Prospective comparison of autologous stem cell transplantation followed by a
dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell
transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma.

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Abstract
For patients with high-risk (beta-2 microglobulin > 3mg/L and chromosome 13 deletion at diagnosis) de novo multiple myeloma, the IFM group has initiated in 1999 two specific trials. In both protocols, induction regimen consisted of VAD followed by a first autologous stem cell transplantation (ASCT) prepared by melphalan 200 mg/m2. Patients with an HLA-sibling donor were subsequently treated with a dose-reduced allogeneic stem cell transplantation (IFM99-03 trial), while patients without an HLA-sibling donor were randomized to receive a second ASCT prepared by melphalan 220 mg/m2 dexamethasone +/- anti-IL6 monoclonal antibody (IFM99-04 protocol). 284 patients were prospectively treated and received at least one course of VAD, 65 in the IFM99-03 trial and 219 in the IFM99-04 trial. On an intent-to-treat basis, the overall survival (OS) and the event-free survival (EFS) did not differ significantly in both studies (median 35 and 25 months in the IFM99-03 trial versus 41 and 30 months in the IFM99-04 trial, respectively). With a median follow-up time of 24 months, the EFS of the 166 patients randomized in the tandem ASCT protocol was similar to the EFS of the 46 patients who received the whole IFM99-03 program, median 35 versus 31.7 months, with a trend for a better OS in patients treated with tandem ASCT, median 47.2 versus 35 months, p = .07. In patients with high-risk de novo MM, the combination of ASCT followed by dose-reduced allogeneic transplantation was not superior to a tandem dose-intensified melphalan-based ASCT.
Introduction

Autologous stem cell transplantation (ASCT) is currently considered as the standard of care for younger patients with multiple myeloma (MM) (1-3). Melphalan 200 mg/m2 (mel200) is considered to be the optimal conditioning regimen (4). The randomized IFM94 trial showed that double transplantation significantly improved both overall survival (OS) and event-free survival (EFS) compared with a single ASCT (5). Allogeneic stem cell transplantation is a possible curative approach in MM. In comparison to ASCT the relapse rate is lower and some patients survive long-term disease free (6). The possible advantage of allogeneic transplantation is a well-proven graft-versus-myeloma (GVM) effect by immunocompetent donor lymphocytes (7-9). However, despite a better control of infectious complications and graft-versus-host disease (GvHD), the treatment-related mortality (TRM) rate of allogeneic transplantation is still 15 to 40% (10-12). Therefore, allogeneic transplantation is only an option for younger patients with an HLA-identical sibling. The introduction of reduced intensity conditioning regimens, with a reduction in immediate TRM and stable engraftment, has renewed interest in allogeneic transplantation for myeloma. Recent studies have reported encouraging results using tandem autograft and dose-reduced allograft approaches in MM patients (13,14).

In newly diagnosed MM patients, a number of biological markers or genetic abnormalities have been shown to adversely influence the outcome after ASCT, including high levels of beta-2 microglobulin (β2m), CRP or LDH, increased plasma cell labelling index, hypodiploidy, chromosome 13 deletion (Δ13), translocation (4;14), or a combination of these factors (2,4,12,15-17). In a retrospective trial of 110 patients treated with high-dose therapy (HDT) followed by ASCT (16), Facon et al have shown that a subgroup of patients, representing approximately 25 to 30% of the de novo
patients less than 65 years, presenting with both high β2m and Δ13 (identified by FISH) at the time of diagnosis had a poor outcome with a median survival and progression-free survival (PFS) of 25 and 15 months, respectively. To treat this subgroup of high-risk patients, the IFM group designed in 1999 two specific trials based upon genetic randomization. When an HLA-identical sibling donor was identified at diagnosis, patients were offered dose-reduced allogeneic stem cell transplantation after a single melphalan-based (melphalan 200 mg/m²: mel200) ASCT: IFM99-03 trial. Those with no donor received tandem autologous transplantation with mel200 followed by further dose-increased melphalan 220 mg/m² (mel220) and dexamethasone (DXM) with or without anti-interleukin-6 monoclonal antibody (BE-8) : IFM 9904 trial (18). We here present the results of the IFM 99-03 trial and the comparison of both protocols.

