RAPID PUBLICATION

# Interferon Alfa-2b Adjuvant Therapy of High-Risk Resected Cutaneous Melanoma: The Eastern Cooperative Oncology Group Trial EST 1684

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***Purpose:*** **Interferon alfa-2b (IFNα-2b) exhibits antitumor activity in metastatic melanoma and on this basis has been evaluated as an adjuvant therapy following surgery for deep primary (T4) or regionally metastatic (N1) melanoma.**

***Methods:*** **A randomized controlled study of IFNα-2b (Schering-Plough, Kenilworth, NJ) administered at maximum-tolerated doses of 20 MU/m$^2$/d intravenously (IV) for 1 month and 10 MU/m$^2$ three times per week subcutaneously (SC) for 48 weeks versus observation, was conducted by the Eastern Cooperative Oncology Group (ECOG) in 287 patients.**

***Results:*** **A significant prolongation of relapse-free survival ($P$ = .0023, one-sided) and prolongation of overall survival ($P$ = .0237, one-sided) was observed with IFNα-2b therapy in this trial, which is now mature with a median follow-up time of 6.9 years. The impact of treatment on relapse rate is most pronounced early during the treatment interval. The overall benefit of treatment in this trial was analyzed stratified by tumor burden and the presence or absence of microscopic nonpalpable and palpable regional lymph node metastasis. The benefit of therapy with IFNα-2b was greatest among node-positive strata. Toxicity of IFNα-2b required dose modification in the majority of patients, but treatment at ≥ 80% of the scheduled dose was feasible in the majority of patients through the IV phase of treatment, and for more than 3 months of SC maintenance therapy. Discontinuation of treatment due to toxicity was infrequent after the fourth month of therapy.**

***Conclusion:*** **IFNα-2b prolongs the relapse-free interval and overall survival of high-risk resected melanoma patients. The increment in median disease-free survival (from 1 to 1.7 years) and overall survival (from 2.8 to 3.8 years) that results from this therapy is associated with a 42% improvement in the fraction of patients who are continuously disease-free after treatment with IFN (from 26% to 37%) in comparison to observation. IFNα-2b is the first agent to show a significant benefit in relapse-free and overall survival of high-risk melanoma patients in a randomized controlled trial.**

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MELANOMA INCIDENCE is increasing at a rate that exceeds all other solid tumors. Although education efforts have resulted in earlier detection of melanoma, patients who have deep primary melanoma (> 4 mm) or melanoma metastatic to regional draining lymph nodes continue to have a high relapse and mortality rate of 50% to 90%.[1-4] No adjuvant therapy has previously shown a significant impact on relapse-free and overall survival of melanoma. Interferon (IFN) alpha of leukocyte origin and recombinant IFN alfa-2 (IFNα-2a, Roche, Nutley, NJ; IFNα-2b, Schering-Plough, Kenilworth, NJ; and IFNα-2c, Boehringer, Indianapolis, IN) have shown antitumor activity in metastatic melanoma, which suggests that the use of IFNα-2 in microscopic or early metastatic tumor might have even greater impact.[5,6] Clinical experience with IFNα-2b in patients with metastatic melanoma has consistently shown responses of 15% to 20% in patients treated with daily or three-times-weekly dosages of ≥ 10 MU by intravenous (IV), intramuscular (IM), or subcutaneous (SC) routes.[6,7] The immunologic effects of IFNα-2b on tumor histocompatibility and other antigens, and host-immune response to tumor cells, would theoretically have their greatest role in the adjuvant setting. The Eastern Cooperative Oncology Group (ECOG) trial EST 1684 tested the ability of IFNα-2b (Intron-A; Schering-Plough) administered at maximum-tolerated doses for 1 year to prevent relapse and death of patients at high risk after curative surgery for melanoma. This randomized controlled trial of IFNα-2b accrued patients between 1984 and 1990 and remained blinded under analysis until 1993. We report here the favorable outcome of treatment with IFNα-2b in terms of relapse and death of

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melanoma patients in EST 1684, as presented preliminarily to the American Society of Clinical Oncology in May 1993,[8] at a median follow-up time of 4.7 years, and here updated to a median follow-up time of 6.9 years.

