

blood

Prepublished online Dec 1, 2009;
doi:10.1182/blood-2009-09-241737

Melphalan 200 mg/m² versus Melphalan 100 mg/m² in newly diagnosed myeloma patients: a prospective, multi-center phase III study

Antonio Palumbo, Sara Bringhen, Benedetto Bruno, Antonietta Pia Falcone, Anna Marina Liberati, Mariella Grasso, Roberto Ria, Francesco Pisani, Clotilde Cangialosi, Tommaso Caravita, Anna Levi, Giovanna Meloni, Andrea Nozza, Patrizia Pregno, Attilio Gabbas, Vincenzo Callea, Manuela Rizzo, Luciana Annino, Valerio De Stefano, Pellegrino Musto, Ileana Baldi, Federica Cavallo, Maria Teresa Petrucci, Massimo Massaia and Mario Boccadoro

Information about reproducing this article in parts or in its entirety may be found online at:
http://bloodjournal.hematologylibrary.org/misc/rights.dtl#repub_requests

Information about ordering reprints may be found online at:
<http://bloodjournal.hematologylibrary.org/misc/rights.dtl#reprints>

Information about subscriptions and ASH membership may be found online at:
<http://bloodjournal.hematologylibrary.org/subscriptions/index.dtl>

Blood (print ISSN 0006-4971, online ISSN 1528-0020), is published semimonthly by the American Society of Hematology, 1900 M St, NW, Suite 200, Washington DC 20036.

Copyright 2007 by The American Society of Hematology; all rights reserved.



**Melphalan 200 mg/m² versus Melphalan 100 mg/m² in newly diagnosed myeloma patients:
a prospective, multi-center phase III study**

Antonio Palumbo¹, Sara Brinchen¹, Benedetto Bruno¹, Antonietta Pia Falcone², Anna Marina Liberati³, Mariella Grasso⁴, Roberto Ria⁵, Francesco Pisani⁶, Clotilde Cangialosi⁷, Tommaso Caravita⁸, Anna Levi⁹, Giovanna Meloni⁹, Andrea Nozza¹⁰, Patrizia Pregno¹¹, Attilio Gabbas¹², Vincenzo Callea¹³, Manuela Rizzo¹⁴, Luciana Annino¹⁵, Valerio De Stefano¹⁶, Pellegrino Musto¹⁷, Ileana Baldi¹⁸, Federica Cavallo¹, Maria Teresa Petrucci⁹, Massimo Massaia¹, Mario Boccadoro¹.

¹Divisione di Ematologia dell'Università di Torino, Azienda Ospedaliero-Universitaria S. Giovanni Battista, Torino, Italy; ²Unità Operativa di Ematologia Trapianto di Cellule Staminali, Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy; ³Clinica Medica I, Policlinico Monteluce, Perugia, Italy; ⁴Divisione di Ematologia, Azienda Ospedaliera S. Croce e Carle, Cuneo, Italy; ⁵Sezione Medicina Interna e Oncologia Clinica, Policlinico di Bari, Bari, Italy; ⁶Divisione di Ematologia, Istituto Regina Elena, Roma, Italy; ⁷Divisione di Ematologia e Trapianto di Midollo Osseo, Azienda Ospedaliera Cervello, Palermo, Italy; ⁸Cattedra e Divisione di Ematologia, Università Tor Vergata, Ospedale S. Eugenio, Roma, Italy; ⁹Dipartimento di Biotecnologie ed Ematologia, Università La Sapienza, Ospedale Umberto I, Roma, Italy; ¹⁰Dipartimento di Oncologia ed Ematologia, Istituto Clinico Humanitas, Rozzano (MI), Italy; ¹¹Ematologia, Azienda Ospedaliera Universitaria S. Giovanni Battista, Torino, Italy; ¹²Ematologia Ospedale di Nuoro, Nuoro, Italy; ¹³Divisione di Ematologia, Ospedale Bianco-Melacrino-Morelli, Reggio Calabria, Italy; ¹⁴Ematologia, Policlinico Tor Vergata, Roma, Italy; ¹⁵Unità Operativa di Ematologia, Complesso Ospedaliero S. Giovanni Addolorata di Roma, Italy; ¹⁶Istituto di Ematologia, Università Cattolica, Roma, Italy; ¹⁷Unità di Ematologia e Trapianto di cellule staminali, CROB, Centro di Riferimento Oncologico di Basilicata, Rionero in Vulture (PZ); ¹⁸Unità di Epidemiologia dei Tumori, Azienda Ospedaliera Universitaria S. Giovanni Battista, CPO Piemonte, Torino, Italy

Running Head Melphalan 200 mg/m² vs. 100 mg/m² in myeloma

Key words myeloma, melphalan, autologous transplantation

Scientific category Clinical Trials and Observations

Correspondence to Antonio Palumbo, Divisione di Ematologia dell'Università di Torino, Azienda Ospedaliero-Universitaria San Giovanni Battista, Via Genova 3, 10126 Torino, Italy; e-mail: appalumbo@yahoo.com.

Tel.: +39 01 1663 5814; fax: +39 01 1696 3737.

ABSTRACT

High-dose (200 mg/m², MEL200) and intermediate-dose melphalan (100 mg/m², MEL100) showed significant activity in myeloma. Differences in toxicity and efficacy between them have never been evaluated. In a phase III study, 298 patients were randomly assigned to receive two autologous transplantations after conditioning with MEL200 or MEL100. Ninety-six/149 (64%) completed the MEL200 arm, 103/149 (69%) the MEL100 arm. Best response to MEL200 was: complete remission (CR) 22/149 (15%); partial remission (PR) 95/149 (64%), for an overall response rate of 79%. Best response to MEL100 was: CR 12/149 (8%); PR 95/149 (64%), for an overall response rate of 72%. Overall-survival did not differ (p=0.13); median progression-free-survival (31.4 vs 26.2 months, p=0.01), median time-to-progression (34.4 vs 27.0 months, p=0.014) were longer in the MEL200. Treatment-related mortality was 3.1% in the MEL200 and 2.9% in the MEL100 group. The incidence of severe neutropenia and infections were marginally superior; whereas severe thrombocytopenia, mucositis, gastrointestinal adverse events and the overall occurrence of at least one non-hematological grade 3-4 adverse event were significantly higher in the MEL200 cohort. We conclude that MEL200 leads to longer remission duration and should be considered the standard conditioning regimen for autologous transplantation. This study is registered at <http://clinicaltrials.gov> as NCT00950768.

