

ORIGINAL ARTICLE

# Low-dose vs. high-dose thalidomide for advanced multiple myeloma: a prospective trial from the Intergroupe Francophone du Myélome

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## Abstract

This multicentre prospective randomised trial compared the efficacy and safety of two doses of thalidomide in patients with relapsed or refractory myeloma. The study was designed to test the non-inferior efficacy and to confirm the better tolerability of low-dose thalidomide as compared to a higher dose. Four hundred patients were randomly assigned to receive either 100 or 400 mg/day of thalidomide. Dexamethasone treatment was added in both arms for patients with stable disease or treatment failure at 12 weeks. The primary endpoint was 1-year overall survival (OS). Thalidomide 100 mg/day was better tolerated than 400 mg/day with less high-grade somnolence, constipation, nausea/vomiting and peripheral neuropathy ( $P < 0.001$ ,  $P = 0.007$ ,  $P = 0.03$  and  $P = 0.007$ , respectively). In the per-protocol population (PP), the estimated 1-year OS rates were of 74.5% ( $n = 149$ ) and 67.3% ( $n = 156$ ) in the 400 and 100 groups, respectively. The upper limit of the difference between these rates was of 15.6% higher than the non-inferiority acceptable limit of 12.75%, and the hypothesis of non-inferiority of 100 could not be established ( $P = 0.14$ ). On the other hand, when intent-to-treat (ITT) population was analysed, the non-inferiority was demonstrated because the 1-year OS rates were of 72.8% ( $n = 195$ ) and 68.8% ( $n = 205$ ) in the same groups, leading to an upper limit of the difference of 11.49% lower than the non-inferiority acceptable limit. In addition, in patients alive 12 weeks postrandomisation and those who received thalidomide plus dexamethasone, there were no significant differences in response rates, time to progression, progression-free survival and OS between the two groups. Collectively, low-dose thalidomide 100 mg/day has significant activity in advanced myeloma with an improved safety profile and can be a good salvage therapy in combination with dexamethasone.

**Key words** thalidomide; multiple myeloma; low dose

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Thalidomide represents a major component of the therapeutic armamentarium of multiple myeloma (MM) in both newly diagnosed patients and those with relapsed or refractory disease (1, 2). However, despite its efficacy, the majority of patients treated with thalidomide will discontinue treatment because of toxicity, mainly peripheral neuropathy (PN). Thus far, doses of thalidomide ranging from 50 to 1200 mg/day have been evaluated in published trials, and the optimum daily dosage has yet to be established. In addition, it is still unclear whether thalidomide-related toxicity is a result of the total daily dose administered or is related to a cumulative effect in relation to the total duration of therapy. A retrospective study by the Intergroup Francophone du Myélome (IFM) (3) assessing 83 patients with advanced MM suggested the efficacy of 400 mg/day of thalidomide as a single agent but showed a high incidence of drug-related toxicity. Interestingly, in the latter study, the mean daily dose of thalidomide administered in the first 90 days of treatment was not found to influence disease response, overall survival (OS) nor disease-free survival (DFS). In contrast, a phase-II trial assessing single-agent thalidomide in advanced MM showed that disease response rates were higher and survival was longer especially in high-risk patients given more than 42 g of thalidomide in 3 months supporting a thalidomide dose-response effect in advanced MM (4). With this background, the IFM conducted a prospective multicentre randomised trial comparing the efficacy and safety of two doses of thalidomide in the treatment of patients with advanced MM.

## Patients and methods

### Study design and endpoints

This was a multicentre prospective non-inferiority trial performed by the IFM cooperative group in 49 centres in France and Belgium between December 2001 and October 2004. The study protocol was approved by the ethics committee of Lille University Hospital and the ethics committees from each participating centre in Belgium. Written informed consent was obtained from all patients. In this open-label study, patients were randomly assigned to 100 or 400 mg/day of thalidomide in a 1 : 1 ratio. Randomisation was centralised, using permutation blocks of size 2 or 4 within each centre, according to centre expected recruitment (block size used in each centre was unknown by centre investigators). The trial was sponsored by Celgene. The primary endpoint of the study was the 'per-protocol' (PP) comparison of OS at 1 year in the two study arms. Secondary objectives included the 'intention-to-treat' comparison of OS at 1 year in the two study arms. Other objectives included

disease response, time to first response during the first 12 weeks of treatment and time to progression after thalidomide alone and, for patients on thalidomide plus dexamethasone, disease response during the first 12 weeks of treatment, time to first response and time to progression. In addition, progression-free survival (PFS), OS and the occurrence of adverse events (AEs) were studied.

### Patients' inclusion and exclusion criteria

Inclusion criteria included patients aged  $\geq 18$  years diagnosed with advanced MM. Patients must have had received a minimum of two lines of prior therapy or one line of therapy including high-dose chemotherapy and autologous stem cell support (e.g. induction chemotherapy plus one or two autologous stem cell transplantations) or one line of therapy incorporating an alkylating agent in the absence of any other alternative treatment.

Exclusion criteria included (i) prior thalidomide treatment, (ii) pregnant or breast-feeding women or women of childbearing potential not using an effective method of contraception or the lack of protection during sexual intercourse with men, (iii) any medical contraindication to thalidomide or dexamethasone, (iv) a history of deep vein thrombosis (DVT) not treated with an effective oral anticoagulant, (v) WHO performance status  $> 2$  unrelated to MM and (vi) any circumstance that would not allow for adequate patient follow-up.

### Study treatments

Patients received either 100 or 400 mg/day of thalidomide once daily at bedtime for up to 1 year, supplied in 50- and 100-mg capsules (thalidomide Laphal, Allauch, France). Per-protocol, thalidomide dose reduction for toxicity was permitted at the investigator's discretion. After the resolution of toxicity, thalidomide could be reintroduced and escalated to the per-protocol dose, but no increase over the initial planned dose was allowed. In case of disease progression at any time after inclusion, or in case of stable disease after 12 weeks of therapy, dexamethasone had to be introduced at a dose of 40 mg/day for four consecutive days of every 4 weeks. All patients received I.V. pamidronate routinely at the dose of 90 mg/month.