**Patients and methods**

**Eligibility**

Both IFM99-03 and IFM99-04 trials were conducted from April 2000 to August 2004. Patients less than 65 years of age, with Durie-Salmon stage I (one bone lesion), II, or III myeloma, who had both initial biologic features Δ13 (FISH analysis) and β2m level > 3 mg/L were eligible and registered at the time of diagnosis. FISH analysis (15) and β2m studies were carried out centrally at the University of Nantes (H.Avet-Loiseau). The criteria for exclusion were prior treatment for myeloma, another cancer, abnormal cardiac function (indicated by a systolic ejection fraction less than 50 percent), chronic respiratory disease (indicated by a vital capacity or carbon monoxide diffusing capacity less than 50 percent of predicted), abnormal liver function (indicated by a serum bilirubin level more than 2mg per deciliter [35 µmol per liter] or an alanine
aminotransferase or aspartate aminotransferase level more than four times the upper limit of normal) and psychiatric disease.

**Study design (Figure 1)**

**VAD and first ASCT**

After registration in the study, patients were initially treated with a continuous intravenous infusion of 0.4 mg of vincristine and doxorubicin 9 mg/m2 over a 24-hour period for four consecutive days, with 40 mg of oral DXM per day on days 1 through 4 (VAD regimen). Three or four cycles of VAD were administered at four-week intervals. After initial chemotherapy, patients with a performance status below World Health Organization grade 3 and adequate cardiopulmonary, hepatic and renal functions underwent peripheral blood stem cell (PBSC) collection. Stem cells were collected after G-CSF priming (10 μg/kg/d for 6 days). Daily apheresis was continued until at least 5 x 106 CD34 cells per kilogram were collected. After PBSC collection, patients received a first ASCT prepared by mel200.

**IFM99-03 trial**

After the first ASCT, patients with an HLA-identical sibling donor available (limit age of donation 65 years, and no severe comorbid illness) were treated according to the IFM99-03 trial. After an interval of 2 months, patients received a dose-reduced conditioning consisting of busulphan 2 mg/kg/d orally administrated over 2 days, fludarabine 25 mg/m2/d for a duration of 5 days, and antithymocyte globulin (Imtix, Genzym) given at a dose of 2.5 mg/kg/d over 12 hours on days -5, -4, -3, -2, and -1, followed by allogeneic PBSC on day 0. Graft-versus-host prophylaxis consisted of cyclosporin A (3 mg/kg/d, given from day -1 to day +100 after transplantation) and short course methotrexate. The dose of cyclosporin A was adjusted to serum levels.
Cyclosporin A was tapered from day 60 and discontinued, if possible, at day 100. Methotrexate (10 mg/m2) was given on days 1, 3 and 6 after transplantation. Chimerism studies were performed using FISH in sex-mismatched pairs, and polymerase chain reaction analyses of polymorphic microsatellite regions in sex-matched pairs. In case of incomplete chimerism or persistent disease on day 90 additional donor lymphocyte infusions (DLI) were scheduled. The standard criteria were used for grading of acute and chronic GVHD (19).

**IFM99-04 (18)**

After the first ASCT, patients without an HLA-identical sibling donor were randomly assigned to one of the two HDT groups. Randomization was stratified according to the centre and carried out by fax. In arm A, patients received a second ASCT prepared by the combination of DXM 40 mg/day during 4 days plus mel220 infused over 30 min 48 hours before stem cell reinfusion. In arm B, patients received a second ASCT prepared by the combination of mel220, DXM and the addition of B-E8, 250 mg total dose. No maintenance therapy was given after the second ASCT.

**Ethics considerations**

Both IFM99-03 and IFM99-04 studies were approved by the local institutional ethics committee of the University of Grenoble and Nantes, respectively, were approved by responsible Institutional Review Board of all participating centres (listed in the Appendix), were approved and registered by the official French agency for health security (Agence Française de Sécurité Sanitaire et des Produits de Santé: AFSSAPS) and patients gave written informed consent.
Assessment of response

The response criteria has been defined previously (5, 18). A complete response was defined as the lack of detectable paraprotein by serum and urine electrophoresis and 5% or fewer plasma cells with normal morphologic features in a bone marrow aspirate. A very good partial response was defined as a 90% decrease in the serum paraprotein level; a partial response was defined as a 50% decrease in the paraprotein level or a 90% decrease in the level of Bence Jones protein (including patients with Bence Jones protein alone) or both; a minimal response was defined as a 25% decrease in the paraprotein level; stable disease was defined as no change in the paraprotein level; progressive disease was defined as a 25% increase in the paraprotein level, as a relapse was defined as the reappearance of paraprotein, the recurrence of bone marrow infiltration, or both in a patient who had had complete response and as a 50% increase above the plateau level of paraprotein in two samples obtained 4 weeks apart in a patient who had had a response.