INTRODUCTION

Several studies support the benefit of high dose melphalan with stem cell rescue in patients with newly diagnosed multiple myeloma.¹⁻³ Results from randomised trials are in favour of tandem autologous transplant rather than only one procedure, even though a real benefit remains to be determined.^{4,5} Most conditioning regimens have been based on either melphalan alone or in combination with other agents. Melphalan at 200 mg/m² (MEL200) is considered the standard dose for conditioning patients younger than 65 years.⁶ Older age and comorbidities may become limiting factors. In a retrospective case-matched study, 90 newly diagnosed patients treated with two courses of melphalan at 100 mg/m² (MEL100) were compared with a control group of 90 pair mates, matched for serum β -microglobulin levels and Durie-Salmon clinical stage, and treated up-front with two MEL200 courses.⁷ Median progression-free survival (PFS) was significantly superior in the MEL200 group, but overall survival (OS) was not different. Moreover, hematological and non-hematological toxicities were significantly reduced in the MEL100 group. Here, we report a phase III clinical trial comparing two doses of melphalan, MEL200 vs MEL100, in newly diagnosed multiple myeloma. The underlying hypothesis was that rather than give two very intensive preparative regimens prior to autologous stem cell infusions, providing effective myeloma cell kill, a less toxic reduced-intensity conditioning would be better tolerated, especially in older patients, and equally effective.

METHODS

Patients From October 2001 to July 2006, 298 newly diagnosed myeloma patients younger than 65 years were enrolled in a prospective phase III trial (Figure 1). Patients were randomized before induction treatment either to receive two courses of MEL200

or two courses of MEL100 without any stratification for prognostic factors. Informed consent was obtained upon enrolment. The protocol was approved by the Institutional Review Boards of the participating Centers according to the Declaration of Helsinki.

Inclusion criteria were: diagnosis of untreated Durie & Salmon stage⁸ IIA-IIIIB; measurable multiple myeloma; age < 65 years. Exclusion criteria were: prior treatment for myeloma; abnormal cardiac function, defined as systolic ejection fraction < 50%; abnormal pulmonary spirometry test; serum bilirubins 2.5 times > normal and ALT and/or AST 2 times > normal; seropositivity for HIV, HCV or HBV; active non-hematological malignancies.

Induction therapy, peripheral blood stem cell (PBSC) mobilization, and autografting Initial treatment plan included induction chemotherapy with 2 courses of vincristine, 1 mg/m² on day 1, adriamycin, 50 mg/m² on day 1, and dexamethasone, 40mg/day days 1-4, administered 28 days apart, followed by PBSC mobilisation and harvest after 1 or 2 cycles of cyclophosphamide, 4 g/m², and G-CSF, 10 µg/kg given i.v. or subcutaneously. After at least one month from PBSC collection, autografting consisted of MEL200 or MEL100 on day -2, and cryopreserved PBSC infusion on day 0. Patients received G-CSF, 5 µg/kg, from day +3 until neutrophil count > 1000/µl was achieved.

Supportive care and toxicity grading Following autografting, all patients received standard prophylaxis against bacterial and fungal infections; herpes simplex and varicella-zoster virus reactivation; and Pneumocystis carinii. Cytomegalovirus (CMV) reactivation was monitored through levels of CMV antigenemia and/or serum CMV DNA levels and treated with ganciclovir or foscarnet as clinically indicated. Standard

criteria (Common Toxicity Criteria version 3.0) were used for grading hematological and non-hematological toxicity.

Disease response Response was evaluated prior to each treatment, monthly for the first six months following autografting and at least every three months thereafter or as clinically indicated. Response criteria were defined according to the International Uniform Response Criteria for multiple myeloma.⁹ Complete remission (CR) required absence of serum monoclonal immunoglobulins and/or Bence-Jones proteinuria by electrophoresis and immunofixation, less than 5% plasma cell infiltration in bone marrow aspirates, absence of soft tissue lesions and no increase in size or number of osteolytic lesions. Very good partial remission (VGPR) was defined as detection of serum monoclonal immunoglobulins and/or Bence-Jones proteinuria by immunofixation but not by electrophoresis or at least 90% reduction in serum monoclonal immunoglobulins or Bence-Jones proteinuria with excretion lower than 100 mg /24-hour, and no increase in size or number of osteolytic lesions. Partial remission (PR) was defined as > 50% reduction in the levels of serum monoclonal immunoglobulin, at least 90% reduction in 24-hour Bence-Jones proteinuria or excretion lower than 200 mg /24-hour, and no increase in size or number of lytic bone lesions. Patients with less than a PR were considered stable (SD). Progressive disease (PD) was considered an increase in serum monoclonal proteins or Bence-Jones proteinuria of at least 25% in patients with at least PR whereas disease relapse was considered as the reappearance of monoclonal proteins by immunofixation in case of previous CR.

Statistical analysis Analyses were performed according to the intention-to-treat principle. Primary endpoints of the study were OS defined as the time from diagnosis

until death from any cause. Secondary endpoints were PFS defined as the time from diagnosis until death from any cause or date of first relapse or progression; time to progression (TTP) defined as the time from the date of diagnosis to relapse or death from progression; incidence of gastrointestinal toxicity and infections; and treatment-related mortality defined as any death occurring within 60 days and attributable to therapy. Patients lost to follow-up or survivors who experienced no event were censored at the date of last contact. Moreover, subgroups analyses were performed in the light of patient age (< 60 years, \geq 60 years).

A sample size of 320 patients (160 per arm) was required to detect a 20% increase in OS at 5 years (from 40% to 60%) with an alpha error of 0.05 and a beta error of 0.10, assuming an accrual of 36 months and a minimum follow up of 24 months.

Proportions between groups were compared by the chi-square test or Fisher's exact test. OS, PFS and TTP were calculated according to the Kaplan-Meier method.¹⁰ Differences in OS, PFS and TTP were tested with the two-tailed log-rank test. Univariate hazard ratios (HR) and corresponding 95% confidence interval (CI) were estimated with the Cox proportional hazards model.¹¹ Analyses of PFS and OS according to response were performed using the landmark analysis method (landmark point at 12 months). SAS 8.2 statistical software (SAS Institute, Cary, NC) was used.

RESULTS

Patients

Because of the declining enrolment, the steering committee decided to stop the trial in July 2006 after the first 298 randomized patients (93% of the planned sample size). Overall, 298 patients were randomized to two cohorts of 149 each at 31 Italian Divisions of Hematology and Bone Marrow Transplantation Units. Patient

characteristics were evenly distributed in both groups (Table 1). Ninety-six/149 (64%) completed the MEL200 arm whereas in the 53 (36%) who did not complete it, main causes of early drop-out were allografting (12 patients, 8%), consent withdrawal (10 patients, 7%), early adverse events (9 patients, 6%), early disease progression (8 patients, 5%), and poor PBSC collections (8 patients, 5%). One-hundred-three/149 (69%) completed the MEL 100 arm and main causes of early drop-out in 46 (31%) were allografting (15 patients, 10%), early disease progression (9 patients, 6%), poor PBSC collection (9 patients, 6%), adverse events (5 patients, 6%) and consent withdrawal (4 patients, 3%) (Figure 1).

