Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial

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Summary

Background Any benefit of adjuvant interferon alfa-2b for melanoma could depend on dose and duration of treatment. Our aim was to determine whether pegylated interferon alfa-2b can facilitate prolonged exposure while maintaining tolerability.

Methods 1256 patients with resected stage III melanoma were randomly assigned to observation (n=629) or pegylated interferon alfa-2b (n=627) 6 μg/kg per week for 8 weeks (induction) then 3 μg/kg per week (maintenance) for an intended duration of 5 years. Randomisation was stratified for microscopic (N1) versus macroscopic (N2) nodal involvement, number of positive nodes, ulceration and tumour thickness, sex, and centre. Randomisation was done with a minimisation technique. The primary endpoint was recurrence-free survival. Analyses were done by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00006249.

Findings All randomised patients were included in the primary efficacy analysis. 608 patients in the interferon group and 613 patients in the observation group were included in safety analyses. The median length of treatment with pegylated interferon alfa-2b was 12 (IQR 3·8–33·4) months. At 3·8 (3·2–4·2) years median follow-up, 328 recurrence events had occurred in the interferon group compared with 368 in the observation group (hazard ratio 0·82, 95% CI 0·71–0·96; p=0·01); the 4-year rate of recurrence-free survival was 45·6% (SE 2·2) in the interferon group and 38·9% (2·2) in the observation group. There was no difference in overall survival between the groups. Grade 3 adverse events occurred in 246 (40%) patients in the interferon group and 60 (10%) in the observation group; grade 4 adverse events occurred in 32 (5%) patients in the interferon group and 14 (2%) in the observation group. In the interferon group, the most common grade 3 or 4 adverse events were fatigue (97 patients, 16%), hepatotoxicity (66, 11%), and depression (39, 6%). Treatment with pegylated interferon alfa-2b was discontinued because of toxicity in 191 (31%) patients.

Interpretation Adjuvant pegylated interferon alfa-2b for stage III melanoma has a significant, sustained effect on recurrence-free survival.

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Introduction

Interferon alfa-2b is the best studied agent for adjuvant treatment of patients with stage IIb (primary tumour thickness ≥4 mm, node-negative) and stage III (any primary tumour, node-positive) melanoma, both groups at high risk of recurrence after definitive surgery.[1] However, the role of an induction period, the optimum dose, and duration for adjuvant interferon alfa in high-risk melanoma remain to be defined.[2,3] Trials of both high and intermediate doses of interferon alfa-2b for patients at high risk of recurrence after resection have shown improvements in recurrence-free survival, but without showing consistent effects on overall survival compared with observation alone.[4–7] Increased length of interferon alfa administration, in the range 12–25 months, has been shown to produce transient improvements in recurrence-free survival or distant metastasis-free survival, again without a significant effect on overall survival.[7–11] A meta-analysis of 13 randomised trials estimated that interferon alfa reduced the risk of recurrence or death by 13% (hazard ratio 0·87, 95% CI 0·81–0·93 for recurrence-free survival; p<0·0001) and the risk of death by 10% (0·90, 0·84–0·97 for overall survival; p=0·008) compared with observation or vaccination, without defining the optimum dose or duration of interferon therapy.[12] Trials have also shown that the effect of interferon on recurrence-free survival is rapidly lost after stopping treatment.[7,8]

Pegylation of interferon alfa-2b has been shown to maintain maximum exposure to interferon alfa with less frequent subcutaneous injections than with unpegylated interferon,[13] and has been assessed for safety in a number of types of cancer.[14–17] By enabling prolonged, weekly self-administered adjuvant therapy, pegylated interferon has the potential to improve the benefit–toxicity balance

for patients with resected stage III melanoma. The European Organisation for Research and Treatment of Cancer (EORTC) trial 18991 was designed to investigate the effect of long-term administration of pegylated interferon alfa-2b in patients with stage III melanoma, for a maximum of 5 years.

Methods

Patients

In this phase III randomised controlled trial, done in 99 centres in 17 countries (mainly in Europe), patients aged 18–70 years with histologically documented stage III melanoma (TxN1–2M0) were eligible for enrolment.[1] The primary cutaneous melanoma must have been completely excised with adequate surgical margins and complete regional lymphadenectomy must have occurred 70 days or less before randomisation. Patients were required to have adequate hepatic, renal, and bone marrow function before enrolment. Exclusion criteria for this study included ocular or mucous membrane melanoma, evidence of distant metastasis or in-transit metastasis, prior malignancy within the past 5 years (other than surgically resected non-melanoma skin cancer or cervical carcinoma in situ), autoimmune disease, uncontrolled infections, cardiovascular disease, liver or renal disease, use of systemic corticosteroids, and previous use of systemic therapy for melanoma.

All patients provided written informed consent before randomisation. The protocol was approved by the EORTC protocol review committee and the local institutional ethical committees.