FISH analysis

FISH analysis of 13q14 has been performed on highly purified human myeloma cells as previously described (16).

Statistical analysis

In the IFM9904 trial, the primary end-point was to compare the CR rates achieved after the second ASCT (HDT with or without anti-IL-6 monoclonal antibody, BE-8) (18). Secondary end-points were to compare both arms regarding OS and EFS, to study the feasibility and the toxicity of a tandem transplant with 2 different dosages of melphalan (mel200, and mel220). Assuming the complete response rate to be 25% in the DXM +
mel220 arm, the study required 200 patients to have 80 percent power to detect an absolute improvement of 15% in the complete response rate in the mel220 + DXM + anti-IL6 moAb arm. The recruitment target was 200 randomized patients. Two interim-analysis were planned, the first one after the first 50 patients in order to check feasibility and toxic death rate, and after 140 randomized patients to check OS and EFS. The board of the IFM group agreed to stop the trial in September 2004 when there was a total of 165 patients randomized, considering the total lack of difference regarding primary and secondary end-points of the study.

In the IFM99-03 trial, the objectives were to evaluate the feasibility and the TRM of dose-reduced allograft. The recruitment target was 60 patients. An interim analysis was planned after to first 20 patients in order to check feasibility and toxic death rate. The protocol should have stopped in case of a TRM superior to 30% at 6 months. At the IFM99-04 trial stopping date of September 2004, 65 patients had been included in the IFM99-03 protocol, and the board of the IFM group agreed to stop the trial at the same date to evaluate the results and to allow comparison between the 2 programs.

Overall survival was calculated from the date of start of therapy to the date of death from any cause. Data on patients who were alive at the time of analysis were censored in the survival analysis on the last date they were known to be alive. Event-free survival was calculated from the date of start of therapy to the date of progression, relapse or death. Data on patients who had not had progression or relapse were censored on the last date they were known to be alive and event-free. Comparison of frequencies between groups were performed using the χ 2 and fisher’s exact tests. Median values were compared by Wilcoxon’s rank-sum test. Survival was estimated by the Kaplan-Meier product limit method, and curves were compared by the stratified log-rank test. A cut-off date of May 15, 2005, was used for survival analysis.
Results

From April 2000 to September 2004, 284 patients from 48 centres met eligibility criteria, were registered and received at least one course of VAD. Sixty-five (22.9%) had an HLA-identical sibling donor available and were included in the IFM99-03 trial while 219 patients (77.1%) were included in the IFM99-04 trial. Among these 219 patients, 4 patients had an HLA-identical sibling but were not included in the IFM 99-03 trial because of underlying disease for the donor: progressive solid tumor n = 2, ongoing infection n = 1, psychiatric disease n = 1. Moreover HLA-typing was not performed in 24 patients included in the IFM99-04 trial because of patient’s refusal n = 5, family’s refusal n = 3, physician’s decision n = 5, age of brother(s) and/or sister(s) above 70 years n = 6 or unknown causes n = 5. Table 1 shows the base-line characteristics of the patients included in both studies. Patients were older in the tandem ASCT trial (median age 58 versus 54, p = .006), and β2m level was also higher in this latter group (median 4.9 mg/L versus 4.1, p = .049).

IFM99-03 trial

Sixty-five patients were included in the study. Nineteen (29.2%) did not complete the whole program, ASCT followed by reduced-intensity allogeneic transplantation, for the following reasons: progressive disease n = 7, donor refusal n = 2, recipient refusal n = 3, ongoing infections n = 4, other unknown causes n = 3. For the 46 patients who completed the whole program, the median time between diagnosis and ASCT was 153 days (range, 120-226), and 73 days (range, 44-92) between ASCT and dose-reduced allograft.
**Engraftment and chimerism**

Peripheral blood was used as the source of stem cells in all 46 cases. Engraftment occurred in 100% of the cases. Chimerism data were available on 29 patients. At best 86.2% (25 patients) achieved full donor chimerism at day 60, and this had fallen to 72.4% (21 patients) on subsequent analysis on day 120. All patients with persisting partial chimerism had progressive disease.