### Study assessments

Laboratory tests, X-ray and clinical evaluation are detailed in the Supporting information. As part of this trial, AEs that have been previously identified as potential side effects of thalidomide were closely monitored and reported. Haematological values and other laboratory measures of AEs were assessed at least monthly.

The response to single-agent thalidomide or to thalidomide plus dexamethasone within the first 12 weeks after randomisation or after dexamethasone initiation was the best observed response during this period, in the absence of any disease progression. Disease response was defined as 'progression' in those patients who experienced MM progression during that period. Patients who died from any cause not related to MM without a previously documented response were considered as missing responses. A minimal response (MR) was defined as a 25–50% decline in the level of serum paraprotein or 50–75% reduction in Bence-Jones paraprotein (BJP). A partial response (PR) was defined as a 50–90% reduction in the serum monoclonal component or 75–95% reduction in BJP. A very good partial response (VGPR) was defined by >90% reduction in the serum monoclonal component or >95% reduction in BJP and bone marrow plasma cells <5%. Complete response (CR) was defined as the resolution of disease symptoms, absence of new sites of bone involvement, recovery of normal laboratory parameters (CBC, serum calcium and undetectable paraprotein by serum and urine electrophoresis) and normal bone marrow aspirate and/or bone marrow biopsy. The disease was classified as 'progressive' at any time point in the presence of any of the following criteria: (i) extension of myeloma bone lesions, (ii) myeloma-related renal impairment, (iii) worsening of hypercalcaemia, (iv) confirmed increase (two consecutive samples) >30% or 5 g/L of the monoclonal component or by 50% of urinary elimination in case of BJP, as compared to the lower level obtained during the previous assessments, and (v) any other situation deemed by the investigator to reflect disease progression. Patients who did not meet disease response or progression criteria were considered as being in stable disease.

### Statistical analyses

Sample size was initially calculated assuming a median survival time of 12 months in the 400 mg/day (control group) and an acceptable maximum loss in median survival time of 4 months in the 100 mg/day arm (tested group). This leads to a 1-year survival rate of 50% in the control group and an acceptable minimum 1-year survival rate of 35.36% in the tested group, estimation based on an exponential survival curve. With a limit of non-inferiority of 14.64% for the difference in 1-year survival rates between the control and tested groups, corresponding to a hazard ratio of 1.493 and expecting a 15% of non-assessable subjects, 159 patients had to be recruited per arm in order to achieve a power of 80% in a non-inferiority test with type I error of 5% (1, 2). Following the interim analysis, the 1-year survival rate was assumed to be 64% in the control group (63.5%

observed). With a hazard ratio of 1.493, as initially calculated, the acceptable minimum 1-year survival rate was 51.25% in the tested group, leading to a limit of non-inferiority of 12.75% for the difference in 1-year survival rates between the control and tested groups. Expecting a 10% of non-assessable subjects, the number of subjects to be enrolled per group was recalculated to be 200 to ensure an 80% power in a non-inferiority test with type I error of 5%.

Response rates to single-agent thalidomide or to thalidomide plus dexamethasone during the first 12 weeks after dexamethasone initiation were compared between groups using the chi-square test or the Fischer's exact test whenever necessary. Also, AEs rates were compared between treatment groups using the chi-square test or the Fisher's exact test, when necessary. The 1-year OS from the time of randomisation was estimated with standard error using the Kaplan–Meier method.

To test the non-inferiority of the 100 mg/day arm as compared to the 400 mg/day arm, the upper limit of the one-sided 95% confidence interval (CI) of the difference in 1-year survival rate between the 100 and the 400 mg/day groups was calculated assuming normal distribution of this difference. If this upper limit is lower than the predetermined level of non-inferiority (12.75%), the non-inferiority of the 100 mg/day arm would be demonstrated according to the predefined definition of non-inferiority.

Curves of time to first response to thalidomide alone during the first 12 weeks after randomisation and to thalidomide plus dexamethasone after the initiation of dexamethasone were calculated using the Kaplan–Meier method. OS and PFS curves were calculated from randomisation, with PFS being defined as the first progression while receiving thalidomide plus dexamethasone or death without progression while receiving thalidomide or thalidomide plus dexamethasone. Details concerning censoring are provided in the Supporting information. Times to event (first response, progression, death, progression or death) were expressed as median  $\pm$  standard error (SE). The log-rank test was used to compare time to event curves between treatment groups. The corresponding hazard ratios (95%CI) were estimated using an unstratified proportional hazards model.

In a landmark analysis, time to first response and time to progression under thalidomide plus dexamethasone, PFS, OS, time to first response and time to progression under thalidomide plus dexamethasone curves were studied in the group of patients alive at 12 weeks after randomisation. (For all curves, follow-up started at 12 weeks.)

The intent-to-treat (ITT) population included all randomised patients analysed as randomised. The PP population included only patients who have actually

received thalidomide without major protocol violation as decided by the blinded review committee, and analysed as treated. The safety population included patients who received at least one dose of study drug and analysed as treated. Analyses of secondary endpoints were performed on the ITT population, except for AEs that were analysed on the safety population.

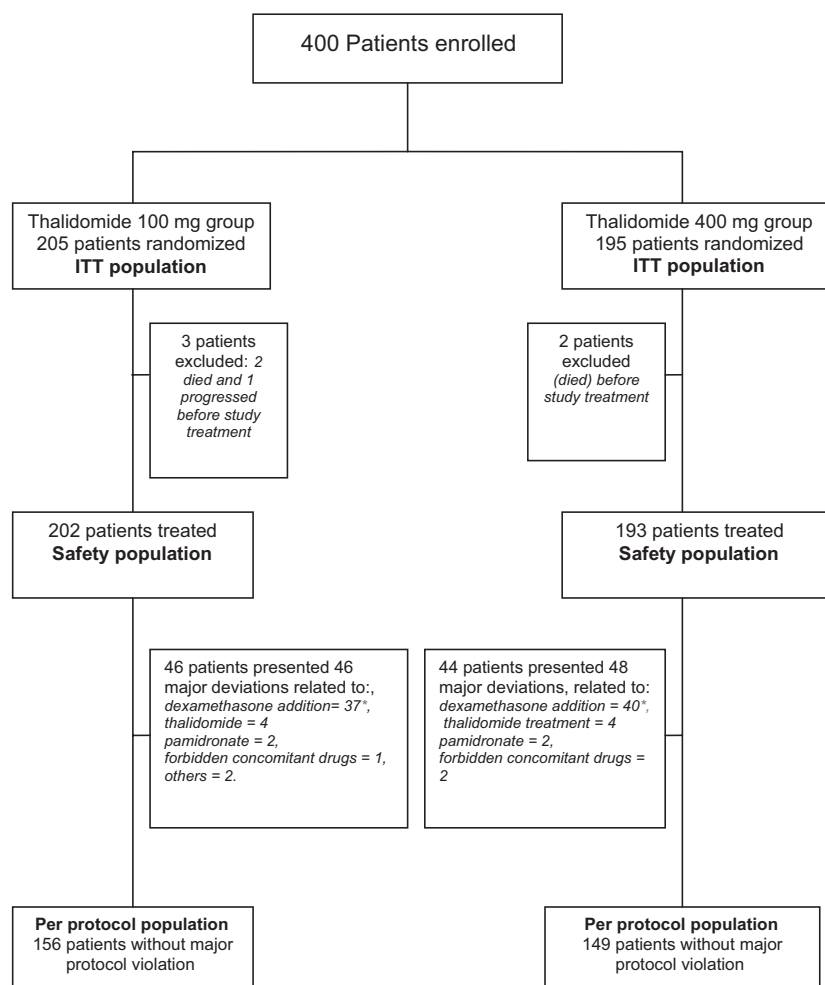
## Results

The reference date for all analyses was 8 October 2005. However, an update of data regarding PFS and OS was performed at the reference date of 8 April 2006 to ensure a median follow-up time of 36 months. In all, a total of 400 patients were enrolled. One hundred and ninety-five patients were randomised into the 400-mg arm and 205 into the 100-mg group (ITT). Two patients in the 400 mg/day group and three patients in the 100 mg/day group did not receive any thalidomide and were excluded from the safety and PP analyses. Another 44 patients

and 46 patients were excluded from the PP population in each group, respectively (Fig. 1). Patients' characteristics, disease features and details of prior therapy are summarised in Table 1. The two groups were well matched in both the ITT or PP populations. However, we observed a little imbalance between the two groups as the 400-mg ITT group had significantly more patients with lower haemoglobin levels and the 100-mg PP-group had more patients with elevated creatinine levels. These differences were not considered as clinically relevant.

## Outcome

When considering the PP population, the 1-year OS rate estimates were 74.5% (95%CI; 67.5–81.5) and 67.3% (95%CI; 60.0–74.7) in the 400 and 100 mg/day groups, respectively. With an upper limit of the one-sided 95%CI of the difference in 1-year OS rate between 400 mg/day ( $n = 149$ ) and 100 mg/day ( $n = 156$ ) estimated at 15.67%, the non-inferiority of thalidomide 100 mg/day



**Figure 1** Patient disposition. \*Addition of dexamethasone outside protocol requirements. See Supporting information for more details.