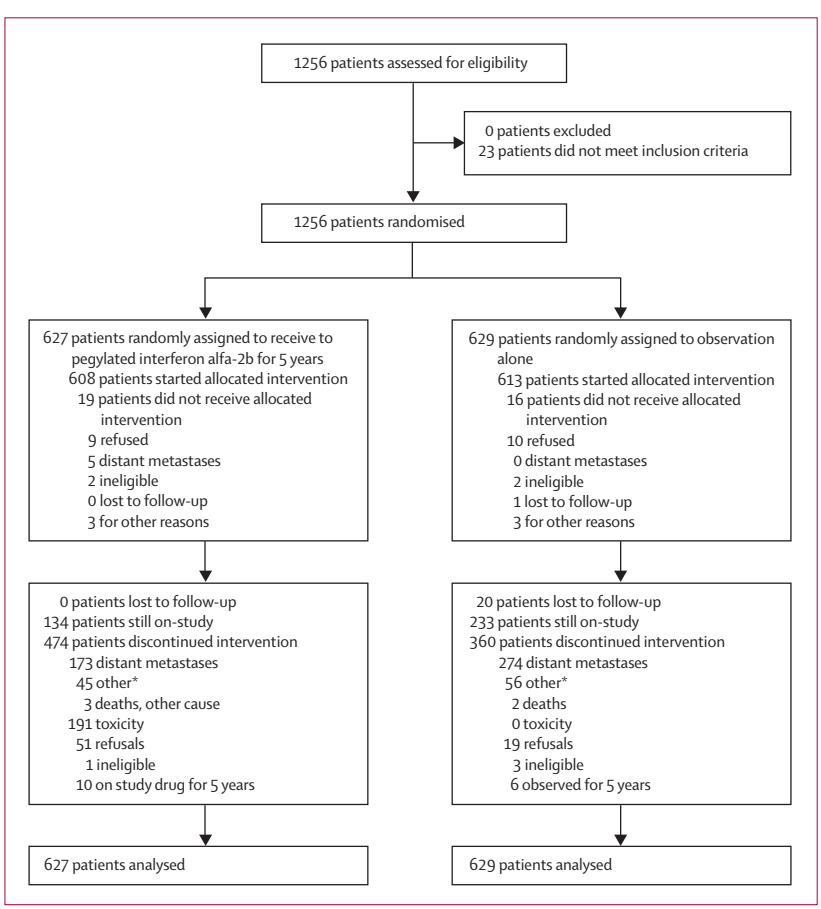

Figure 1: **Trial profile**
*Generally due to a loco-regional relapse.

Procedures

Patients were randomly assigned in a one to one ratio to receive pegylated interferon alfa-2b for 5 years or observation alone. Randomisation was done centrally at the EORTC data centre with minimisation techniques; the sequence was generated by computer.[18,19] Patients were stratified by disease substage (N1: microscopic, non-palpable nodal involvement, including those staged with sentinel node biopsy *vs* N2: clinically palpable lymph nodes, synchronous with removal of the primary tumour or discovered after removal of the primary tumour), number of involved lymph nodes, Breslow thickness of the primary tumour, ulceration of the primary tumour (present *vs* absent *vs* unknown), sex, and centre. N1 patients were almost exclusively sentinel node-positive patients.

Pegylated interferon alfa-2b was administered at 6 μg/kg a week subcutaneously for 8 weeks (induction phase), followed by 3 μg/kg per week subcutaneously for an intended treatment duration of 5 years (maintenance phase). Stepwise dose adjustments (6 μg/kg a week to 3, 2, and 1 μg/kg a week during the induction phase and from 3 μg/kg a week to 2 and 1 μg/kg a week during the maintenance phase) were specified by the study protocol to adjust for toxicity and to maintain an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 for each patient. Treatment could be interrupted for surgery for local or regional recurrence of melanoma, then resumed after surgery.

Patients in both study groups were assessed for recurrence and distant metastases every 3 months during the first 3 years and every 6 months thereafter. Physical examination, chest radiography, computed tomography, and other imaging techniques were used as clinically indicated. Recurrence or metastatic lesions were confirmed pathologically.

The study was designed to measure changes in distant metastasis-free survival so that treatment could be continued in the event of local or regional relapse. However, after consultation with the European regulatory authorities and at the request of the US Food and Drug Administration, the endpoint was revised before the data were analysed to recurrence-free survival, defined as the length of time from randomisation to the first of local regional or distant recurrence of melanoma or death owing to any cause. Secondary endpoints included distant metastasis-free survival, overall survival, and safety. An independent review committee used a blinded review process to determine the dates of events and censoring from individual patient data (ie, the last date of disease

	Pegylated interferon group N=627	Observation group N=629
Sex*		
Female	261 (42%)	262 (42%)
Male	366 (58%)	367 (58%)
Age (years)	50 (19–70)	50 (18–70)
18 to <50	311 (50%)	311 (49%)
50 to <65	252 (40%)	238 (38%)
≥65	64 (10%)	80 (13%)
Stage of disease*		
Microscopic nodal disease	271 (43%)	272 (43%)
Clinically palpable nodes	356 (57%)	357 (57%)
Number of positive lymph nodes*		
1	339 (54%)	337 (54%)
2–4	204 (33%)	204 (32%)
≥5	76 (12%)	79 (13%)
Not evaluable	8 (1%)	9 (1%)
Breslow thickness*		
<1·5 mm	145 (23%)	142 (23%)
1·5–3·99 mm	267 (43%)	270 (43%)
≥4·0 mm	141 (22%)	143 (23%)
Unknown	74 (12%)	74 (12%)
Ulceration of primary tumour*		
No	302 (48%)	304 (48%)
Yes	156 (25%)	156 (25%)
Unknown	169 (27%)	169 (27%)
Ulceration of primary tumour†		
No	315 (50%)	338 (54%)
Yes	192 (31%)	181 (29%)
Unknown	120 (19%)	110 (17%)

Data are n (%) or median (range). *At baseline, used for stratification of randomisation. †As indicated on case report forms.