## METHODS

### *Patient Selection*

Eligible patients had histologically proven primary cutaneous melanoma without prior systemic adjuvant therapy and without evidence of distant metastatic disease, with normal organ function, and no significant medical or psychiatric comorbidity. Patients were randomized by permuted blocks to treatment within the four strata defined by clinical and pathologic extent of disease, originally designated by the classical three-stage system and now encompassed within the current American Joint Committee on Cancer (AJCC) stage IIB and stage III disease categories, as follows: (1) deep primary melanomas of Breslow depth more than 4 mm (designated CS1 PS1: T4N0M0); (2) primary melanomas of any tumor stage in the presence of N1 regional lymph node metastasis detected at elective lymph node dissection with clinically inapparent regional lymph node metastasis (designated CS1 PS2: any TpN1M0); (3) clinically apparent N1 regional lymph node involvement synchronous with primary melanoma of T1-4 (designated CS2 PS2: any TcN1M0); and (4) regional lymph node recurrence at any interval after appropriate surgery for primary melanoma of any depth (designated CS2R: TxrN1M0 recurrent). Patients in groups 1 to 3 were required to enter this study within 56 days of first primary melanoma biopsy. Patients with regional nodal relapse in group 4 were required to enter this study within 42 days of lymphadenectomy. The type and extent of surgery was specified and reviewed for quality control in all cases for primary margins and minimal numbers of inguinal, axillary, and cervical nodes ($n \geq 5$, 10, or 15, respectively).

### *Intervention*

Patients were assigned at random either to receive IFN $\alpha$-2b at 20 MU/m$^2$/d IV 5 days per week for 4 weeks, then three times weekly at 10 MU/m$^2$/d SC for 48 weeks, or to receive close observation (standard therapy). The schema (Fig 1) illustrates the study design. Dose modification was performed in accordance with a two-level toxicity scale for biologic agents by the ECOG.[9]

### *Outcome Measures*

Patients were monitored weekly during the first month on study, then at intervals of 1 to 3 months in year 1, 4 months in year 2, and 6 months in subsequent years. Site and interval of first and subsequent relapses were recorded, as well as cause and date of death. Analysis of this trial was originally planned in terms of relapse-free survival. However, before analysis the goals of the trial were enlarged to include an assessment of the impact of IFN$\alpha$-2b therapy on survival. A group sequential analysis that used O'Brien-Fleming stopping boundaries was adopted with three planned annual evaluations of the outcome. A monitoring committee was appointed to review the emerging data annually. Planned treatment comparisons for relapse-free and overall survival were performed in March 1990, 1991, and 1992 using a stratified log-rank test. The O'Brien-Fleming group sequential boundaries were adjusted at each analysis for the number of events actually observed, and served as a guide for the monitoring committee to interpret the significance level of the comparisons. The decision to continue or end the trial at each analysis was based on all data available. In 1992, at the time of the third planned analysis, the number of events had not reached the target, and the results of this trial were judged to be in sufficient flux to require another year of observation. A further analysis was therefore conducted in March 1993, at which time the monitoring committee voted unanimously to unblind the trial. A subsequent analysis of overall survival by intent to treat (ITT) was performed on 280 randomized patients, excepting one administratively cancelled patient and three patients in each of the treatment and observed arms for whom data was incomplete due to withdrawal for refusal of the patient's insurers to compensate costs of treatment or refusal to accept the assigned treatment. The results of analyses including and excluding these patients do not differ significantly. These data were submitted to the Oncology Drug Advisory Committee of the Food and Drug Administration (FDA) for product licensure of the IFN$\alpha$-2b (Intron A) in July 1995, which resulted in a recommendation for the approval of IFN$\alpha$-2b for adjuvant therapy of stage IIB to III resected melanoma. During the FDA application process, multiple data audits of the trial were conducted and the present analysis reflects extensively verified data and additional follow-up data through May 15, 1995.