**Table 1** Characteristics of the patients at randomisation

| Characteristics                                   | ITT population                  |                                 | <i>P</i> | PP population                   |                                 | <i>P</i> |
|---------------------------------------------------|---------------------------------|---------------------------------|----------|---------------------------------|---------------------------------|----------|
|                                                   | 100 mg/day<br>( <i>N</i> = 205) | 400 mg/day<br>( <i>N</i> = 195) |          | 100 mg/day<br>( <i>N</i> = 156) | 400 mg/day<br>( <i>N</i> = 149) |          |
|                                                   | Patients (%)                    | Patients (%)                    |          | Patients (%)                    | Patients (%)                    |          |
| Age ≥70 years                                     | 91/205 (44)                     | 76/195 (39)                     | 0.27     | 69/156 (44)                     | 61/149 (41)                     | 0.56     |
| Male sex                                          | 100/205 (49)                    | 90/195 (46)                     | 0.60     | 78/156 (50)                     | 65/149 (44)                     | 0.26     |
| Disease status                                    |                                 |                                 |          |                                 |                                 |          |
| Refractory                                        | 40/204 (20)                     | 40/195 (21)                     | 0.82     | 32/156 (21)                     | 30/149 (20)                     | 0.93     |
| Relapse                                           | 164/204 (80)                    | 155/195 (80)                    |          | 124/156 (80)                    | 119/149 (80)                    |          |
| International Scoring System                      |                                 |                                 |          |                                 |                                 |          |
| I                                                 | 78/177 (44)                     | 71/175 (41)                     | 0.66     | 55/135 (41)                     | 52/134 (39)                     | 0.43     |
| II                                                | 48/177 (27)                     | 55/175 (31)                     |          | 35/135 (26)                     | 44/134 (33)                     |          |
| III                                               | 51/177 (29)                     | 49/175 (28)                     |          | 45/135 (33)                     | 38/134 (28)                     |          |
| Performance status ≥2 WHO grade                   | 53/205 (26)                     | 43/194 (22)                     | 0.39     | 37/156 (24)                     | 33/148 (22)                     | 0.77     |
| IgG paraprotein isotype                           | 121/199 (61)                    | 127/194 (66)                    | 0.34     | 95/152 (63)                     | 98/149 (66)                     | 0.55     |
| Chromosome 13 deletion                            | 45/103 (44)                     | 52/100 (52)                     | 0.24     | 29/77 (38)                      | 32/70 (46)                      | 0.32     |
| >50% plasma cells                                 | 38/170 (22)                     | 44/165 (27)                     | 0.36     | 25/128 (20)                     | 34/126 (27)                     | 0.16     |
| Haemoglobin <10 g/dL                              | 78/205 (38)                     | 94/195 (48)                     | 0.04     | 59/156 (38)                     | 75/149 (50)                     | 0.03     |
| Platelet count                                    |                                 |                                 |          |                                 |                                 |          |
| <90 × 10 <sup>9</sup> /L                          | 39/204 (19.1)                   | 35/195 (17.9)                   | 0.88     | 33/156 (21.2)                   | 22/149 (14.8)                   | 0.34     |
| 90–200 × 10 <sup>9</sup> /L                       | 87/204 (42.6)                   | 88/195 (45.1)                   |          | 64/156 (41.0)                   | 68/149 (45.6)                   |          |
| ≥200 × 10 <sup>9</sup> /L                         | 78/204 (38.2)                   | 72/195 (36.9)                   |          | 59/156 (37.8)                   | 59/149 (39.6)                   |          |
| Serum CRP >6 mg/L                                 | 70/180 (39)                     | 73/177 (41)                     | 0.65     | 60/138 (44)                     | 51/136 (38)                     | 0.31     |
| Serum β <sub>2</sub> -microglobulin               |                                 |                                 |          |                                 |                                 |          |
| <4 mg/L                                           | 95/179 (53.1)                   | 94/175 (53.7)                   | 0.50     | 66/136 (48.5)                   | 68/134 (50.7)                   | 0.92     |
| 4–6 mg/L                                          | 46/179 (25.7)                   | 37/175 (21.1)                   |          | 34/136 (25.0)                   | 33/134 (24.6)                   |          |
| ≥6 mg/L                                           | 38/179 (21.2)                   | 44/175 (25.1)                   |          | 36/136 (26.5)                   | 33/134 (24.6)                   |          |
| Serum creatinine >150 μM                          | 27/204 (13)                     | 17/194 (9)                      | 0.15     | 24/155 (16)                     | 10/149 (7)                      | 0.01     |
| Serum albumin <35 g/L                             | 39/202 (19)                     | 38/195 (20)                     | 0.96     | 29/154 (19)                     | 28/149 (19)                     | 0.99     |
| Serum calcium >3 mm                               | 2/205 (1)                       | 3/194 (2)                       | 0.61     | 2/156 (1)                       | 2/148 (1)                       | 1.00     |
| Duration of prior therapy <sup>1</sup> ≥24 months | 63/201 (31)                     | 62/193 (32)                     | 0.87     | 52/155 (34)                     | 44/149 (30)                     | 0.45     |
| LDH ≥250 IU/L                                     | 154/179 (86)                    | 138/175 (79)                    | 0.08     | 116/135 (86)                    | 108/135 (80)                    | 0.20     |
| Prior therapy                                     |                                 |                                 |          |                                 |                                 |          |
| One line without high-dose therapy                | 34/205 (17)                     | 26/195 (13)                     | 0.57     | 23/156 (15)                     | 19/149 (13)                     | 0.64     |
| One line with high-dose therapy                   | 77/205 (37)                     | 81/195 (42)                     |          | 58/156 (37)                     | 63/149 (42)                     |          |
| ≥2 lines                                          | 94/205 (46)                     | 88/195 (45)                     |          | 75/156 (48)                     | 67/149 (45)                     |          |
| Prior high-dose therapy                           | 106/205 (52)                    | 112/195 (57)                    | 0.25     | 80/156 (51)                     | 86/149 (58)                     | 0.26     |
| Prior dexamethasone                               | 154/205 (75)                    | 152/195 (78)                    | 0.51     | 118/156 (76)                    | 115/149 (77)                    | 0.75     |
| History of deep vein thrombosis                   | 27/205 (13)                     | 31/195 (16)                     | 0.44     | 23/156 (15)                     | 26/149 (17)                     | 0.52     |
| Abnormal ENP examination                          | 84/186 (45)                     | 81/185 (44)                     | 0.84     | 62/140 (44)                     | 58/140 (41)                     | 0.72     |

Parameter distribution at inclusion was described per treatment through number of patients and percentages. Distributions of parameters evaluated at inclusion were compared between treatment groups using chi-square test or Fischer's exact test, as appropriate.

ENP, electroneurophysiological; ITT, intent-to-treat; PP, per protocol; LDH, lactate dehydrogenase.

<sup>1</sup>The time elapsed from the first treatment of myeloma to randomisation.

could not be established ( $P = 0.14$ ). In the ITT population, the 1-year OS estimates were 72.8% (95%CI; 66.6–79.1) and 68.8% (95%CI; 62.4–75.1) in the 400 mg/day ( $n = 195$ ) and 100 mg/day ( $n = 205$ ) groups, respectively. In this perspective, the upper limit of the one-sided 95%CI of the difference was 11.49%. Thus, the non-inferiority of 100 mg/day could be established ( $P = 0.03$ ).

Table 2 summarises the prognostic factors associated with 1-year OS in the multivariate logistic regression analysis on the ITT population. Performance status, high

serum β<sub>2</sub>-microglobulin, low platelet count, high serum LDH level and short time from first treatment to thalidomide initiation were the strongest independent risk factors associated with OS at 1 year.