**Graft versus host disease**

Acute GvHD occurred in 15 patients (32.6%) with 4 (8.7%) experiencing grade I and 11 (23.9%) grade II-IV disease. Forty-two patients were evaluable for cGvHD of whom 3 (7.1%) developed limited and 15 (35.7%) extensive cGvHD. Five out of 15 extensive cGvHD were observed after DLI.

**Transplant related mortality**

Five patients (10.9%) died of procedural related complications, of whom 2 died before day 100 from infections (viral pneumonitis n = 1, septicaemia with brain metastasis n = 1) and 3 after day 100 from infections associated with GvHD (bacterial pneumonitis n = 2, disseminated aspergillosis n = 1).

**Response post-transplant**

Forty-five patients (one early death) were evaluable for response assessment following allogeneic transplant. One month after ASCT, 17 (37.8%) were in CR (n = 5) or VGPR (n = 12), 21 (46.6%) were in PR, and 7 (15.5%) had stable or progressive disease. Two months after allogeneic transplantation, 28 (62.2%) were in CR (n = 15) or VGPR (n = 13), 9 (20%) were in PR, and 8 (17.8%) had stable or progressive disease.

**Overall and event-free survivals**

At the reference date of 15 May, 2005, the median OS for the whole group of 65 patients was 35 months, and the 56-month survival was 33.1%. The median EFS from
diagnosis for the whole group of 65 patients was 25 months, and the 5-year EFS was 0%. Overall survival and EFS of the 46 patients who received the allogeneic transplantation were not different as compared with those of the 19 patients who could not received the allogeneic graft (OS median 35 versus 36.6 months, p = .66, and EFS median 31.7 versus 23 months, p = .14). Progression or relapse of disease occurred in 26 out of 46 patients (56.5%). The cumulative probability of progression was 57% at three years and the projected 5-year probability of relapse was 100%. There was a trend for a delayed progression among patients who developed cGVHD (median time-to-progression from the date of allogeneic transplantation 24 months in patients without cGVHD vs 32 in patients with cGVHD p = .14), but this delayed progression time did not translate into better OS (median survival from the date of allogeneic transplantation 27 months in patients without cGVHD vs 34 months in patients with cGVHD, p = .59, figure 2). For acute GVHD no effect on OS or relapse rate was observed for either the presence or severity of disease. Out of 46 patients who received the whole program, 22 have died, 5 from TRM and 17 from disease progression. The median follow-up time for living patients who received the whole program was 28 months (11-57).

**Donor Lymphocyte Infusions**

Seventeen patients received DLI. In 8 cases, DLI were infused for persistent disease without GvHD at day 90. The starting dose in each case was 1 x 10^7 CD3+ cells / kg, 2 patients received a second infusion of DLI at an increased dose of 5 x 10^7 CD3+ cells / kg, and one patient received a third dose of 1 x 10^8 CD3+ cells / kg. In 5 cases DLI induced disease response (CR or VGPR), and 3 patients progressed despite DLI infusions. Nine patients received DLI later in the course of the disease at the time of relapse and response was never observed in this situation.
IFM99-04 trial

Overall results

Patients' characteristics, response rates, TRM, OS and EFS have been described elsewhere (18). Briefly, a total of 53 / 219 (24.2%) enrolled patients did not proceed to randomization to receive or not anti-IL6 moAb because of severe complications or disease progression before the second ASCT. Thus, 166 (75.8%) patients were randomised (85 patients in arm A and 81 patients in arm B) and were treated according to the whole protocol. Response rates (CR + VGPR) were 16% after VAD induction therapy, 34% after the first ASCT prepared by mel200 and 51% after the second ASCT. The addition of BE-8 to the second conditioning regimen did not increase the response rate. The TRM was 5%: 6 patients died during the induction therapy with VAD, 2 patients died during the first ASCT, and 3 patients died during the second ASCT (1 in arm A and 2 in arm B).

Overall survival and event-free survival (18)

At the reference date of 15 may, 2005, the median OS for the whole group of 219 patients was 41 months, and the 56-month survival was 44.4%. The median EFS from diagnosis for the whole group of 219 patients was 30 months, and the 5-year EFS was 0%. The median follow-up time for living patients who were randomized was 24 months (9-59). The EFS was identical in both arms of the study, median 35 months in arm A vs 31 in arm B, and 0% at 59 and 57 months, respectively, p = .39. The OS was not statistically different in arm A vs arm B, 46% vs 51% at 54 months, respectively, p = .90.