Plots of estimated relapse-free and overall survival were calculated by the Kaplan-Meier method. Estimated hazards plots corresponding to the overall survival curves were smoothed with a simple kernel technique (and a fixed length span of 1.5).[10] The distribution of

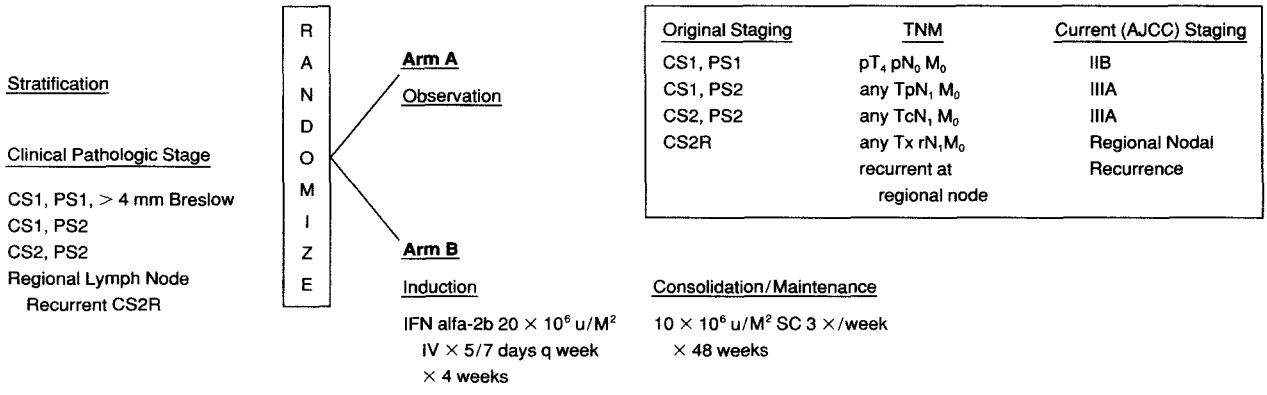


**Fig 1. Schema for the E1684 trial: randomized controlled trial of high-dose IFN $\alpha$-2b in resected high-risk cutaneous melanoma.**

patient factors of potential prognostic importance was compared between treatments with Fisher's exact test to verify the success of the randomization procedure. Cox's proportional hazards regression was used to assess the impact of treatment after adjustment for other patient characteristics. All analyses used the randomized treatment assignment regardless of treatment received. Overall survival for the ITT sample (n = 286) was compared between treatments using a stratified log-rank test and more fully with the Cox model (not reported). This confirmed and reinforced the results obtained in the analyses of the efficacy sample (n = 280).

## RESULTS

### *Definition of Study Population*

Of 287 patients entered onto the study, seven were cancelled before treatment and 28 were ineligible. Of the seven cancelled patients, four were randomized to IFN and three to observation, while of the 28 ineligible, 14 were randomized to IFN and 14 to observation. The ineligible entries most frequently resulted from staging errors (n = 12); eg, primary depth less than 4 mm in the absence of lymph node metastasis (n = 4), failure to perform lymphadenectomy (n = 3), and unknown primary site of cutaneous melanoma (n = 2); time interval violations (n = 12), such as excessive interval from primary or lymph node surgery to study entry,[11] and other eligibility criteria related to normal organ function, age, and comorbid illness (n = 4). A total of 280 patients with both end point and toxicity information available were analyzed for the efficacy sample report (137 received observation and 143 IFN), while the entire randomized population except one administratively cancelled patient is summarized in the ITT report. Cancelled patients were not monitored for toxicity, having received no protocol therapy, and were followed only for relapse, at intervals. All patients were monitored for survival.

### *Risk Factor Distribution in the Study Populations*

Randomization performed after stratification according to relapse risk achieved excellent balance for known prognostic factors between the trial arms. No factor was identified as being significantly different between the treatment groups. Table 1 lists the distribution of major prognostic factors between the treated and observed groups in this trial.