The overall response rates (better than stable disease) in patients receiving thalidomide alone within the first 12 weeks after randomisation were higher in patients treated with 400 mg/day in comparison with patients receiving 100 mg/day (60% vs. 40%;  $P < 0.001$ ; Table 3). Nevertheless, the overall response rates in patients receiving thalidomide plus dexamethasone within

**Table 2** Factors related to poor survival<sup>1</sup>

| Factors                                                            | Odds ratio |       |       | <i>P</i> value |
|--------------------------------------------------------------------|------------|-------|-------|----------------|
|                                                                    | Estimate   | 95%CI |       |                |
| Performance status (grade >1 vs. ≤1)                               | 6.21       | 3.14  | 12.30 | <0.001         |
| β <sub>2</sub> -microglobulin (mg/L)                               |            |       |       |                |
| 4–6 vs. <4                                                         | 2.44       | 1.116 | 5.15  | 0.02           |
| ≥6 vs. <4                                                          | 4.94       | 2.33  | 10.46 | <0.001         |
| Platelet count (10 <sup>9</sup> /L)                                |            |       |       |                |
| 90–200 vs. ≥200                                                    | 2.26       | 1.04  | 4.93  | 0.04           |
| ≤90 vs. ≥90                                                        | 6.17       | 2.56  | 14.89 | <0.001         |
| LDH (IU/L) (≥250 vs. <250 IU/L)                                    | 3.50       | 1.21  | 10.11 | 0.02           |
| Time from first treatment to thalidomide onset (years) (<2 vs. ≥2) | 2.63       | 1.38  | 5.01  | 0.003          |
| Treatment arm 400 mg/day vs. 100 mg/day <sup>2</sup>               | 1.19       | 0.64  | 2.20  | 0.59           |

CI, confidence interval; LDH, lactate dehydrogenase.

<sup>1</sup>The multivariate logistic regression was performed on 327 subjects (73 subjects had missing data).<sup>2</sup>Adjusted on all prognostic factors.**Table 3** Response rates – ITT population

| Response under thalidomide alone within the first 12 weeks after randomisation                   |                                              |                                              |
|--------------------------------------------------------------------------------------------------|----------------------------------------------|----------------------------------------------|
| Response                                                                                         | 100 mg/day ( <i>N</i> = 205)<br>Patients (%) | 400 mg/day ( <i>N</i> = 195)<br>Patients (%) |
| Progression                                                                                      | 82 (41)                                      | 45 (24)                                      |
| Stable disease                                                                                   | 37 (19)                                      | 30 (16)                                      |
| ORR                                                                                              | 79 (40)                                      | 112 (60)                                     |
| MR                                                                                               | 50 (25)                                      | 61 (33)                                      |
| PR                                                                                               | 26 (13)                                      | 46 (25)                                      |
| VGPR/CR                                                                                          | 3 (2)                                        | 5 (3)                                        |
| NE                                                                                               | 7                                            | 8                                            |
| Response under thalidomide and dexamethasone within 12 weeks after the addition of dexamethasone |                                              |                                              |
|                                                                                                  | 100 mg/day ( <i>N</i> = 119)<br>Patients (%) | 400 mg/day ( <i>N</i> = 90)<br>Patients (%)  |
| Progression                                                                                      | 42 (36)                                      | 33 (37)                                      |
| Stable disease                                                                                   | 17 (15)                                      | 16 (18)                                      |
| ORR                                                                                              | 57 (49)                                      | 40 (45)                                      |
| MR                                                                                               | 41 (35)                                      | 24 (27)                                      |
| PR                                                                                               | 15 (13)                                      | 15 (17)                                      |
| VGPR/CR                                                                                          | 1 (1)                                        | 1 (1)                                        |
| NE                                                                                               | 3                                            | 1                                            |

MR, minimal response; PR, partial response; VGPR, very good partial response; CR, complete response; ORR, MR plus PR plus VGPR plus CR; ITT, intention-to-treat; NE, not evaluable.

the first 12 weeks after the addition of dexamethasone were similar in the two groups, for a total response rate of 45% vs. 49% in patients from the 100 and 400 mg/day groups, respectively ( $P = 0.55$ ). Introduc-

tion of dexamethasone was more frequent in patients of the 100 mg/day group as compared to the 400 mg/day group (58% vs. 46%;  $P = 0.02$ ; the detailed reasons for dexamethasone introduction during therapy are provided in the Supporting information). Time to first response in patients receiving thalidomide alone and time to progression on thalidomide were in favour of the 400 mg/day group ( $P < 0.001$  and  $P = 0.02$ ; Fig. 2C,D, respectively). However, and most importantly, there was only a trend for difference in the ITT population between the two groups with respect to OS and PFS (Fig. 2A,B,  $P = 0.22$  and  $P = 0.06$ , respectively).

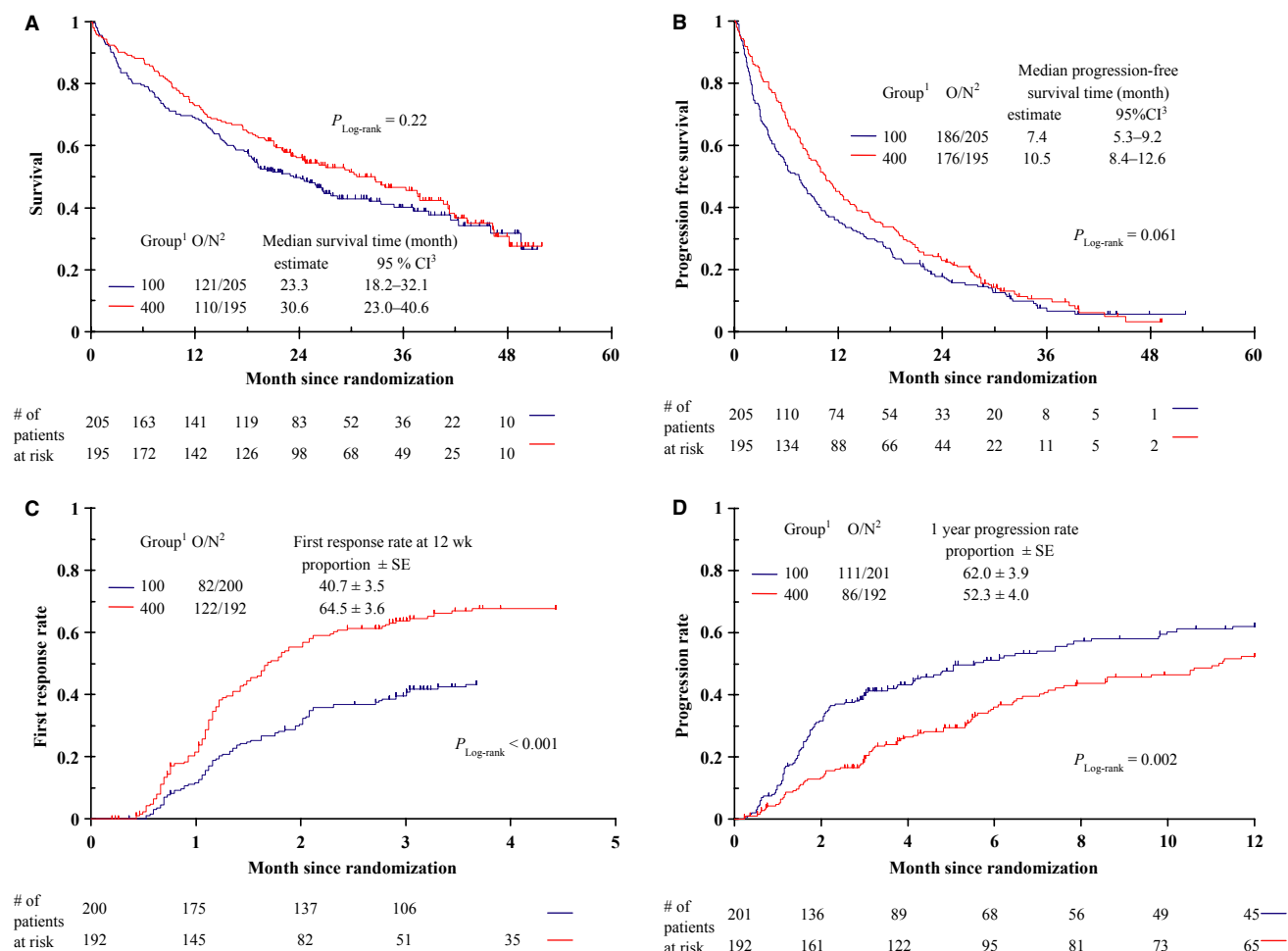
Using a landmark analysis focusing only on patients alive at 12 weeks after randomisation and following them up thereafter, we did not find any significant difference between the two groups in terms of OS (Fig. 3A), PFS (Fig. 3B), time to first response (Fig. 3C) or time to progression on thalidomide plus dexamethasone (Fig. 3D).

### Tolerance, safety and adverse events

The main AEs observed in this study are summarised in Table 4. The DVT/PE rate was 6% and 7% in the 100 and 400 mg/day arms, respectively ( $P = 0.58$ ). Overall, the 100 mg/day dosage was better tolerated than the 400 mg/day dosage. The proportion of patients in whom treatment was discontinued because of AE was similar in the 100-mg group (83/202; 41%) as compared to the 400-mg group (90/193; 47%;  $P = 0.27$ ). In those patients, the most frequently encountered AEs were related to peripheral neuropathy and other disorders of the nervous system (27/202; 13% vs. 40/193; 21% in the 100 and 400 mg/day groups, respectively;  $P = 0.051$ ). Furthermore, the proportion of patients in whom dose was reduced at least once because of AE was significantly higher in the 400 mg/day group as compared to the 100 mg/day group (29/202; 14% vs. 126/193; 65%;  $P < 0.001$ ). In those patients, the most frequent AEs leading to dose reduction were also related to peripheral neuropathy and other disorders of the nervous system (17/202; 8% vs. 81/193; 42%,  $P < 0.001$ ). Moreover, 63/104 patients (62%) from the 100 mg/day group and who remained on study at week 48 kept their initial thalidomide dose unchanged vs. 28/105 patients (27%) in the thalidomide 400-mg group ( $P < 0.001$ ), highlighting the improved safety profile of the 100 mg/day dosage. Of note, the median received daily dose was of 331 mg/day (range, 117–400) and 100 mg/day (range, 52–100) in 400 mg/day and 100 mg/day groups, respectively.

### Discussion

Although the anti-MM efficacy of thalidomide has been largely established (5), the side effects of thalidomide are

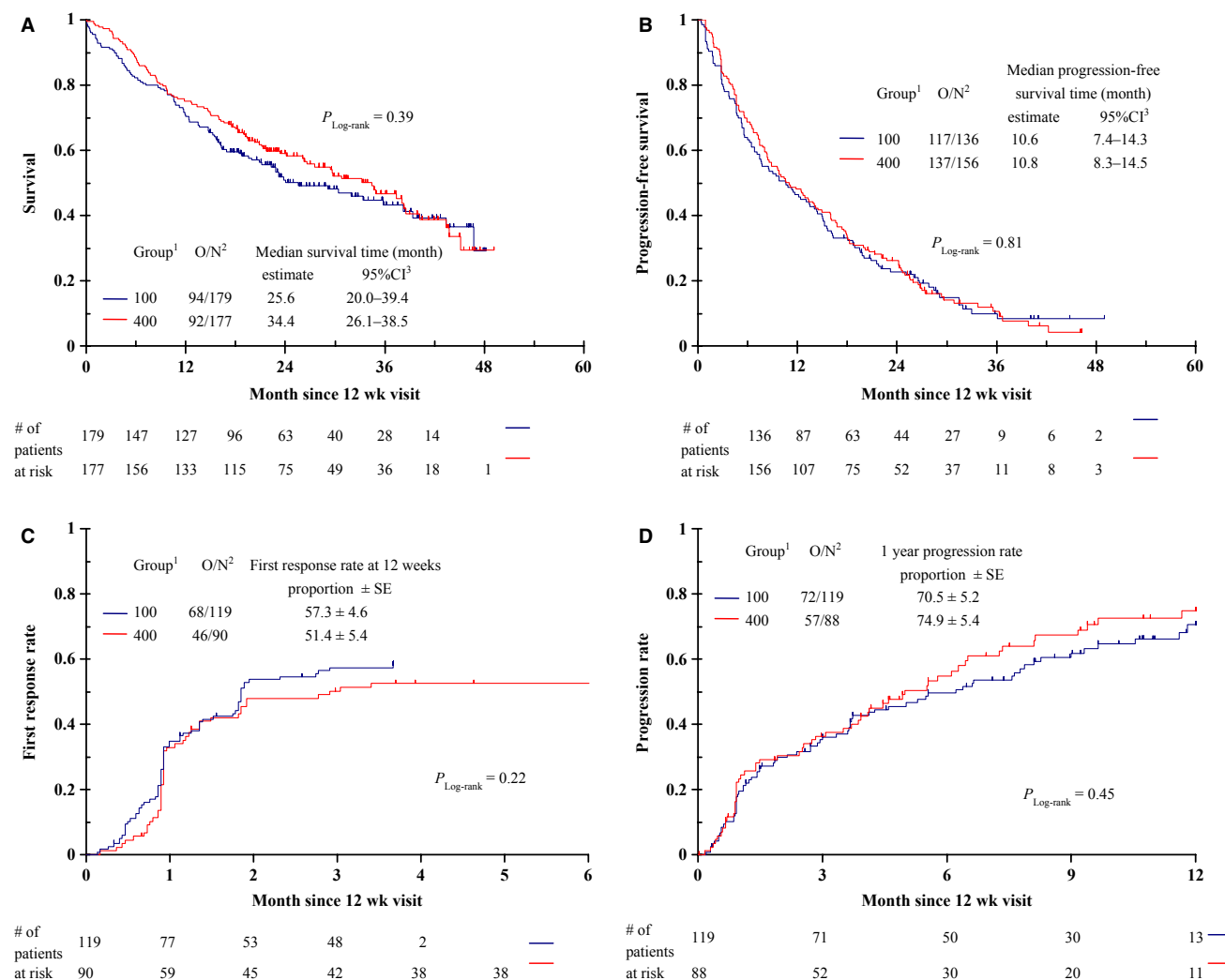


**Figure 2** Outcome of the 400 patients enrolled in the study. (A) Overall survival; (B) progression-free survival; (C) time to first response under thalidomide alone observed within 12 weeks after randomisation and (D) time to progression on thalidomide within the first year of treatment. All analyses were performed in intent-to-treat population. <sup>1</sup>Group: 100 mg/day and 400 mg/day; <sup>2</sup>O/N: number of observed events/number of patients; <sup>3</sup>CI: confidence interval.

still a matter of concern and may offset the drug overall efficacy (2, 3, 6–10). With this background and because some reports suggested that lower doses of thalidomide may be associated with a better tolerability profile, we conducted this comparative trial in patients with advanced MM to determine whether it is possible to reduce thalidomide-related toxicity through dose reduction while maintaining efficacy. Indeed, a non-inferiority trial aims to demonstrate that the test product (low dose) is not worse than the comparator (high dose) by more than a prespecified amount that could be clinically acceptable, knowing the benefit in terms of avoided toxicities.

This study confirmed that thalidomide 100 mg/day was better tolerated than 400 mg/day. In the study design and in the absence of a curative treatment for advanced MM, we opted for 1-year OS as the primary endpoint rather than response rate. Also, in the absence

of thalidomide dose-finding studies, we also felt that 400 mg/day may be accepted as a 'standard' or 'control' dosage (2–4, 11–13). Indeed, except for some small studies that have assessed low-dose thalidomide (14–17), most of the large studies used a 400 mg/day dosage (2–4, 11–13, 18). Moreover, as the antimyeloma effect of thalidomide is usually potentiated by dexamethasone (12, 16, 17, 19, 20), another feature of the current trial was to combine thalidomide and dexamethasone in both arms in case of treatment failure defined by disease progression or stable disease after 12 weeks from randomisation. In this regard, some investigators may question the absence of use of dexamethasone from the time of therapy initiation. Indeed, higher response rates of 45–57% by combining thalidomide with dexamethasone (12, 21, 22) and of 67–79% by the addition of chemotherapy to thalidomide + dexamethasone (23–26) have been reported in uncontrolled studies. However, it is still



**Figure 3** Landmark analysis of the outcome of patients who survived over 12 weeks after randomisation (for all curves, follow-up started at week 12). (A) Overall survival; (B) progression-free survival; (C) time to first response observed within 12 weeks after addition of dexamethasone and (D) time to progression on thalidomide + dexamethasone within the first year of treatment. All analyses were performed on intent-to-treat basis. <sup>1</sup>Group: 100 mg/day and 400 mg/day; <sup>2</sup>O/N: number of observed events/number of patients; <sup>3</sup>CI: confidence interval.

unclear whether these combinations improve event-free or OS as compared with thalidomide alone (27). Therefore, thalidomide monotherapy can be considered as a reasonable choice with the option to extend the therapy according to disease control (28). In terms of supportive therapy, antithrombosis prophylaxis was not routinely recommended in the trial, except for those patients with a history of DVT. Such caution helped in reducing the overall incidence of DVT in both arms, which was lower than what has been reported by others (29–31). Finally, per protocol all patients had to receive pamidronate as this drug was shown to have a beneficial impact on the survival and quality of life in patients with MM receiving salvage therapy (32).

From the statistical standpoint, the non-inferiority of the 100 mg/day dosage for 1-year OS could not be dem-

onstrated in the PP population (possibly because of the sample size of this PP population that was significantly decreased owing to the number of patients with major protocol deviations, mainly related to dexamethasone introduction;  $n = 95$ ). Nevertheless, the non-inferiority hypothesis was shown in the ITT population. In terms of disease response, the 400 mg/day dosage was associated with a higher response rate. Interestingly, a systematic review of 1674 patients receiving thalidomide in the salvage setting concluded that the dose–response data of thalidomide may be compatible with a small increase in the response rate in patients receiving above 200 mg/day (28). However, this higher response rate with higher doses of thalidomide is achieved at the cost of a higher rate of toxicities and AEs. Of note, dose reduction or drug discontinuation was more likely to occur in the

**Table 4** Number of patients who had an aggravation of specifically monitored events (safety population)

| Specifically monitored events                                 | Number (%) of subjects       |                              | <i>P</i> <sup>2</sup> |
|---------------------------------------------------------------|------------------------------|------------------------------|-----------------------|
|                                                               | Thalidomide 100 mg (N = 202) | Thalidomide 400 mg (N = 193) |                       |
| Constipation all grades <sup>1</sup>                          | 132 (68)                     | 150 (81)                     | 0.002                 |
| Constipation with WHO grade $\geq 2$ <sup>1</sup>             | 52 (27)                      | 73 (40)                      | 0.007                 |
| Somnolence all grades <sup>1</sup>                            | 115 (59)                     | 131 (71)                     | 0.013                 |
| Somnolence with WHO grade $\geq 2$ <sup>1</sup>               | 25 (13)                      | 60 (33)                      | <0.001                |
| Peripheral neurotoxicity all grades <sup>1</sup>              | 109 (56)                     | 125 (68)                     | 0.016                 |
| Peripheral neurotoxicity with WHO grade $\geq 2$ <sup>1</sup> | 38 (19)                      | 58 (31)                      | 0.007                 |
| Depression/mood disorders all intensities <sup>1</sup>        | 85 (44)                      | 84 (46)                      | 0.651                 |
| At least moderate depression/mood disorders <sup>1</sup>      | 23 (12)                      | 28 (15)                      | 0.319                 |
| Peripheral oedema all intensities <sup>1</sup>                | 62 (31)                      | 71 (37)                      | 0.200                 |
| Nausea/vomiting all grades <sup>1</sup>                       | 60 (31)                      | 71 (39)                      | 0.110                 |
| Nausea/vomiting with WHO grade $\geq 2$ <sup>1</sup>          | 15 (8)                       | 27 (15)                      | 0.031                 |
| At least moderate cardiac rhythm disorders <sup>1</sup>       | 0                            | 2 (1)                        | 0.238                 |

<sup>1</sup>The percentages were calculated among the total number of subjects in each treatment group. Missing values were taken into account for percentages calculation.

<sup>2</sup>The comparison between the two treatment groups was made using the chi-square test or the Fischer's exact test.

400 mg/day arm. On the other hand, addition of dexamethasone to low-dose thalidomide resulted in improved tolerability without little loss of efficacy, suggesting that initiating treatment with 100 mg/day of thalidomide plus dexamethasone may represent an attractive option and should be considered. The latter is in line with the conclusions of a recent review by Palumbo *et al.* (5) highlighting that thalidomide dose reduction is a prerequisite to decrease the severity of side effects, especially neuropathy. In addition, the OPTIMUM trial has looked at 100-mg vs. 200-mg vs. 400-mg thalidomide vs. high-dose dexamethasone, showing – as one most essential result – that 400-mg thalidomide is indeed difficult for the patients to tolerate for substantial treatment durations [median daily thalidomide dose in the 200-mg vs. 400-mg group were 198.2 mg vs. 255.5 mg, suggesting that both groups were really taking almost 200 mg (in the 200-mg group) and a little over 200 mg (in the 400-mg thalidomide group)] (M. Kropff, H. G. Baylon, J. Hillengass, T. Robak, R. Hajek, P. Liebis, S. Goranov, C. Hulin, J. Blade, T. Caravita, H. Avenet-Loiseau, T. Moehler, C. Pattou, L. Lucy, E. Kueenburg, A. Glasmacher, R. Zerbib, and T. Facon, submitted).

The advent of novel antimyeloma drugs (thalidomide, lenalidomide and bortezomib) (33–37) has considerably improved patients' survival, even in the advanced setting. Therefore, in addition to antitumour efficacy, improving quality of life will become an integral part of treatment assessments. Unfortunately, this study did not include any specific quality of life measures. However, given the significantly improved safety profile and tolerability of the 100 mg/day dosage of thalidomide, it is reasonable to assume that such low-dose thalidomide schema would be associated with improved quality of life parameters.

From a practical standpoint, some investigators may advocate that the issue of decreasing thalidomide-related toxicity may be of less interest presently, given the availability of its analogue lenalidomide that, unlike thalidomide, has a better tolerability profile and does not cause peripheral neuropathy (35). The latter is partially true, as thalidomide is still widely used worldwide for both cost and availability reasons.

This prospective trial demonstrated that low-dose thalidomide 100 mg/day has an improved safety profile compared with 400 mg/day with significant activity in advanced MM and can represent an acceptable salvage therapy in combination with dexamethasone. The opportunities afforded by thalidomide and its analogues and by bortezomib are considerable and highlight the need for continuous prospective assessments of novel biologically derived therapies in the management of newly diagnosed and advanced MM.

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## Conflict of interest

I. Yakoub-Agha, T. Facon, J.L. Harousseau, M. Mohty and P. Moreau report having received consulting and lecture fees from Pharmion & Celgene. Robert Zerbib was an employee of Celgene. I.Y.A. is the lead investigator of the study. R.Z. is the study manager. J.Y.M. is the statistician of the study. I.Y.A., R.Z. and J.Y.M. analysed data. I.Y.A., R.Z., M.M. and J.Y.M. wrote

and edited the manuscript. I.Y.A., J.Y.M., C.H., C.D. and R.Z. designed study and participated in the blind review of the data. I.Y.A., C.H., C.D., G.M., L.B., L.V., P.M., C.B., A.M.S., F.M., P.R., M.D., B.P., P.C., P.F., G.D., X.L., J.L.H., M.M. and T.F. are all investigators who included the most important number of patients in this study.

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## Appendix

In addition to the authors, the following investigators participated in the study: Belgium – P. Mineur (Gilly); France – *Angers*: M. Gardembas, M. Hunault, M. Truchant; *Annecy*: P. Cony-Makhoul; *Avignon*: S. Assadourian; *Besançon*: A. Brion, C.-E. Bulabois, J. Fontan, A.

## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Treatment modifications during the study.

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