Comparison of both studies
On an intention-to-treat basis, considering the whole population of 284 patients, i.e., 65 in the IFM99-03 protocol and 219 in the IFM99-04 trial, the OS did not differ significantly in both studies (median survival 35 months in the IFM99-03 trial versus 41 months in the 99-04 protocol, p = .27, figure 3). Similarly, considering the whole population of 284 patients, the EFS did not differ significantly in both studies (median EFS 25 months in the IFM99-03 trial versus 30 months in the IFM99-04 protocol, p = .56, figure 4).

Overall survival and EFS were similar in the 2 treatment arms of the IFM99-04 trial. Thus the results of patients in arm A (n = 85) and arm B (n = 81) were pooled to be compared to those of the 46 patients included in the IFM99-03 study who received the whole ASCT plus allogeneic transplantation program. The EFS of the 166 patients randomized in the tandem ASCT protocol was similar to the EFS of the 46 patients who received the whole IFM99-03 program, median 35 months versus 31.7, p = .35 (figure 5). There was a trend for a better OS for the randomized patients in the tandem transplant trial as compared with the OS of patients treated with the combination of ASCT followed by mini-allogeneic transplantation, median OS 47.2 months versus 35 months, p = .07 (figure 6).
Discussion

Despite improvements in the results of conventional myeloablative allogeneic transplantation in the late 90s (10), this treatment is associated with a high TRM and a low survival rate in patients with MM (11,12). In both case-matched retrospective (6) and prospective comparisons (20-21) the overall short-term results of allogeneic transplantation have always been considered inferior to those of ASCT. This is mostly explained by a high TRM even when allogeneic transplantation is used as front-line therapy. However the immunologic effect of the graft, so-called graft-versus-myeloma (GVM), has been clearly demonstrated by the use of DLI and long-term remission, including molecular remission can be obtained (7-9). In an effort to reduce the toxicity and TRM associated with myeloablative allogeneic but maintaining the GVM effect, reduced intensity conditioning have been developed. Several groups have studied the impact of a tandem approach combining the reduction of tumor burden obtained by ASCT and the GVM effect of minialloSCT (13, 14, 22). Nevertheless, few data are available regarding the outcome of this cytoreductive autografting followed by reduced intensity geno-identical allogeneic transplantation as part of initial therapy in patients with MM. In the series of the Seattle group (14), 48% of the patients had received more than one treatment regimen, and the median time between diagnosis and ASCT was 282 days. In the German study of tandem auto-miniallotransplant protocol (13), the median time from diagnosis to autotransplantation was 13 months. In the recent retrospective trial from the EBMT group (22), the majority of the 229 patients treated with dose-reduced allografts had received at least one prior autograft, but the median time from diagnosis to allotransplant was 1.6 years (range, 2-11). Nevertheless, even in the setting of advanced patients, results of the combination ASCT plus dose-reduced allografts were encouraging. The TRM was low ranging from 4 (14) to 11 % (13). The CR rate
and the 2-year estimated survival were 73 and 74%, respectively in the series of Kroger et al (13), and the overall response rate was 81%, the 2-year estimated survival was 78% and 46% of the patients survived in CR at a median follow-up of 18 months in the series of the Seattle group (14).

Given the good results of tandem ASCT in “standard risk” patients (5,16), the IFM group considered that the risk of TRM and cGVHD were not justified in these patients. Therefore we decided to study the impact of this combination auto/minialllotransplant in a subset of high-risk patients with geno-identical siblings and to compare prospectively this approach with a tandem melphalan-based dose-intensified ASCT in the same subgroup of patients without sibling donors available. Our study confirmed that this strategy is relatively safe with a 100-days mortality of 4.3% and an overall TRM of 10.9%. These results are comparable to those previously published (13, 14, 22). However this low TRM did not translate into a better long-term survival, with a 2-year estimated survival of 58% but a 5-year estimated EFS of 0%, without any plateau. This was attributed to a high relapse rate, due mostly to the selection of the patients with poor prognostic disease at the time of diagnosis. All patients included in the present trial presented with high β2m and chromosome 13 deletion, which has already been described as an adverse prognostic factor in the setting of dose-reduced allograft (23).