Engraftment and Response Median numbers of CD34+ cells collected pre-transplant in the MEL200 and MEL100 arms were $12 \times 10^6/\text{Kg}$ (range, $0-54 \times 10^6$) and $14 \times 10^6/\text{Kg}$ (range, $0-72 \times 10^6$) respectively. Median numbers of CD34+ cells infused in each arm were as follows: $5 \times 10^6/\text{Kg}$ (range, $2-12 \times 10^6$) and $5 \times 10^6/\text{Kg}$ (range, $2-10 \times 10^6$) patient body weight in the MEL200 group for the first and second transplant respectively; and $4 \times 10^6/\text{Kg}$ (range, $2-15 \times 10^6$) and $3 \times 10^6/\text{Kg}$ (range, $2-15 \times 10^6$) patient body weight in the MEL100 group for the first and second transplant respectively. In the MEL200 patients, best response to DAV was: at least VGPR 6/149 (4%); at least PR 50/149 (33%); stable disease 90/149 (60%); and progressive disease 4 (3%). In the MEL100 patients, best response to DAV was: at least VGPR 3/149 (2%); at least PR 47/149 (31%); stable disease 91/149 (61%); and progressive disease 7 (5%). Best response to MEL200 was as follows: CR 22/149 (15%); at least VGPR 55/149 (37%); at least PR 117/149 (78%); stable disease 27/149 (18%); and progressive disease 1 (1%). Best response to MEL100 was as follows: CR 12/149 (8%); at least VGPR

32/149 (21%); at least PR 107/149 (72%); stable disease 34/149 (23%); and progressive disease 5 (3%) (Table 2).

Clinical Outcomes After a median follow up of 44,6 (range 0.5-79.9+) months from diagnosis in each group, median OS was not reached in the MEL200 group and was 60 months in the MEL100 group (HR 0.74, 95% CI 0.50-1.09, p=0.13) (Figure 2, Panel A). Projected OS at 5 years was 61.8% and 47.7% in the MEL200 and MEL100 groups respectively. Median PFS was 31.4 (95% CI 27.8-43.5) and 26.2 (95% CI 21.5-29.1) months in MEL200 and MEL100 respectively (HR 0.69, 95% CI 0.52-0.93, p=0.01) (Figure 2, Panel B). PFS at 4 years was 37.1% and 19.6% in the MEL200 and MEL100 groups respectively. Median TTP were 34.4 (95% CI 29.8-44.7) and 27.0 (95% CI 21.8-30.0) months in MEL200 and MEL100 respectively (HR 0.69, 95% CI 0.51-0.93, p=0.01). Projected TTP at 4 years was 39.5% and 22.1% in the MEL200 and MEL100 groups respectively. By applying a 12-month landmark analysis, the achievement of CR was not predictive of better OS (HR 1.18, 95% CI 0.65-2.14, p=0.58) and PFS (HR 0.96, 95% CI 0.62-1.48, p=0.85). Similarly, the achievement of at least VGPR did not influence OS (HR 0.85, 95% CI 0.50-1.44, p=0.55) or PFS (HR 0.77, 95% CI 0.55-1.10, p=0.15).

Age and response to DAV were prognostic factors for both OS and PFS. In patients older than 60 years, MEL200 did not prolong OS (HR 0.83, 95% CI, 0.47-1.45) and PFS (HR 0.84, 95% CI, 0.54-1.30); in patients younger than 60 years, MEL200 marginally improved OS (HR 0.61, 95% CI, 0.34-1.08) and significantly enhanced PFS (HR 0.60, 95% CI, 0.41-0.88) (Figure 3). In patients who achieved at least PR to DAV, MEL200 improved neither OS (HR 0.90, 95% CI, 0.46-1.75) nor PFS (HR 0.83, 95% CI, 0.51-1.40); in patients who did not achieve at least PR to DAV, MEL200 prolonged both OS (HR 0.65, 95% CI, 0.40-1.07) and PFS (HR 0.63, 95% CI, 0.44-0.90).

Salvage treatments Overall, 179 (60%) patients had progression or relapse: 80 (54%) in the MEL200 group and 99 (66%) in the MEL100 group respectively. Second line treatment was given to 64 (43%) patients assigned to MEL200 and to 84 (56%) assigned to MEL100. Thirteen (9%) MEL200 patients and 16 (11%) MEL100 patients did not receive any salvage regimen, mainly because of death due to rapid disease progression. Chemotherapy-based salvage regimens were used in 10 (6%) MEL200 patients and 16 (11%) MEL100 patients. Thalidomide-based salvage regimens were used in 15 (10%) MEL200 patients and 34 (23%) MEL100 patients; bortezomib-based salvage regimens were used in 40 (27%) MEL200 patients and 27 (18%) MEL100 patients; lenalidomide-based regimens were used in 2 (1%) MEL200 patients and in 6 (4%) MEL100 patients.

Toxicities Three patients died of treatment-related complications in both arms accounting for a treatment-related mortality of 3.1% and 2.9% in the MEL200 and in the MEL100 group respectively. In the MEL200 cohort, causes of death were stroke after induction, cardiac failure after the first cycle of cyclophosphamide, and pneumonia after the first MEL200, whereas in the MEL100 group they were septic shock after induction, pneumonia after the first cycle of cyclophosphamide, and cerebral hemorrhage after the first MEL100.

Hematological and non-hematological toxicities are listed in Table 3. Platelet transfusion requirement was significantly higher in the MEL200 group (56% vs 38%, $p=0.002$) as well as the use of intravenous broad-spectrum antibiotics (41% vs 29%, $p=0.03$), gastrointestinal toxicities (11% vs 1%, $p=0.0007$) and mucositis (17% vs 3%, $p<0.0001$). Other non-hematological grade 3-4 toxicities were evenly distributed. The overall occurrence of at least one non-hematological grade 3-4 adverse event during treatment was significantly higher in the MEL200 group (45% vs 30%, $p=0.008$).

DISCUSSION

In this randomized study two different doses of melphalan have been evaluated as preparative regimen for autologous transplantation in newly diagnosed patients. MEL200 was more effective than MEL100: the median PFS was 31.4 vs 26.2 months, $p=0.01$. This advantage was more pronounced in patients younger than 60 years.

The longer PFS and TTP, seen in the MEL200 group, did not translate into a survival advantage, although a plateau phase was observed after 50 months in patients who received MEL200. These data are consistent with previous observations, where the availability of several new effective agents, used as salvage therapies in both study groups, may offset the initial benefit of a more effective treatment at diagnosis.¹² In the past, when melphalan-based regimens were the only effective treatments, the advantage induced at diagnosis translated into a longer OS. More recently, at least three other effective agents are available and their use at relapse may highly reduce the clinical benefit induced at diagnosis. In our study about 60-70% of relapsed patients received new drugs as first salvage treatments and this may have affected OS. A longer follow-up is needed to better evaluate the effect of salvage therapy.

The superiority of autografting over conventional therapy for younger patients has been reported in prospective randomised trials. In the IFM-90 study, CR rates (22% vs. 5%), 5 year PFS (28% vs. 10%) and OS (52% vs. 12%) were significantly better in the transplant group.¹³ Similarly, in the Medical Research Council Myeloma VII Trial, the CR rate (44% vs. 8%; $p < 0.001$), PFS (28 vs. 20 months) and OS (54 vs. 42 months) were superior in the transplant group.² The most appropriate preparative regimen for autologous transplantation is generally considered MEL200.¹⁴

The introduction of thalidomide, bortezomib and lenalidomide, in the late '90s and early 2000s, has dramatically changed the treatment options and the clinical

outcome of both relapsed/refractory¹⁵ and newly diagnosed myeloma patients.¹⁶ Patients diagnosed after December 1996, when thalidomide was first introduced, have shown a 50% improvement in OS.¹⁵ The introduction of bortezomib as induction regimen before autologous transplantation has significantly improved response rate and PFS.¹⁷⁻²⁰ According to these data, novel agents should be consistently used in the induction regimens before autologous transplantation. Which between MEL200 and MEL100 is the most appropriate preparative regimen for autologous transplantation in association with novel agents remains to be determined. MEL100 induces less adverse events and may be equally effective when new agents are included in the induction.

Alkylating agents such as intravenous melphalan still play an important role in the treatment of patients with myeloma. High dose melphalan, 200 mg/m², is the standard dose for the preparative regimen to autologous transplantation under the age of 60-65 years. In a large study, the outcome of patients > 65 years, who received MEL200, was significant inferior to those < 65 years.²¹ Most trials have primarily included patients with good organ functions. Though age per se should not be a contraindication for an autograft, comorbidities can be a limiting factor even in younger patients. Our study is the first phase III trial conducted in untreated newly diagnosed myeloma patients younger than 65 to compare two different doses of melphalan followed by autologous stem cell rescue. Our findings suggest that the greater benefit of MEL200 is in patients < 60 years and that MEL200 should be considered the standard conditioning regimen for autologous transplantation.

In elderly patients, conflicting results have been reported on the clinical efficacy of MEL100. An IFM study showed no differences in efficacy between MEL100 and the oral combination melphalan-prednisone in patients aged 65–75 years,²² whereas a GIMEMA study showed a superiority of MEL100 in patients aged 65–70.³ In a recent

phase II study, including bortezomib in the induction, MEL100 as preparative regimen for autologous stem cell rescue, and lenalidomide as maintenance, clinical outcome was superior in patients aged 65-70 as compared to those aged 70-75.²⁰ Although caution is imperative when evaluating non randomized trials, overall, these studies suggest that age 60-65 years and 65-70 years should be considered the upper age limits for MEL200 and MEL100 respectively.

In our report, treatment-related mortality was some 3% in both arms which is consistent with the mortality reported in other studies after a standard autograft.^{2,13,23} The occurrence of at least one grade 3-4 adverse event, either haematological or non-haematological, was significantly higher in the MEL200 group. The higher toxicity of MEL200 is also confirmed by the higher transfusion requirement and the higher use of intravenous antibiotics requiring inpatient hospital admittance. Overall, these findings may further support the use of MEL100 as an alternative option for patients younger than 65 years with co-morbidities that may significantly increase the risks of toxicity after MEL200.

In conclusion, our study suggests that MEL200 is the conditioning regimen of choice in younger medically fit patients undergoing an autologous transplant. However, MEL100, given the low toxicity profile, may be considered in younger patients with non-haematological co-morbidities.

ACKNOWLEDGEMENTS

Our thanks to the nurses and medical staff for caring for the patients and to the study co-ordinators who collected the trial and follow-up data.

AUTHORSHIP

Contributions A.P. and M.B. designed the study, supervised its conduct and data analysis and wrote this paper; B.B. contributed patients to the study and assisted in drafting and editing the manuscript; S.B. and F.C. participated in designing research/protocol, contributed patients to the study, verified data, assisted in drafting manuscript; A.P.F., A.M.L., M.G., R.R., F.P., C.C., T.C., A.L., G.M., A.N., P.P., A.G., V.C., M.R., L.A., V.D.S., P.M., M.T.P., and M.M. contributed patients to the study, reviewed manuscript; I.B. did the statistical analysis and reviewed the manuscript.

Conflict of interest disclosure The authors declare that they have no conflict of interest

REFERENCES

1. Attal M, Harousseau JL, Stoppa AM, et al. A Prospective, Randomized Trial of Autologous Bone Marrow Transplantation and Chemotherapy in Multiple Myeloma. *N Engl J Med.* 2003;335(2):91-97.
2. Child JA, Morgan GJ, Davies FE, et al. High dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med* 2003;348(19):1875-1883.
3. Palumbo A, Bringhen S, Petrucci MT, et al. Intermediate-dose melphalan improves survival of myeloma patients aged 50 to 70: results of a randomized controlled trial. *Blood.* 2004;104(10):3052-3057.
4. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med.*2003;349:2495-2502.
5. Goldschmidt H. Single vs. Double high-dose therapy in multiple myeloma: Second analysis of the GMMG-HD2 trial [abstract]. *Haematologica.* 2005;90(S1):38: abstract PL8.02.
6. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m² melphalan and 8 Gy total body irradiation plus 140 mg/m² melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. *Blood.* 2002;99(3):731-735.
7. Palumbo A, Bringhen S, Bertola A, et al. Multiple Myeloma: Comparison of two dose-intensive melphalan regimens (100 vs 200 mg/ m²). *Leukemia.* 2004;18(1):133-138.

8. Durie BG, Salmon SE. A clinical staging system for multiple myeloma. Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer*. 1975;36(3):842–854.
9. Durie BGM, Harousseau J-L, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20(9):1464-1473.
10. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association*. 1958;53:457-481.
11. Cox DR. Regression Models and Life-Tables. *J R Stat Soc B*. 1972;34(2):187-220.
12. Palumbo A, Rajkumar SV. Treatment of newly diagnosed myeloma. *Leukemia*. 2009;23(3):449-456.
13. Attal M, Harousseau J-L, Stoppa A-M, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med*. 1996;335(2):91-97.
14. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m² melphalan and 8 Gy total body irradiation plus 140 mg/m² melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. *Blood*. 2002;99(3):731-735.
15. Kumar SK, Rajkumar Sv, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood*. 2008;111(5):2516-2520.
16. Harousseau JL. Induction Therapy in Multiple Myeloma. *Am Soc Hematol Educ Program*. 2008: 306-312.
17. Cavo M, Tacchetti P, Patriarca F, et al. Superior Complete Response Rate and Progression-Free Survival after Autologous Transplantation with up-Front

- Velcade-Thalidomide- Dexamethasone Compared with Thalidomide-Dexamethasone in Newly Diagnosed Multiple Myeloma [abstract]. *Blood*. 2008;112:abstract 158.
18. Harousseau JL, Attal M, Leleu X, et al. Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: results of an IFM phase II study. *Haematologica*. 2006;91(11):1498-505.
19. Harousseau JL, Mathiot C, Attal M, et al. VELCADE/Dexamethasone (Vel/D) Versus VAD as Induction Treatment Prior to Autologous Stem Cell Transplantation (ASCT) in Newly Diagnosed Multiple Myeloma (MM): Updated Results of the IFM 2005/01 Trial [abstract]. *Blood*. 2007;110:abstract 450.
20. Palumbo A, Gay F, Falco P, et al. Bortezomib as Induction Before Autologous Transplantation, Followed by Lenalidomide as Consolidation-Maintenance in untreated Multiple Myeloma Patients. *J Clin Oncol*. 2009; in press.
21. Barlogie B, Tricot G, Anaissie E, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med*. 2006;354(10):1021-1030.
22. Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet*. 2007;370(9594):1209-1218.
23. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. *J Clin Oncol*. 2006; 24(6):929-936.

Table 1. Patient Characteristics according to treatment group		
Characteristic	MEL200 (N=149)	MEL100 (N=149)
Sex-male no (%)	78 (48)	78 (48)
Age-yr		
Median age (range)	58 (33-65)	57 (32-65)
Age-no (%)		
60-65 years	67 (45)	51 (34)
55-59 years	37 (25)	37 (25)
50-54 years	21 (14)	38 (25)
< 50 years	24 (16)	23 (15)
Stage-no (%)		
IIA	42 (28)	46 (31)
IIB	5 (3)	3 (2)
IIIA	94 (63)	90 (60)
IIIB	8 (5)	10 (7)
M-protein class-no (%)		
IgG	88 (59)	83 (56)
IgA	33 (22)	42 (28)
Bence Jones protein	27 (18)	21 (14)
Other	0 (0)	3 (2)
Haemoglobin		
No. of patients	77	81
Median (g/dL)	11.0	11.4
Range (g/dL)	6.2-15.3	5.2-16.4
Serum creatinine		
No. of patients	149	149
Median (mg/dL)	0.8	0.8
Range (mg/dL)	0.6-2.4	0,35-2.5
Serum calcemia		
No. of patients	74	72
Median (mmol/L)	2.29	2.36
Range (mmol/L)	1.25-3.22	1.75-3.12
International Staging System		
1	60 (40)	71 (48)
2	49 (33)	38 (25)
3	18 (12)	23 (15)
Data missing	22 (15)	17 (11)
Serum β 2-microglobulin		
No. of patients	127	132
Median (mg/L)	3.03	2.94
Range (mg/L)	0.2-17.35	0.17-38.2
β 2-microglobulin-no (%)		
\leq 3.5 mg/L	73 (49)	84 (57)
$>$ 3.5 mg/L	54 (36)	48 (32)
Data missing	22 (15)	17 (11)
Albumin		
No. of patients	63	59
Median (g/dL)	3.5	3.6
Range (g/dL)	1.5-4.8	2.2-5.2
Plasma C-reactive protein		
No. of patients	119	121
Median (mg/L)	0.90	0.6
Range (mg/L)	0.005-43	0.002-63

Response	MEL200 (N=149)	MEL100 (N=149)	p value*
	No of patients (%)	No of patients (%)	
Complete, very good partial or partial response	117 (78.5)	107 (71.8)	0.23
Complete response	22 (14.8)	12 (8.1)	0.07
Very good partial response	33 (22.1)	20 (13.4)	
Partial response	62 (41.6)	75 (50.3)	
Stable disease	27 (18.1)	34 (22.8)	0.31
Progressive disease	1 (0.7)	5 (3.4)	0.10
<i>Not available</i>	4 (2.7)	3 (2.0)	0.7

* Proportions were compared with the use of chi-square test or Fisher's exact test. ^(§)(≥90% myeloma protein reduction). Seven patients were not evaluated because their follow up was less than 1 month for lost to follow-up (6) and withdrawal of consent (1).

Table 3. Hematological and non-hematological toxicity			
Grade 3-4 Adverse Events	MEL200 (N=149)	MEL100 (N=149)	p value*
	No (%)	No (%)	
Hematological			
Grade 4 neutropenia-no (%)	114 (77)	100 (67)	0.07
Grade 4 neutropenia duration-days			
Median	6	6	
Range	0-15	0-15	
Grade 4 thrombocytopenia-no (%)	113 (76)	73 (49)	0.0001
Grade 4 thrombocytopenia duration-days			
Median	1	1	
Range	0-20	0-21	
Red cell transfusion-no (%)	43 (29)	48 (33)	0.45
Platelet transfusion-no (%)	82 (56)	55 (38)	0.002
Hospitalization post-engraftment			
No of patients (%)	100 (68)	90 (62)	0.23
Median days	3	2	
Range days	1-25	1-23	
Intravenous antibiotics			
No of patients (%)	60 (41)	42 (29)	0.03
Median days	7	6	
Range days	2-28	2-13	
Non-hematological			
Mucositis-no (%)	26 (17)	5 (3)	<0.0001
Gastrointestinal-no (%)	16 (11)	2 (1)	
Diarrhea	7	1	0.0007
Vomiting	9	1	
Infection-no (%)	60 (40)	44 (30)	0.06
Neutropenic fever	26	26	
Pneumonia	11	6	
Sepsis	14	6	
Central venous catheter	2	3	
Viral	4	2	
Other	3	1	
Thromboembolism-no (%)	3 (2)	4 (3)	1
Deep vein thrombosis	1	4	
Pulmonary embolism	2	0	
Renal-no (%)	1 (1)	0 (0)	1
Cardiac-no (%)	1 (1)	0 (0)	1
Pulmonar-no (%)	1 (1)	0 (0)	1
Neurologic-no (%)	1 (1)	0 (0)	1
Bleeding-no (%)	1 (1)	1 (1)	1
Coagulation-no (%)	0 (0)	1 (1)	1
At least 1 event-no (%)	67 (45)	45 (30)	0.008

* Proportions were compared with the use of chi-square test or Fisher's exact test.

FIGURE LEGENDS

Figure 1 Design of the trial

Abbreviations: MEL200, melphalan 200 mg/m²; MEL100, melphalan 100 mg/m²; DAV, dexamethasone, adriamycin, vincristine; CTX, cyclophosphamide.

Figure 2 Clinical outcomes by intent-to-treat analysis of the two study cohorts: overall survival (Panel A); progression free survival (Panel B). Abbreviations: MEL200, melphalan 200 mg/m²; MEL100, melphalan 100 mg/m²; hazard ratio, HR; CI, confidence interval.

Figure 3 Overall survival in patients older (Panel A) and younger than 60 years (Panel B); progression-free survival in patients older (Panel C) and younger than 60 years (Panel D). Abbreviations: MEL200, melphalan 200 mg/m²; MEL100, melphalan 100 mg/m²; HR, hazard ratio; CI, confidence interval.

Figure 1

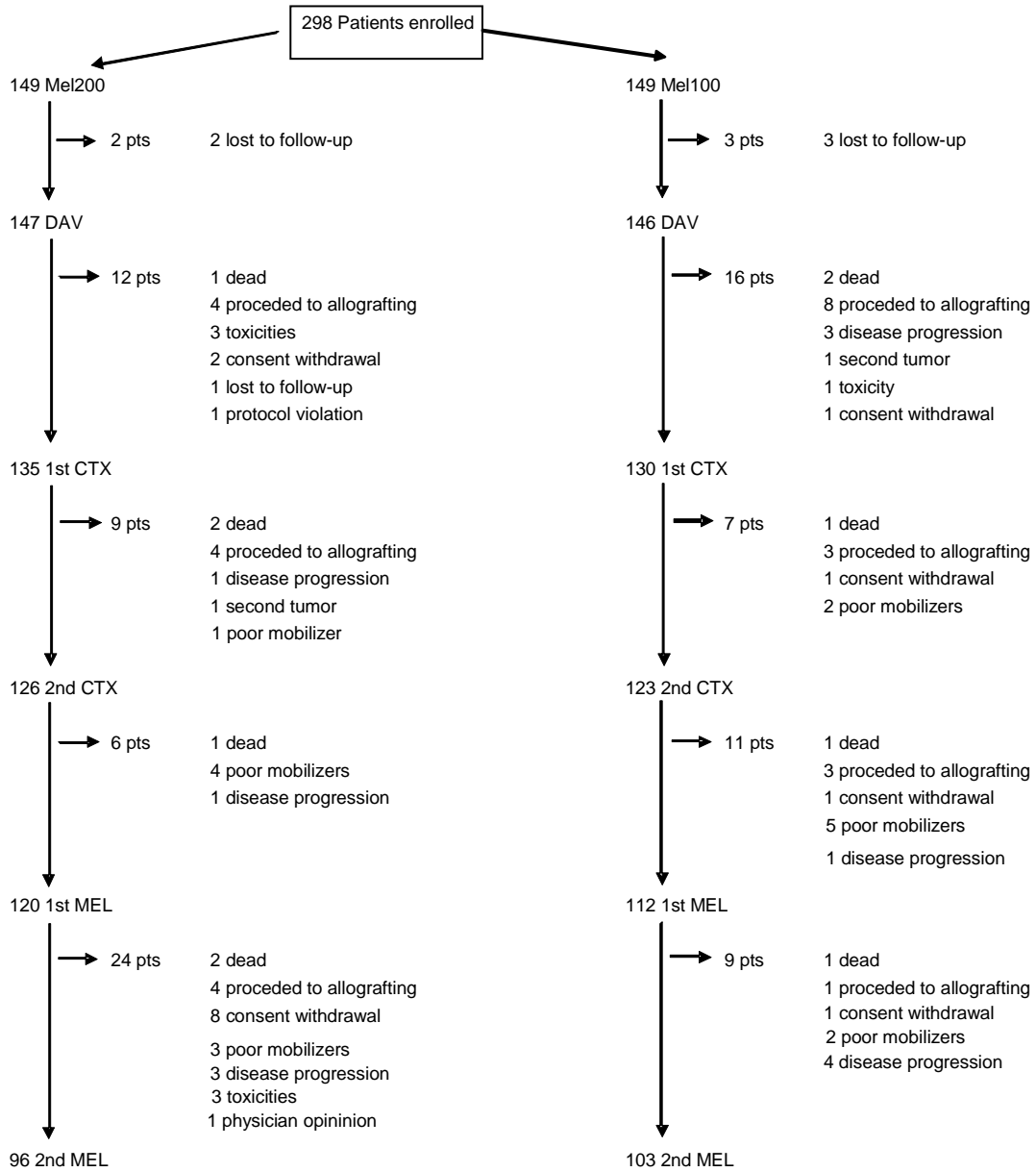
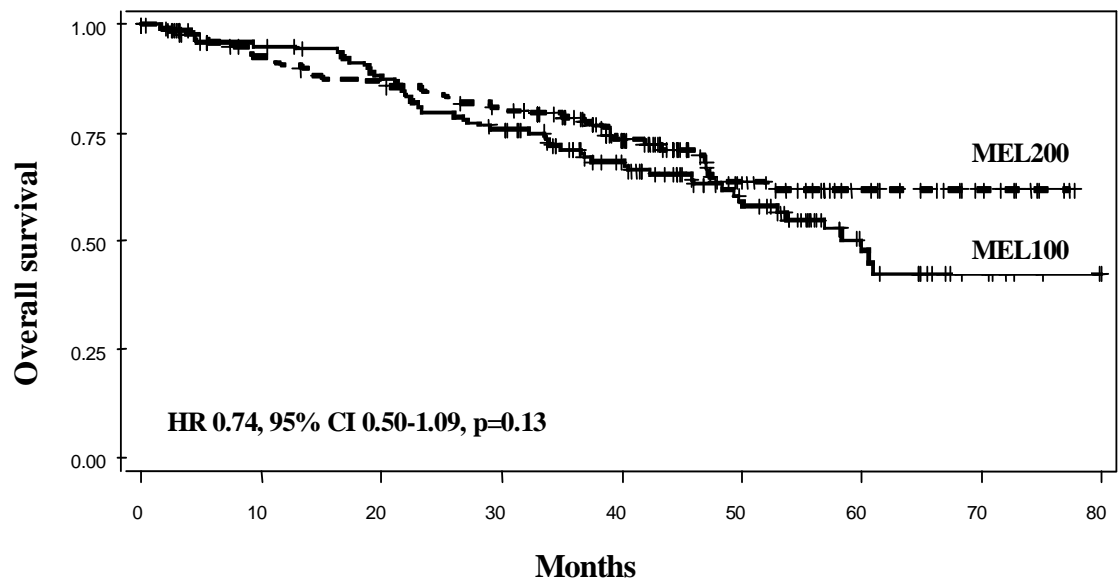


Figure 2

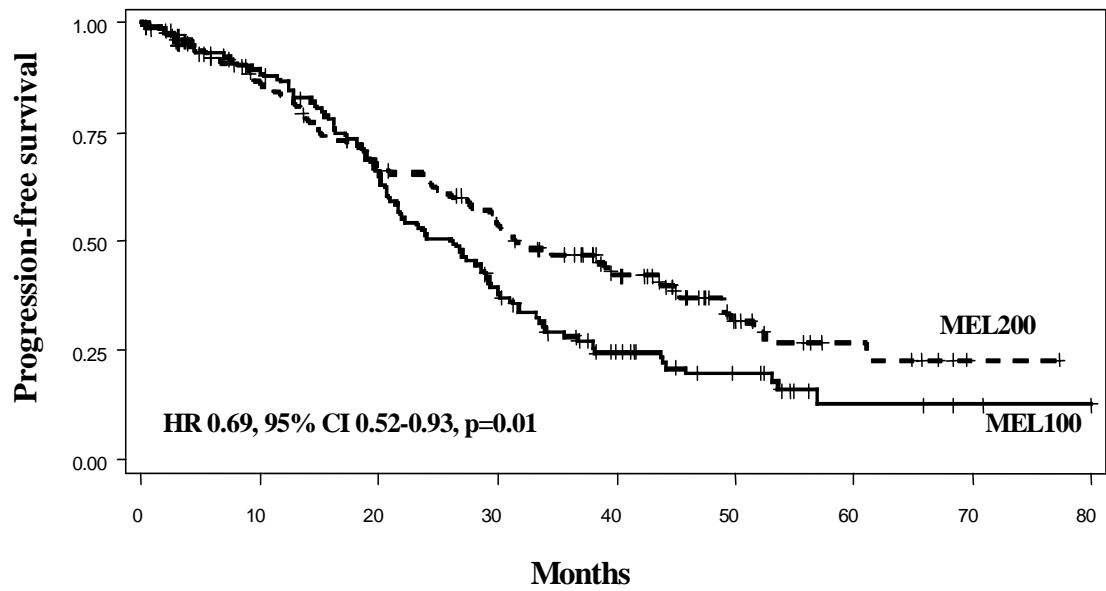
Panel A



No. at risk	0	10	20	30	40	50	60
MEL200	149	127	116	107	77	38	20
MEL100	149	132	119	102	72	45	18

Figure 2

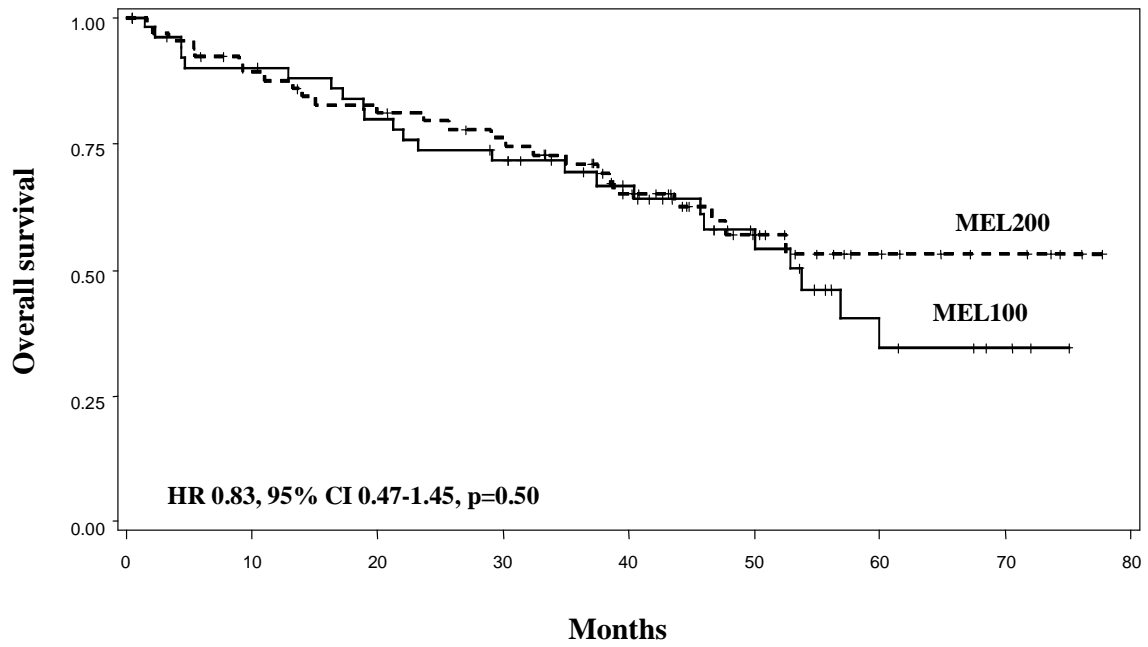
Panel B



No. at risk	0	10	20	30	40	50
MEL200	149	115	89	69	43	16
MEL100	149	119	86	51	24	13

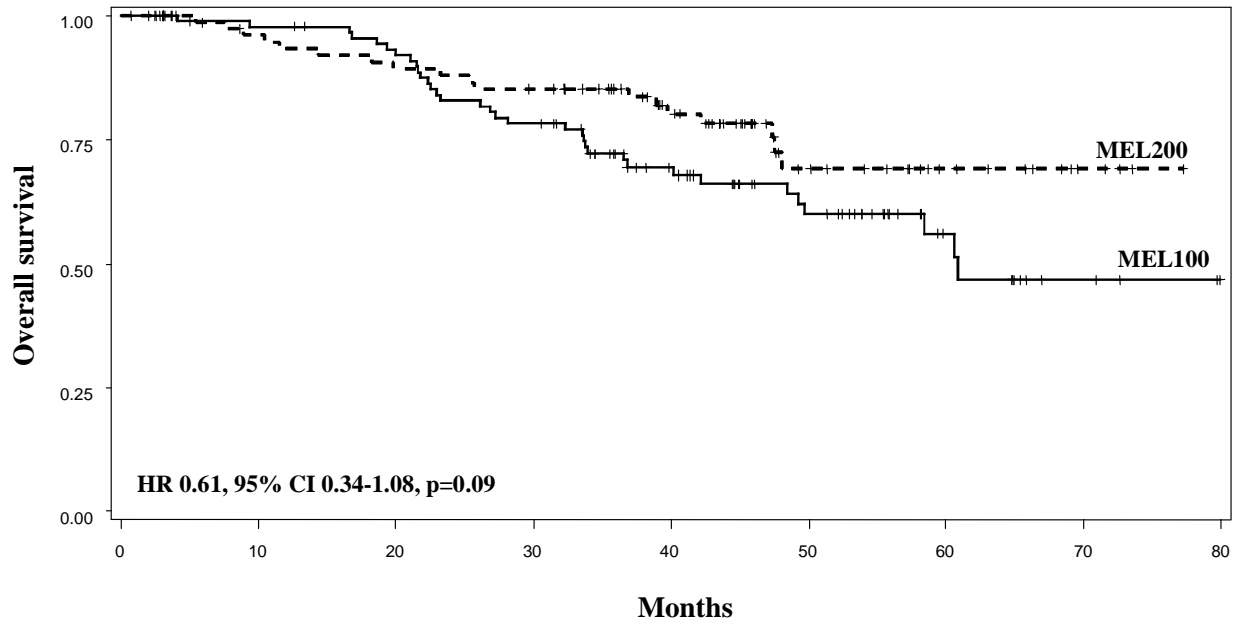
Figure 3

Panel A



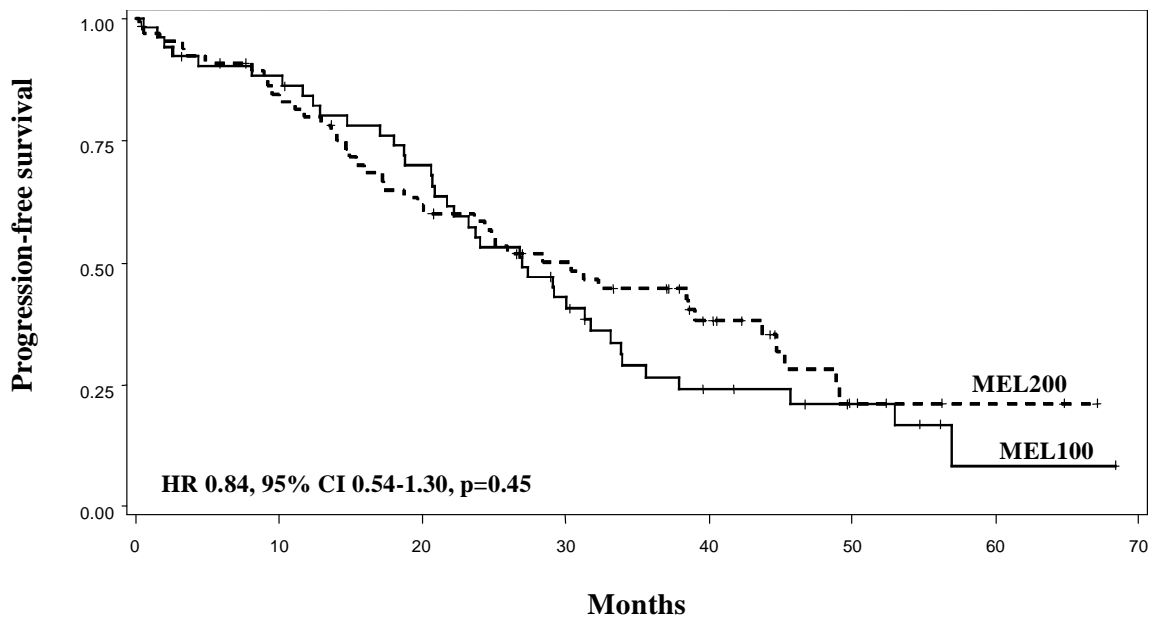
No. at risk	0	10	20	30	40	50	60
MEL200	67	56	51	45	32	18	9
MEL100	51	45	39	34	26	15	6

Panel B



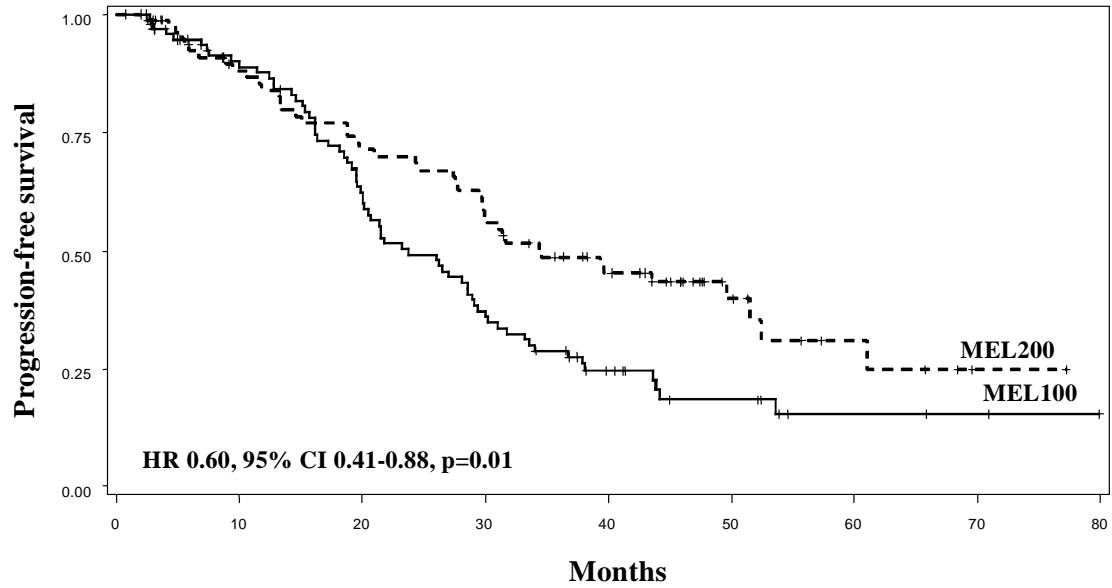
No. at risk	0	10	20	30	40	50	60
MEL200	82	71	66	62	45	20	11
MEL100	98	87	80	68	46	30	12

Panel C



No. at risk	0	10	20	30	40	50
MEL200	67	52	38	28	16	5
MEL100	51	44	34	20	9	5

Panel D



No. at risk	0	10	20	30	40	50
MEL200	82	64	51	41	27	11
MEL100	98	75	52	31	15	8