Table 1: **Demographic and baseline characteristics and stratification factors for randomisation by treatment group**

	Recurrence-free survival	Distant metastasis-free survival	Overall survival
Number of events			
Interferon group	328	304	262
Observation group	368	325	263
4-year rate (SE)			
Interferon group	45·6% (2·2)	48·2% (2·2)	56·8% (2·2)
Observation group	38·9% (2·2)	45·4% (2·3)	55·7% (2·1)
Median time to event (months)			
Interferon group	34·8	45·5	NR
Observation group	25·6	36·0	NR
Univariate analysis			
Hazard ratio (95% CI)	0·82 (0·71–0·96)	0·88 (0·75–1·03)	0·98 (0·82–1·16)
p value	0·01	0·11	0·78
Multivariate analysis*			
Hazard ratio (95% CI)	0·84 (0·73–0·98)	0·90 (0·77–1·06)	1·00 (0·84–1·18)
p value	0·02	0·20	0·98
p value for treatment×stage interaction†	0·34	0·18	0·48

NR=not reached. *Adjusted for stage, number of lymph nodes involved, sex, ulceration, and Breslow thickness at randomisation. †Cox model, treatment, stage, and treatment×stage included.

Table 2: **Recurrence-free survival, distant metastasis-free survival, and overall survival in the intention-to-treat population**

assessment for recurrence-free survival and for distant metastasis-free survival). These dates form the basis of the primary analysis.

The occurrence of adverse events was assessed at each follow-up visit by physical examination, specific questioning of the patient, and by spontaneous reports. All reported adverse events were graded according to the common toxicity criteria version 2.0.[20] Haematological and laboratory measurements were assessed at each visit and also as clinically indicated.

Statistical analysis

We calculated that a sample size of at least 1200 patients would be needed to observe about 576 distant metastases or deaths. With 576 events, the study would have approximately 90% power to detect a hazard ratio of 0·76 for distant metastasis-free survival, or a 9·75% difference (from 40% to 49·75%) at 4 years. An interim analysis was scheduled after 450 distant metastases or deaths (O'Brien-Fleming method). This was done in April, 2005, when 503 such events had occurred. The EORTC independent data and monitoring committee reviewed the data and recommended not to disclose the results, since the stopping boundaries had not been crossed.

Actuarial curves for recurrence-free survival, distant metastasis-free survival, and overall survival were calculated with the Kaplan-Meier technique and the SE of the estimated rates at 4 years from randomisation were obtained via the Greenwood formula.[21] The Cox proportional hazards model was used to obtain the hazard ratio for the treatment comparison and its 95% CI, unadjusted or adjusted for all factors used at randomisation. For subgroup analyses, the treatment comparison was deemed to be significant at the 1% level and, therefore, the 99% CI of the hazard ratio was computed. All efficacy analyses were based on the intention-to-treat population, whereas for toxicity analysis only patients who started the regimen allocated to them by randomisation and who had documentation regarding adverse events were included.

The cutoff date was March 31, 2006. All visits that were due on or before this date were completed, retrieved, and computerised. Survival status of all patients was assessed as of this cutoff date, with a 2-week window. The database, located at the EORTC data centre, was frozen in December, 2006. All analyses were done with SAS version 9.1. This study is registered with ClinicalTrials.gov, number NCT00006249.

Role of the funding source

The study sponsor had no role in the design and conduct of the study, or in the collection, analysis, and