In the Seattle series, 32% of the patients only presented with β2m above 2.5 mg/L and chromosome 13 data were not available (14), while the median value of β2m among the cases included in the German study was 3 mg/L and again chromosome 13 status was not mentioned in that cohort of patients (13). Another possible explanation for this high relapse rate is that the conditioning regimen of the IFM99-03 trial, differing from the regimens usually proposed in dose-reduced allograft for MM (13,22), did not include melphalan and lost its cytotoxic activity. However melphalan was used prior to ASCT
for tumor burden reduction and we wanted to use dose reduced allograft mostly for its immune effects. The use of high-dose ATG given for 5 days in the preparative regimen might have contributed by its in vivo T cell depletion to the low incidence of GvHD (13, 24), but might have also inhibited for prolonged time the donor cytotoxic cells responsible for the GVM effect. The development of cGVHD seemed to be associated with a delayed progression time but disappointingly, there was no convincing plateau of any of the survival curves, the efficacy was only transient, and in the majority of the cases the disease progressed despite transplantation. Therefore, a logical interpretation could be that the GVM effect in our series was serving only to delay progression.

The results of the IFM99-04 have been discussed in details elsewhere (18) but the OS and EFS rates were superior to the 2-year and 18-month survival and EFS rates previously described in high-risk patients treated by ASCT (16,25,26). This could be attributed to the dose-intensity of mel420 (mel200 plus mel 220). The median EFS was 30 months in this cohort of 219 high-risk patients, strictly identical to the median EFS of the double transplant arm of the IFM94 trial in which 200 patients received a tandem mel140, mel140 + 8 Gy total body irradiation program (5). In this latter study, patients with de novo MM were included regardless β2m level or chromosome 13 abnormality. Nevertheless, the median OS was 58 months, much longer than the median OS of 41 months of the IFM99-04 trial, indicating that in high-risk patients the duration of survival after relapse was short and that salvage regimens were less frequently active in relation with disease severity. In such cases relapse after tandem HDT was explosive and often refractory.

In comparison with those of the IFM99-04 protocol, the results of the IFM99-03 trial could be interpreted negatively. The tandem ASCT followed by dose-reduced allograft was not superior to the tandem ASCT protocol neither for EFS nor for OS, without any
plateau on survival curves. The dose-reduced allograft as used in this study carries the risk of cGVHD which dramatically decreases the quality of life of the patients. Therefore it should not be recommended in the specific subgroup of high-risk patients. The main objective of the IFM99-03 trial was to reduce TRM and this goal was achieved, but the tumor control as previously discussed was only transient, and long-term results need to be improved. Apart from focusing on subgroup of patients with better prognosis at diagnosis or using conditioning regimen with cytotoxic anti-myeloma activity or without high-dose ATG evaluated in other ongoing European trials, it could be possible to explore systematically immunologic effects of prophylactic DLI enhancing reconstitution of donor T cells, conversion to donor hematopoiesis as well as promoting antitumor immunity as it has been reported in the context of myeloablative BMT (27). Some authors have also reported in the setting of reduced-intensity conditioning that the addition of drug such as thalidomide to DLI could improve the antitymoma effect (28). Other novel anti-myeloma agents could be investigated. It has recently been reported in a murine model that the proteasome inhibitor bortezomib given at the time of allogeneic SCT was able to inhibit acute GvHD with retention of graft-versus-tumor effect (29). All of these promising strategies should be explored in the context of prospective clinical studies.
References


Table. Patient’s characteristics

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<td></td>
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<td>n = 219</td>
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<td>58 (28-65)</td>
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<td>CRP (mg/L)</td>
<td>5 (1-132)</td>
<td>6 (1-279)</td>
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Figure 1. Study design

**de novo MM, < 65 years**

\[ \beta_{2}M > 3 \text{ mg/L and } \Delta 13 \]

VAD x 4

Stem cell collection

ASCT n°1 : HDM 200

- HLA-sibling donor available
  - Mini-allo
  - Bu-Fluda-ATG

- IFM9903 trial

- No donor available
  - ASCT n°2
  - HDM 220 +/- anti-IL6

- IFM9904 trial
Figure 2. Survival according to cGVHD

$p = .59$
Figure 3. Overall survival. IFM99-03 vs 99-04

$p = .27$

IFM 99-04, 219 patients
IFM 99-03, 65 patients
Figure 4. Event-free survival. IFM99-03 vs 99-04

$p = .56$
Figure 5. Event-free survival, protocol completed
Figure 6. Overall survival, protocol completed

$p = .07$
The following additional centres and investigators from The Intergroupe Francophone du Myélome and the SAKK participated in this study:

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Prospective comparison of autologous stem cell transplantation followed by a dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma