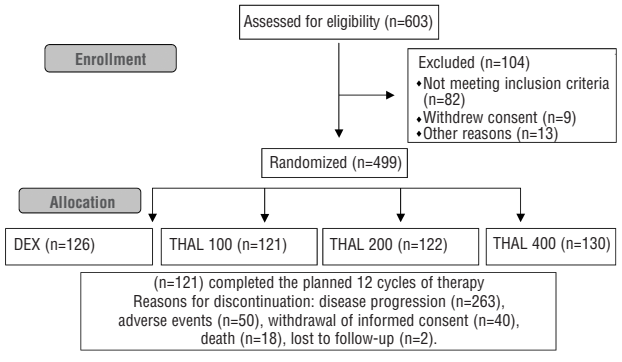


Figure 1. CONSORT 2010 flow diagram of participants in the trial.

Table 1. Patients' characteristics at baseline in the intent-to-treat population.

Characteristic	DEX (n=126)	THAL 100 (n=121)	THAL 200 (n=122)	THAL 400 (n=130)
Age, median years (range)	63 (40-86)	64 (37-86)	63 (33-85)	65 (38-84)
Male sex, %	45	45	46	59
International Staging System stage, %				
I	39	44	43	40
II	29	32	30	35
III	32	24	27	25
Time since MM diagnosis, median years (range)	2.5 (0.05-14.0)	2.7 (0.4-18.4)	2.6 (0.2-15.5)	2.5 (0.1-13.4)
Treated at centers outside of Europe, %	34	28	32	31
Prior treatment regimens, %				
1	57	56	57	57
2	29	28	30	32
3	14	15	12	12
Prior autologous stem cell transplantation, %	34	34	32	32
Prior bortezomib, %	13	11	14	20
Baseline β_2-microglobulin, n. (%)				
≤3.5 mg/L	52 (41.3)	58 (47.9)	58 (47.5)	56 (43.1)
>3.5 mg/L	73 (57.9)	62 (51.2)	64 (52.5)	74 (56.9)
Missing	1 (0.8)	1 (0.8)	0	0
Baseline cytogenetic risk*, n. (%)				
Standard risk	46 (36.5)	46 (38.0)	56 (45.9)	52 (40.0)
High risk	15 (11.9)	14 (11.6)	6 (4.9)	14 (10.8)
Not assessed	65 (51.6)	61 (50.4)	60 (49.2)	64 (49.2)

** Standard risk: neither chromosome 17 deletion nor translocation (4:14) is present; High risk: presence of either chromosome 17 deletion or translocation (4:14); not assessed: unable to classify subject as a result of either missing data or test failure for chromosome 17 deletion or translocation (4:14). DEX: dexamethasone; THAL: thalidomide.*

icantly longer in patients in all the THAL groups than in those in the DEX group (Figure 2B). In the THAL 200 group, for example, the median duration of response was approximately double that in the DEX group (13.1 *versus* 6.5 months; *P*=0.005). The median duration of responses was similarly high in the THAL 100 group (12.7 months; *P*=0.046) and THAL 400 group (11.6 months; *P*=0.016) *versus* DEX.

The median progression-free survival was 6.0 months in the DEX group and 6.7, 7.3, and 8.1 months in the THAL 100, THAL 200, and THAL 400 groups, respectively. The difference between the patients in the THAL 400 and DEX groups had a *P* value of 0.051 and was not, therefore, statistically significant in the intent-to-treat group (HR, 0.74; 95% CI 0.55-1.00; *P*=0.051). However, it was statistically significant in the per-protocol population (HR, 0.72; *P*=0.039).

The median overall survival has not been reached in the DEX group and the THAL 400 group (Figure 2C). In the THAL 100 and THAL 200 groups, the median survival was 30.0 and 25.6 months, respectively. There was no significant difference in survival between the DEX group and the individual THAL groups.

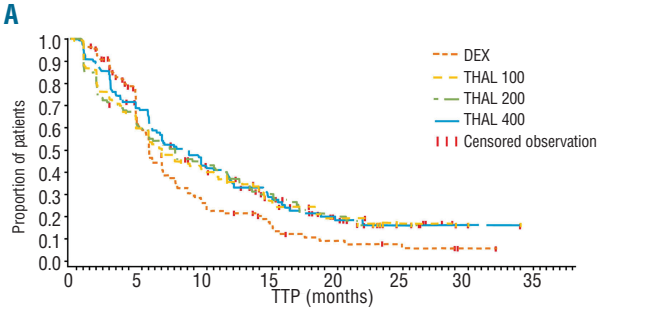
Safety

Of the 499 patients randomized, 497 received at least one dose of study medication and were, therefore, included in the safety assessment. Overall, 24% of patients completed 12 cycles of therapy; the proportion of patients completing therapy was higher in the THAL groups than in the DEX group. The median number of treatment cycles received was also lower in the DEX group than in the THAL groups (6 *versus* 7 cycles, respectively). The median average dose intensity was 40 mg/day in the DEX group and 100, 198, and 256 mg/day in the THAL 100, THAL 200, and THAL 400 groups, respectively. The median time to first dose reduction was 2.6 months in the DEX group and 4.0, 2.1, and 1.0 months in the THAL 100, THAL 200, and THAL 400 groups, respectively. Adverse events led to treatment discontinuation in 17% of patients in the DEX group and 12%, 15%, and 18% of patients in the THAL 100, THAL 200, and THAL 400 groups, respectively. The most common treatment-emergent adverse events that led to discontinuation were nervous system disorders (4.0%), renal failure (1.8%) and pneumonia (0.8%) in patients treated with thalidomide, and infections (4.0%) and psychiatric disorders (3.2%) in patients treated with dexamethasone.

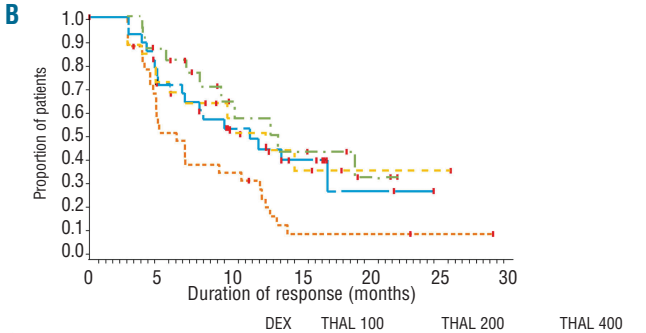
In the THAL groups, the most frequently reported treatment-emergent adverse events of any grade were constipation (42.1%), fatigue (23.9%), asthenia (13.9%), anemia (13.1%), dizziness (12.9%), back pain (12.1%), and nausea (11%). The most commonly reported treatment-emergent adverse events in the DEX group were fatigue (22.6%), insomnia (19.4%), constipation (16.1%), peripheral edema (14.5%), diarrhea (14.5%), arthralgia (12.1%), asthenia (12.1%), anemia (11.3%), bone pain (10.5%) and bronchitis (10.5%).

Grade 3 or 4 treatment-emergent adverse events were reported in 38% of patients treated with dexamethasone and 44% of patients treated with thalidomide, and appeared to be dose-related (32% in THAL 100, 38% in THAL 200, and 60% in THAL 400). The incidence of grade 3 or 4 hematologic adverse events was low in all treatment groups (Table 4). The most commonly reported grade 3 or 4 treatment-emergent adverse events were neutropenia (THAL 6% and DEX 0%), anemia (THAL 6% and DEX 4%), fatigue (THAL 5% and DEX 2%), and pneumonia (THAL 4% and DEX 4%). Febrile neutropenia of grade 3 or 4 severity was reported for only one patient in the THAL 100 group. Grade 3 or 4 constipation was reported in 1% of patients in the THAL 200 group and 5% in the THAL 400 group. Severe rash was reported in 2% of patients in the THAL 400 group.

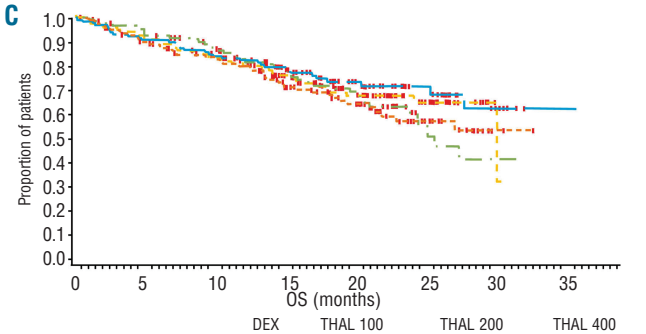
Clinical evidence of neuropathy was seen in all THAL groups (34%, 35%, and 41% of patients in the THAL 100, 200, and 400 groups, respectively). The incidence of grade 2 or higher neuropathy increased as the dose of thalidomide increased (12%, 20%, and 22%, for THAL 100, 200, and



	DEX	THAL 100	THAL 200	THAL 400
Median TTP, months	6.1	7.0	7.6	9.1
Hazard ratio *versus* DEX (95% CI)	NA	0.88 (0.63-1.21)	0.86 (0.63-1.19)	0.73 (0.53-1.00)
P value *versus* DEX	NA	0.421	0.363	0.055



	DEX	THAL 100	THAL 200	THAL 400
Median duration of response, months	6.5	12.7	13.1	11.6
Hazard ratio *versus* DEX (95% CI)	NA	0.42 (0.18-1.02)	0.23 (0.08-0.68)	0.4 (0.19-0.86)
P value *versus* DEX	NA	0.046	0.005	0.016



	DEX	THAL 100	THAL 200	THAL 400
Median OS, months	Not reached	30.0	25.6	Not reached
Hazard ratio *versus* DEX (95% CI)	NA	0.86 (0.55-1.35)	1.03 (0.66-1.59)	0.84 (0.52-1.34)
P value *versus* DEX	NA	0.521	0.904	0.457

Figure 2. According to treatment group in the intent-to-treat population: (A) time-to-progression (TTP); (B) duration of response; and (C) overall survival (OS). DEX: dexamethasone; NA: not applicable; THAL: thalidomide.

400, respectively). Severe (grade 3 or 4) neuropathy occurred in 2% of patients in the THAL 200 group and 1% of patients in the THAL 400 group (Table 4). Patients with preexisting neuropathy were predisposed to either development or aggravation of neuropathy during thalidomide treatment. Clinical evidence of neuropathy was confirmed by electrophysiological studies, such as measurement of sensory nerve action potentials (Table 5).

The incidence of any grade of venous thromboembolism was similar in the THAL groups and the DEX group (3.2% each), and the incidence of grade 3 or 4 venous thromboembolic events was similarly low in all treatment groups (1-2%). Events reported in the THAL groups included deep-vein thrombosis, thrombophlebitis, pulmonary embolism, and retinal vein thrombosis. In the DEX group, events included deep-vein thrombosis and pulmonary embolism. Patients with a history of venous thromboembolism were not predisposed to experience thromboembolic events in any treatment group. There was no evidence of a pattern with regard to the timing of venous thromboembolism. The use of antithrombotic agents such as aspirin was more common in the THAL groups than in the DEX group (36% *versus* 15%, respectively).

Cardiac arrhythmias were more frequently reported in the THAL groups than in the DEX group (8% *versus* 2%). In the THAL groups, reported arrhythmias included: bradycardia (3%); syncope (2%); arrhythmia, cardio-respiratory arrest, and palpitations (1% each); sick sinus syndrome (0.5%); and Adams-Stokes syndrome, first degree atrioventricular block, bradyarrhythmia, sinus bradycardia, and tachycardia (0.3% each). In the DEX group, cardiac arrhythmias included syncope, tachycardia, and sudden death (1% each). Compared with the DEX group, more patients in the THAL groups had a history of cardiac arrhythmia and were more likely to be receiving a beta-blocker (26% *versus* 17%).

The incidence of adverse events was not affected by age or gender. Older patients (aged ≥65 years) treated with thalidomide had a slightly higher incidence of adverse events than younger patients (95% *versus* 89%), whereas the incidence in older and younger patients treated with dexamethasone was comparable (88% *versus* 90%). In female patients, the incidence of adverse events was 93% with thalidomide and 91% with dexamethasone. In male patients, the incidence of adverse events was 91% with thalidomide and 88% with dexamethasone.

Discussion

Since the first recognition by Barlogie *et al.* that thalidomide has substantial antimyeloma activity,[12] several questions have arisen regarding its optimal dose, and its efficacy

Table 2. Time to progression according to treatment subgroup.

	DEX	THAL 100	THAL 200	THAL 400
One prior therapy (n=277)				
Number of patients	69	70	68	70
Median TTP, months (95% CI)	9.0 (6.1-10.5)	6.3 (5.0-10.0)	8.0 (5.2-13.2)	9.9 (6.6-12.0)
Log-rank *P* value	–	0.552	0.875	0.747
Two or more prior therapies (n=222)				
Number of patients	57	51	54	60
Median TTP, months (95% CI)	5.0 (5.0-6.0)	8.0 (5.0-12.0)	7.0 (4.0-10.0)	9.1 (6.0-12.4)
Log-rank *P* value	–	0.014	0.043	0.003
International Staging System stage I or II (n=356)				
Number of patients	84	91	86	95
Median TTP, months (95% CI)	6.3 (6.0-8.1)	10.1 (6.8-14.4)	8.1 (5.2-13.1)	10.0 (7.0-12.4)
Log-rank *P* value	–	0.029	0.162	0.019
International Staging System stage III (n=143)				
Number of patients	42	30	36	35
Median TTP, months (95% CI)	5.2 (5.0-8.1)	3.0 (1.8-5.0)	6.1 (3.7-9.4)	6.1 (3.0-9.1)
Log-rank *P* value	–	0.015	0.961	0.614
Baseline serum β_2-microglobulin level ≤3.5 mg/L (n=224)				
Number of patients	52	58	58	56
Median TTP, months (95% CI)	7.11 (6.04, 9.21)	11.04 (6.82, 14.89)	7.64 (3.68, 12.18)	11.04 (7.07, 14.82)
Log-rank *P* value	–	0.163	0.800	0.069
Baseline serum β_2-microglobulin level >3.5 mg/L (n=273)				
Number of patients	73	62	64	74
Median TTP, months (95% CI)	5.82 (5.04, 7.04)	5.96 (3.29, 7.04)	8.04 (6.04, 13.14)	7.04 (5.04, 10.46)
Log-rank *P* value	–	0.930	0.119	0.304
Baseline cytogenetic risk = Standard risk (n=200)				
Number of patients	46	46	56	52
Median TTP, months (95% CI)	6.04 (5.04, 9.04)	10.11 (6.00, 14.89)	8.07 (6.04, 14.61)	12.54 (6.07, 16.82)
Log-rank *P* value	–	0.014	0.036	0.002
Baseline cytogenetic risk = High risk (n=49)				
Number of patients	15	14	6	14
Median TTP, months (95% CI)	5.71 (5.04, 10.04)	2.11 (2.04, 5.07)	4.66 (2.04, 21.18)	5.00 (3.11, 7.25)
Log-rank *P* value	–	0.022	0.868	0.904

DEX: dexamethasone; DNE: does not exist (due to small number of events); THAL: thalidomide.

and safety in this setting. The present study was the first randomized controlled trial to evaluate thalidomide monotherapy in patients with relapsed and/or refractory MM and was designed to answer many of these questions. Although the study did not demonstrate the superiority of thalidomide over dexamethasone in terms of TTP, our results confirm those from previous uncontrolled trials[13-16] indicating that thalidomide is an effective treatment option for relapsed and/or refractory MM and has a dose-dependent safety profile.

The median TTP achieved with a starting dose of thalidomide 400 mg/day was 3 months longer than that achieved with dexamethasone (9.1 *versus* 6.1 months) but the difference did not reach statistical significance (P=0.055). Previous studies had shown that dexamethasone is an acceptable treatment option for patients with MM.[6,7] In one study, dexamethasone produced a response rate of approximately 25% and a median duration of tumor control of 9 months in patients with relapsed and/or refractory MM; these results were comparable to those achieved with the combination of dexamethasone, vincristine, and doxorubicin (VAD), suggesting that most of the antimyeloma effects of this standard regimen can be attributed to dexamethasone.[6] Our study results show that, in patients with relapsed and/or refractory MM, thalidomide monotherapy is at least as effective as standard dexamethasone.

The observed TTP with dexamethasone in our trial (6.1 months) was longer than expected (5 months). This expectation was based on results from recent phase III studies in which dexamethasone was used as a control; dexamethasone produced a median TTP of 3.49 months in the Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial[8] and 4.7 months in the MM-009 and MM-010 trials.[9,10] One possible reason for the discrepancy may lie in the types of patients enrolled. Compared with the APEX, MM-009, and MM-010 studies, our study had fewer patients who had received two or more prior therapies. This may have been a result of the high proportion of patients in our study (approximately 30%) who were treated at centers outside of Europe, where fewer treatment options may have been available. Our less heavily pretreated population may account for the better-than-expected results in the control arm.

It should be noted that the definition of TTP used in this study differed from that used in other recent phase III studies. In our study, patients who received subsequent antimyeloma therapy before independent review committee-documented progression were followed until progression rather than being censored. Patients without documented progression, including those who received subsequent therapy, were censored at the date of their last disease assessment prior to data cut-off. Sensitivity analyses using TTP revealed a statistically significant improvement in TTP in the THAL 400 group compared to that in the DEX group. It should also be noted that, in the subgroup of patients who had received two or three prior lines of therapy, thalidomide, at all dose levels studied, prolonged TTP significantly compared with dexamethasone.

Response rates were similar in all four treatment groups, but the duration of response was significantly longer with thalidomide (at any dose) than with dexamethasone. Dexamethasone appeared to produce early responses (within 5 months) of short duration. This pattern may correspond with the protocol-specified reduction in dexamethasone dose intensity after the fourth cycle, which was required to conform to other recent phase III trials.[8-10] Compared with this dexamethasone regimen, daily thalidomide appeared to provide more durable responses. Moreover, overall survival was similar in all four groups of patients. This comparable overall survival between the groups is likely to be due to two factors. Firstly, as this study focused on efficacy (response rate, TTP, progression-free survival) and safety, the survival data were gathered at a relatively early time-point and patients were not followed for long enough to obtain reasonable overall survival estimates. Secondly, the proportion of censored patients in this analysis was high in all four treatment groups (65-75%), resulting in few observed deaths. This may also have been confounded by the use of subsequent therapy.

The safety data from this study confirm and extend our

Table 3. Best response according to the independent review committee.

Best response, %	DEX (n=126)	THAL 100 (n=121)	THAL 200 (n=122)	THAL 400 (n=130)
Overall response rate*	25	21	18	21
Complete response	2	3	2	2
Partial response	23	18	16	19
Minimal response	17	16	16	17

*Defined as complete response + partial response. DEX: dexamethasone; THAL: thalidomide.

Table 4. Clinically relevant grade 3 or 4 adverse events.

Adverse event, %	DEX (n=124)	THAL 100 (n=122)	THAL 200 (n=123)	THAL 400 (n=128)
Neutropenia	0	7	7	6
Anemia	4	6	6	6
Thrombocytopenia	0	1	2	1
Constipation	0	0	1	5
Fatigue	2	2	2	11
Bradycardia	0	0	0	1
Rash	0	0	0	2
Neuropathy	0	0	2	1
Venous thromboembolism	2	1	1	1

DEX: dexamethasone; THAL: thalidomide.

Table 5. Assessment of peripheral neuropathy in patients treated with thalidomide.

%	THAL 100 (n=122)	THAL 200 (n=123)	THAL 400 (n=128)	THAL Total (N=373)
Sensory neuropathy grade ≥2	12	20	22	18
Discontinued THAL due to neuropathy	1	4	3	3
Clinical evidence of neuropathy	34	36	41	37
Decline in SNAP >50%	21	22	23	22
Clinical evidence of neuropathy and decline in SNAP >50%	10	8	14	11

SNAP: sensory nerve action potential; THAL: thalidomide.

knowledge of the effects of thalidomide.[4] Severe adverse events associated with thalidomide included fatigue, constipation, neutropenia, and anemia. Rates of severe rash, bradycardia, neuropathy, and venous thromboembolism were low. As expected, thalidomide was associated with a higher risk of cardiac arrhythmias, mostly bradycardia and syncope. However, more patients in the THAL groups had a history of arrhythmias and were more likely to have been taking beta-blockers, which may have contributed to the increased incidence of sinus bradycardia. Dose-dependent peripheral neuropathy was observed clinically with thalidomide which, as previously observed,[17] correlated with electrophysiological findings. It is of note, however, that among patients with clinical evidence of peripheral neuropathy, concomitant reductions in sensory nerve action potentials of greater than 50% were observed in only around a fourth of patients (Table 5). Hence, in routine practice clinical evidence and symptoms appear to be the most reliable indicators of peripheral neuropathy. Dose reductions for neuropathy allowed for continued thalidomide treatment. For example, in the THAL 400 group, the mean daily dose was 256 mg, but treatment duration was similar to that in the other treatment groups. There was no indication of an increased risk of venous thromboembolism with thalidomide monotherapy at any of the doses studied. A large proportion of patients (36%) treated with thalidomide were also given antithrombotic agents. This was as per-protocol, as investigators were concerned about the prothrombotic effects observed when thalidomide is used in combination with other active agents,[18,19] although the risk appears to be reduced when the drug is given as monotherapy.[20]

Combination therapy regimens are now the standard of care for relapsed and/or refractory MM, and most patients should continue to receive combination therapy. Nevertheless, based on our findings, thalidomide monotherapy represents an effective salvage therapy option, particularly for patients with a good prognosis and those who have already received two or three regimens for relapsed and/or refractory MM. Thalidomide was associated with low rates of hematologic adverse events and a low rate of venous thromboembolism, despite the fact that only about a third of patients received thromboprophylaxis. With regard to the optimal dose of thalidomide, the 400 mg/day dose generally provided better efficacy outcomes than lower doses. Sensitivity analyses also indicated improved TTP in the THAL 400 group *versus* the DEX group. However, the actual median dose received by patients in the THAL 400 group was 256 mg/day compared with 198 mg/day in the THAL 200 group. Patients in the THAL 200 group also had the longest duration of response and a lower number of serious adverse events. Based on these observations, a starting dose of 400 mg/day could be recommended for optimum efficacy with timely dose reductions for patients who cannot tolerate this treatment.

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