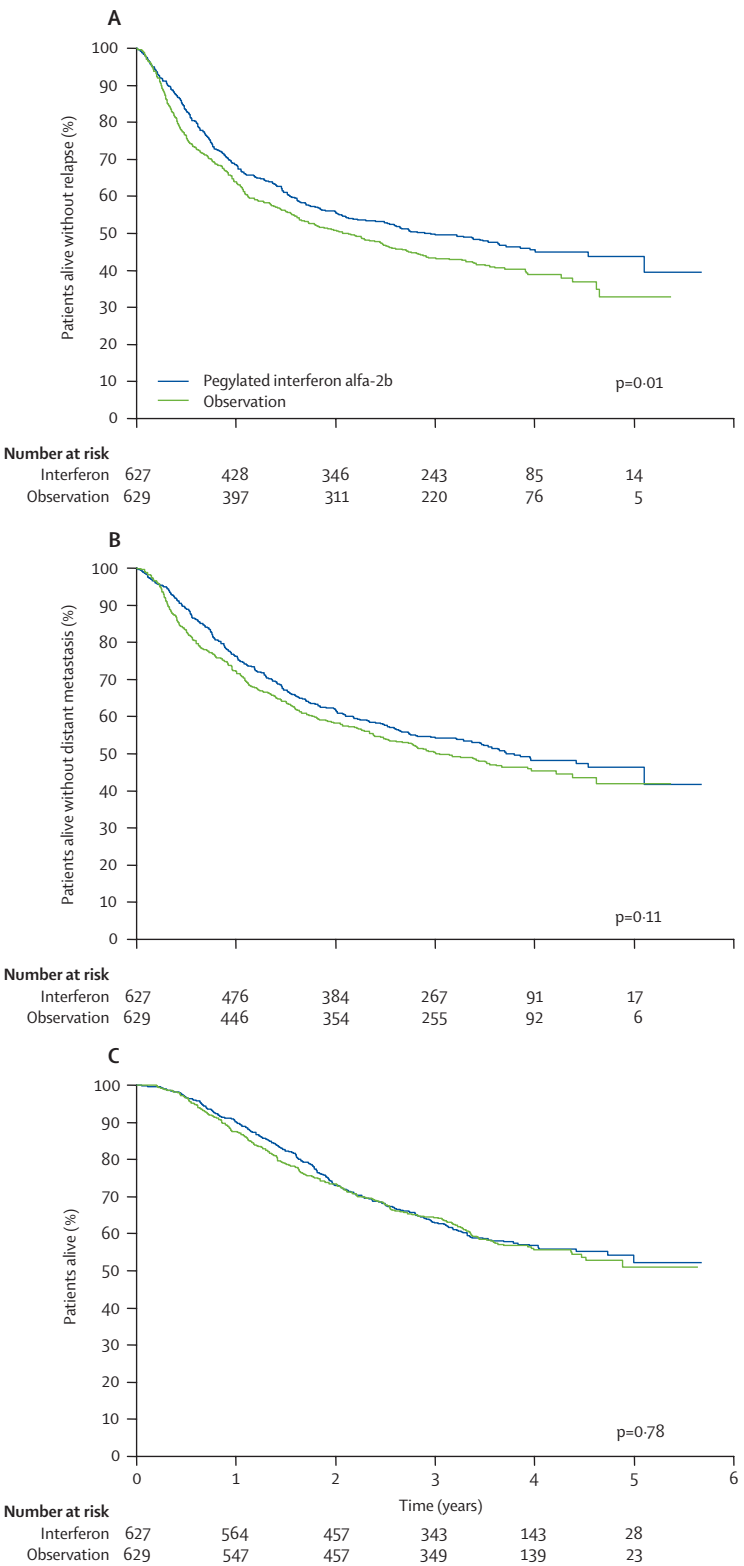

Figure 2: **Kaplan-Meier curves of recurrence-free survival (A), distant metastasis-free survival (B), and overall survival (C)**

interpretation of the data. SS, AMME, and EM had access to all the data in the study, and took the final decision to submit for publication.

Results

The trial profile is shown in figure 1. The median age of the study population was 50 (IQR 18–70) years, with 144 (11%) patients aged over 65 years (table 1). Demographics and baseline characteristics were well balanced across both groups. 543 (43%) of patients had microscopic nodal disease and 713 (57%) had clinically palpable nodal disease. At baseline, 1061 (84%) patients had an ECOG performance status of 0, and 195 (16%) a performance status of 1.

23 (1·8%) randomised patients were deemed to have not met inclusion criteria—nine in the interferon group and 14 in the observation group. Six patients were ineligible because of delays of over 70 days between surgery and randomisation, six because of incorrect staging, one because of additional malignancy, one with unacceptable concomitant treatment, four with abnormal laboratory values, and five for other reasons. As per the intention-to-treat principle, these patients were included in efficacy analyses.

Median treatment duration was 8 (IQR 7·3–8·0) weeks for the induction phase and 12 (3·8–33·4) months for the maintenance phase. 12 months after randomisation, 311 (50%) patients who had been randomly assigned to receive interferon were actually receiving pegylated interferon alfa-2b. After 4 years, 22·5% (SE 1·7) of patients remained in the treatment group, compared with 37·7% (2·0) of those in the observation group; 21·1% (1·8) of patients in the interferon group and 35·2% (2·1) of those in the observation group remained in their initial treatment group and were free of distant metastases. 191 (31%) of the 608 patients who started treatment with pegylated interferon alfa-2b discontinued treatment because of toxicity. Grade 1 to 4 adverse events most frequently associated with drug discontinuation included fatigue (154 patients, 25%), depression (100, 16%), anorexia (90, 15%), liver function tests (77, 13%), myalgia (76, 13%), headache (75, 12%), nausea (74, 12%), and pyrexia (64, 11%).

After a median 3·8 (IQR 3·2–4·2) years of follow-up, significantly fewer recurrences or deaths had occurred in the interferon group than in the observation group in both univariate and multivariate analyses (table 2). There was a 6·7% (95% CI 0·6–12·8) absolute difference in the estimated 4-year rates (45·6% in the interferon group *vs* 38·9% in the observation group). Kaplan-Meier analyses showed that the benefit of treatment began early and was consistent throughout the study (figure 2). Distant metastasis-free survival was longer in the interferon group than in the observation group, although the difference was not statistically significant (table 2 and figure 2). No significant difference was seen in overall survival between the two groups (table 2 and figure 2).

	Recurrence-free survival			Distant metastasis-free survival			Overall survival		
	Interferon group	Observation group	Hazard ratio (99% CI; p value)	Interferon group	Observation group	Hazard ratio (99% CI; p value)	Interferon group	Observation group	Hazard ratio (99% CI; p value)
Microscopic non-palpable nodal involvement (N1)									
Number of events	108	137	..	93	117	..	73	81	..
4-year rate (SE)	57·7% (3·3)	45·4% (3·5)	..	60·5% (3·6)	52·6% (3·5)	..	71·0% (3·0)	67·2% (3·2)	..
Median time to event (months)	NR	42·6	..	NR	55·4	..	NR	NR	..
Univariate analysis	..	..	0·73 (0·53–1·02; 0·016)	..	..	0·75 (0·52–1·07; 0·03)	..	..	0·88 (0·64–1·21; 0·43)
Multivariate analysis*	..	..	0·71 (0·51–1·00; 0·01)	..	..	0·70 (0·49–1·00; 0·011)	..	..	0·82 (0·54–1·25; 0·22)
Clinically palpable lymph node involvement (N2)									
Number of events	220	231	..	211	208	..	189	182	..
4-year rate (SE)	36·3% (2·8)	33·9% (2·6)	..	38·7% (2·8)	39·9% (2·7)	..	45·8% (2·8)	46·8% (2·8)	..
Median time to event (months)	18·2	13·4	..	24	21·5	..	36	40·3	..
Univariate analysis	..	..	0·86 (0·68–1·10; 0·12)	..	..	0·94 (0·73–1·21; 0·53)	..	..	1·01 (0·83–1·24; 0·91)
Multivariate analysis*	..	..	0·88 (0·69–1·13; 0·18)	..	..	0·97 (0·75–1·24; 0·72)	..	..	1·04 (0·80–1·36; 0·70)
Only one positive lymph node									
Number of events	129	163	..	118	146	..	98	112	..
4-year rate (SE)	59·6% (2·9)	48·4% (3·0)	..	62·4% (2·9)	52·9% (3·1)	..	69·4% (2·6)	63·6% (3·0)	..
Median time to event (months)	NR	44·4	..	NR	55·4	..	NR	NR	..
Univariate analysis	..	..	0·71 (0·53–0·97; 0·004)	..	..	0·73 (0·53–1·00; 0·01)	..	..	0·83 (0·58–1·19; 0·18)
Multivariate analysis*	..	..	0·69 (0·51–0·94; 0·002)	..	..	0·70 (0·51–0·97; 0·005)	..	..	0·82 (0·57–1·17; 0·15)
Two to four positive lymph nodes									
Number of events	132	133	..	122	116	..	109	94	..
4-year rates (SE)	32·8% (3·8)	33·0% (3·6)	..	35·9% (4·1)	41·7% (3·7)	..	44·9% (3·7)	52·3% (3·7)	..
Median time to event (months)	18·5	18·7	..	24	28·4	..	37·7	53·6	..
Univariate analysis	..	..	0·94 (0·69–1·29; 0·62)	..	..	1·01 (0·73–1·42; 0·91)	..	..	1·17 (0·81–1·68; 0·26)
Five or more positive lymph nodes									
Number of events	61	65	..	58	56	..	49	51	..
4-year rate (SE)	18·6% (4·5)	15·7% (4·5)	..	20·3% (5·2)	26·0% (5·2)	..	34·8% (6·0)	33·0% (5·5)	..
Median time to event (months)	9·1	7·7	..	11·3	13·1	..	23·3	24·2	..
Univariate analysis	..	..	0·96 (0·61–1·53; 0·84)	..	..	1·14 (0·71–1·85; 0·47)	..	..	1·02 (0·61–1·70; 0·93)

..=not applicable. NR=not reached. *Adjusted for number of positive lymph nodes, sex, ulceration, and Breslow thickness at randomisation.

Table 3: **Recurrence-free survival, distant metastasis-free survival, and overall survival in patient subgroups**

The effects of treatment with pegylated interferon alfa-2b were more pronounced in patients with earlier stage III melanoma disease than in those with later stage disease (table 3). Among patients with microscopic nodal disease (N1), there were fewer recurrences or deaths in the interferon group than in the observation group, although the 99% CI of the hazard ratios crossed or included the point of no effect in both univariate and multivariate analyses. Likewise, there were fewer distant metastases or deaths in the interferon group than in the observation group, although again the 99% CI of the hazard ratios crossed or included the point of no effect in both multivariate and univariate analyses. Kaplan-Meier curves for patients with microscopic nodal disease showed that the effect of pegylated interferon began quite early in the study and was maintained throughout the follow-up period (figure 3). By contrast, among patients with palpable nodal disease (N2), similar numbers of recurrences, distant metastases, and deaths were seen in the two groups (table 3 and figure 4).

Similarly, lower rates of recurrence, distant metastasis, and death were seen in patients who were randomly allocated to received interferon than in those in the observation group in patients with tumour involvement limited to one lymph node, compared with patients with more than one involved lymph nodes, for whom such reductions were more limited or not seen at all (table 3).

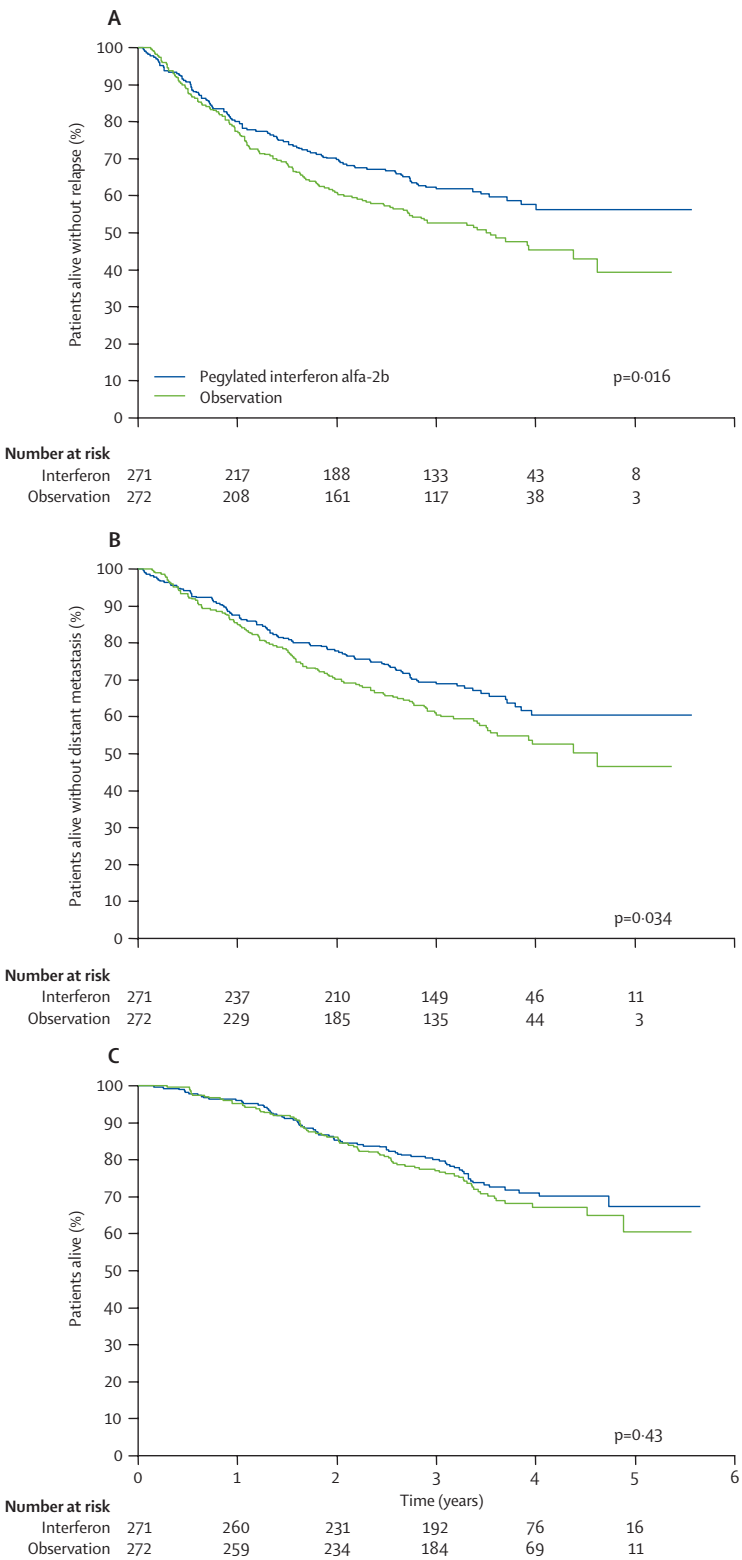

Figure 3: **Recurrence-free survival (A), distant metastasis-free survival (B), and overall survival (C) in stage III-N1 (microscopic nodal involvement only) patients**

In patients with the lowest tumour burden (microscopic nodal involvement of only one node; n=382), interferon significantly improved recurrence-free survival and distant metastasis-free survival, but not overall survival, compared with observation alone (table 4). In the subgroup of patients with microscopic involvement of any number of nodes and who had an ulceration in the primary tumour (n=186), pegylated interferon alfa-2b seemed to reduce the risk of recurrence, distant metastasis, and death, although the 99% CI for the hazard ratios crossed the null point for all endpoints except distant metastasis-free survival (table 4). Such decreases in risk were not seen in patients with microscopic nodal involvement and who had a non-ulcerated primary tumour (n=321; data not shown). Treatment effects in patients with a macroscopic involvement of only one node (n=294), and in those with macroscopic involvement of more than one node (n=403) were not significant (data not shown).

Sensitivity analyses of recurrence-free survival linked to the time of detection of relapse showed that treatment differences were robust (data not shown). Likewise, sensitivity analyses in which patients who stopped treatment with pegylated interferon alfa-2b because of toxicity were, from that moment, no longer deemed to be at risk of having an event in the interferon group, or were switched from the interferon group to the observation group and deemed to be at risk of having an event in the observation group, suggest that our findings are robust (data not shown). However, these later analyses are subject to bias.[22]

Adverse events of any severity that were recorded in more than 4% of patients are shown in table 5. Grade 3 and 4 events occurred in more patients in the interferon group than in patients in the observation group. 525 deaths were reported during the trial—262 in the interferon group and 263 in the observation group. The incidence of the most frequent cause of death—malignant disease—was similar in the two groups: 249 (40%) of 627 patients in the interferon group and 244 (39%) of 629 in the observation group. Cardiovascular disease was the main cause of death for five patients (one patient without previous relapse) in the interferon group and three patients in the observation group; infection was the cause of death for one patient in each group. Other causes of death were rare and equally distributed between the two groups.

Discussion

The results of this large phase III study of adjuvant therapy in patients with stage III melanoma suggest that prolonged treatment with pegylated interferon alfa-2b significantly improves recurrence-free survival compared with observation alone. Although distant metastasis-free survival was numerically better in patients treated with pegylated interferon than in those who received observation alone, this difference was not statistically significant. No effect on overall survival was seen.

The toxicity profile of pegylated interferon alfa-2b seems to be acceptable over a maximum 5-year duration of treatment. The most commonly observed side-effects of interferon treatment are fatigue and depression. The incidence of these symptoms was higher early in treatment and did not increase as treatment progressed (data not shown). Patients also reported being affected by these symptoms for less time as treatment progressed (data not shown). Although a third of patients discontinued treatment because of toxicity, the safety of this regimen seemed to be acceptable and compared favourably with that reported in earlier trials of high-dose interferon alfa-2b, which reported an incidence of grade 3–4 fatigue of up to 24%, depression of 10%, and liver toxicity of 29%.[5] Furthermore, toxicity did not seem to increase with longer duration of treatment, by contrast with high-dose interferon alfa-2b.[5]

Our results suggest that the effect of a median of 12 months' treatment with pegylated interferon alfa-2b on recurrence-free survival is sustained throughout the 5-year treatment period (figure 2). This finding contrasts with those from ECOG 1684 (6·9 years' follow-up)[4] and the study by Grob and colleagues (5·0 years' follow-up),[8] in which the treatment benefit vanished rapidly after the end of treatment with unpegylated interferon (1–1·5 years' duration). However, assessment of the effect of duration of treatment has limitations. Correlation of the actual treatment duration and delivery with the efficacy outcomes is difficult, since patients who stayed on treatment longer would most likely do better than those who discontinued treatment earlier. Nonetheless, the observation that, in the N1 population, the Kaplan-Meier curves for recurrence-free survival in the interferon and observation groups separate from one another increasingly over time (figure 3), suggests that prolonged administration of pegylated interferon alfa-2b could be of value. Only a randomised trial to assess the duration of administration of pegylated interferon can elucidate the real effect of the treatment duration.

In EORTC 18952,[7] which examined the use of adjuvant interferon alfa-2b in patients with stage IIb and III melanoma, subgroups of patients with earlier stage disease or lower disease burden experienced a more pronounced treatment effect, with greater risk reductions and longer durations of recurrence-free and distant metastasis-free survival. Our data suggest that pegylated interferon alfa-2b could be an option for adjuvant treatment of patients with resected high-risk melanoma, especially those with lower nodal tumour burden. The aim of adjuvant therapy for high-risk melanoma, as for other major cancers, is to provide a tolerable treatment that reduces the risk of relapse for many patients and potentially achieves a cure. We noted an absolute difference in 4-year recurrence-free survival of about 12% in patients with microscopic nodal disease in resected stage III melanoma. Thus, pegylated interferon alfa-2b treatment could be considered in this subgroup, since the observation

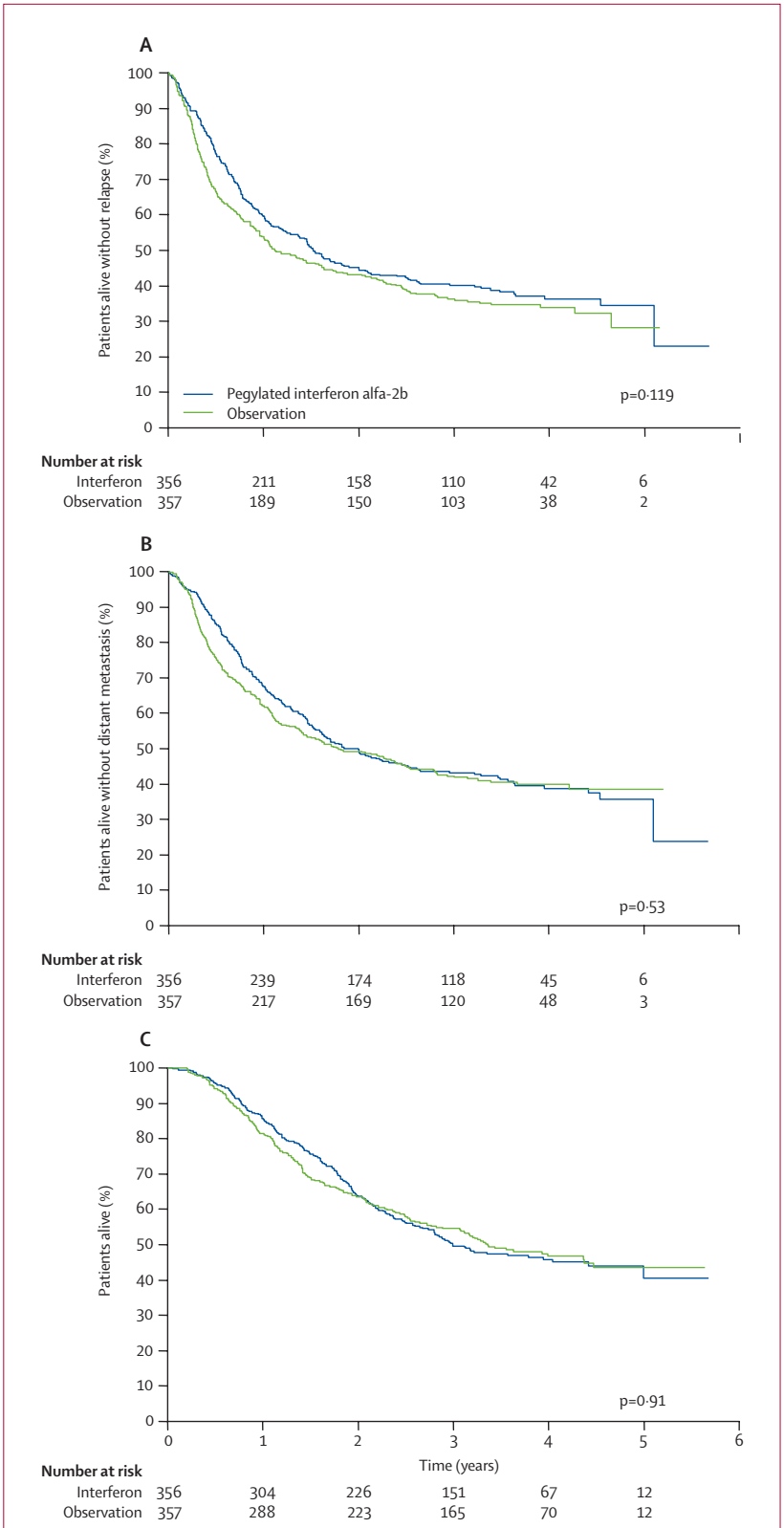

Figure 4: **Recurrence-free survival (A), distant metastasis-free survival (B), and overall survival (C) in stage III-N2 (palpable nodal involvement) patients**

	Recurrence-free survival			Distant metastasis-free survival			Overall survival		
	Interferon group	Observation group	Hazard ratio (99% CI; p value)	Interferon group	Observation group	Hazard ratio (99% CI; p value)	Interferon group	Observation group	Hazard ratio (99% CI; p value)
N1 disease, one positive lymph node									
Number of events/ number of patients	65/194	87/188	..	56/194	76/188	..	42/194	51/188	..
4-year rate (SE)	63·8% (3·8)	49·2% (4·2)	..	66·7% (4·0)	55·0% (4·2)	..	76·7% (3·3)	69·4% (3·8)	..
Median time to event (months)	NR	47·2	..	NR	NR	..	NR	NR	..
Univariate analysis	..	..	0·64 (0·42–0·98; 0·006)	..	..	0·63 (0·40–1·00; 0·009)	..	..	0·76 (0·44–1·30; 0·18)
Ulceration present									
Number of events/ number of patients	53/96	62/90	..	45/96	59/90	..	33/96	44/90	..
4-year rate (SE)	43·8% (5·4)	26·8% (5·3)	..	47·4% (6·1)	30·1% (5·3)	..	65·0% (5·2)	45·4% (5·9)	..
Median (months)	31·0	18·7	..	47·4	26·3	..	NR	42·2	..
Univariate analysis	..	..	0·69 (0·43–1·12; 0·05)	..	..	0·59 (0·35–0·98; 0·006)	..	..	0·61 (0·34–1·10; 0·03)

..=not applicable. NR=not reached.

Table 4: **Subgroup analysis in patients with stage III-N1 (microscopic) disease with only one positive lymph node or with an ulcerated primary melanoma, as indicated on case report forms**

of interferon-mediated efficacy in early stage III disease is consistent with observations in EORTC 18952.[7] Patients with microscopic nodal involvement represented about 40% of our study population, and microscopic nodal involvement in stage III disease can be expected to increase substantially because of the increasingly widespread use of sentinel node (SN) biopsy.[23]

Our data are also consistent with the findings of Grob and colleagues[8] and Pehamberger and co-workers,[9] who used low-dose interferon as an adjuvant in non-SN-staged stage II melanoma patients—populations in which the overall findings were most likely caused by events in N1 (SN-positive) patients. In these trials, there was a clear effect on recurrence-free survival. Less advanced disease (ie, N1) might differ biologically from advanced disease (N2) and it seems to be more sensitive to the effects of interferon. With regard to N2 disease, in high-dose interferon trials there was an effect on recurrence-free survival, especially early during treatment, which was probably related to the high dose, 4-week intravenous induction phase of these treatment regimens.[4,5] One should note that although our trial included a high-dose induction phase, the kinetics and bioavailability of interferon are different from those seen in intravenous regimens because of pegylation and subcutaneous administration.

Exploratory analyses of subgroups indicated that ulcerated primary melanomas seemed more sensitive to interferon than were non-ulcerated melanomas. Markers of patients likely to respond to interferon are clearly needed, and this trial indicates that the combination of low tumour volume and an ulcerated primary tumour might be such a marker. This observation requires confirmation, and also investigation to establish its biological basis. Another such marker could be the emergence of autoimmune antibodies during treatment with interferon, as reported by Gogas and colleagues.[24] However, no definite relation between the development of autoantibodies and the risk of relapse has thus far been identified;[25,26] further investigation is warranted. Identification of markers will ensure that interferon can be administered to those patients who most need it, while protecting those unlikely to respond to the drug from unnecessary toxicity.

	Interferon group (N=608)			Observation group (N=613)		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Any	605 (99%)	246 (40%)	32 (5%)	484 (79%)	60 (10%)	14 (2%)
Fatigue	574 (94%)	89 (15%)	8 (1%)	252 (41%)	7 (1%)	0
Liver function test*	479 (79%)	64 (10%)	2 (<1%)	221 (36%)	8 (1%)	2 (<1%)
Pyrexia	454 (75%)	24 (4%)	1 (<1%)	53 (9%)	0	0
Headache	425 (70%)	24 (4%)	0	118 (19%)	4 (1%)	0
Myalgia	408 (67%)	22 (4%)	1 (<1%)	140 (23%)	3 (<1%)	0
Depression	360 (59%)	38 (6%)	1 (<1%)	153 (25%)	2 (<1%)	1 (<1%)

*Alanine and aspartate aminotransferases/bilirubin/alkaline phosphatase.

Table 5: **Adverse events occurring in 4% or more of patients (grade 3 and 4)**

Contributors

AMME, SS, and RM prepared the manuscript with the help of the other co-authors. SS was the statistician, EM the co-ordinating physician, and AS the pathologist for this trial. AH did the blinded independent review. All other co-authors were major contributors in patient accrual for the EORTC 18991 trial.

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Conflict of interest statement

AMME, MG, AH, and UK have acted as consultants to Schering Plough Research International within the past 3 years. MG, AH, EM, and SS have received research funding or funding for equipment or drugs from Schering Plough Research International. AH has received travel or accommodation payments from Schering Plough Research International. AT, WHJK, JM, CJAP, FS, RM, ZK, RD, AS, and MS declare that they have no conflict of interest.

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