### *Follow-Up Interval for EST 1684*

At the time of this analysis, patients have been monitored for a range of 0.6 to 9.6 years, with a median follow-up time among 109 surviving participants now more than 6.9 years. Among 47 patients alive on observation alone, 36 have been contacted within the last year. Six of the 11 remaining patients have been monitored for more than 6 years. Similarly, among 62 patients who survived after treatment with IFN, 51 have been contacted within the past year. Of the 11 remaining patients, eight have been

**Table 1. Distribution of Patient Characteristics Across Treatments for Efficacy Sample**

| Characteristic | Observation (n = 137) | | IFN (n = 143) | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Age at randomization, years | | | | |
| < 50 | 75 | 54.7 | 80 | 55.9 |
| ≥ 50 | 62 | 45.3 | 63 | 44.1 |
| Performance status | | | | |
| Fully active | 123 | 89.8 | 126 | 88.1 |
| Ambulatory | 14 | 10.2 | 17 | 11.9 |
| Strata | | | | |
| CS1/PS1 | 15 | 11.0 | 16 | 11.2 |
| CS1/PS2 | 14 | 10.2 | 20 | 14.0 |
| CS2/PS2 | 21 | 5.3 | 20 | 14.0 |
| Recurrent | 87 | 63.5 | 87 | 60.8 |
| Sex | | | | |
| Male | 79 | 57.7 | 90 | 62.9 |
| Female | 58 | 42.3 | 53 | 37.1 |
| Site of primary tumor | | | | |
| Head/neck | 12 | 8.8 | 17 | 11.9 |
| Upper limb | 22 | 16.1 | 18 | 12.6 |
| Lower limb | 30 | 21.9 | 25 | 17.5 |
| Subungual | 2 | 1.5 | 0 | 0.0 |
| Trunk | 58 | 42.3 | 68 | 47.6 |
| Anogenital | 2 | 1.5 | 1 | 0.7 |
| Other | 10 | 7.3 | 11 | 7.7 |
| NA | 1 | 0.7 | 3 | 2.1 |
| Type of primary tumor | | | | |
| Lentigo maligna | 4 | 2.9 | 6.6 | 4.2 |
| Superficial | | | | |
| Spreading | 45 | 32.9 | 51 | 35.7 |
| Nodular | 67 | 48.9 | 60 | 42.0 |
| Acral lentiginous | 1 | 0.7 | 0 | 0.0 |
| Other | 4 | 2.9 | 8 | 5.6 |
| NA | 16 | 11.7 | 18 | 12.6 |
| Breslow depth (mm) | | | | |
| < 2 | 44 | 32.1 | 55 | 38.5 |
| 2-3 | 17 | 12.4 | 17 | 11.9 |
| 3-4 | 14 | 10.2 | 18 | 12.6 |
| > 4 | 49 | 35.8 | 38 | 26.6 |
| NA | 13 | 11.4 | 15 | 10.5 |
| Clark level | | | | |
| 1 | 3 | 2.2 | 3 | 2.1 |
| 2 | 14 | 10.2 | 16 | 11.2 |
| 3 | 34 | 24.8 | 28 | 19.6 |
| 4 | 58 | 42.3 | 69 | 48.3 |
| 5 | 21 | 15.3 | 14 | 9.8 |
| NA | 7 | 5.1 | 13 | 9.1 |
| Ulceration of primary tumor | | | | |
| No | 105 | 76.6 | 112 | 78.3 |
| Yes | 23 | 16.8 | 23 | 16.1 |
| NA | 9 | 6.6 | 8 | 5.6 |

Abbreviation: NA, not available.

monitored for more than 6 years. Therefore, we believe the follow-up data are complete.

*Analysis of IFNα-2b Impact on Relapse-Free and Overall Survival*

The median relapse-free survival time for patients who received IFN is 1.72 years (95% confidence interval [CI], 1.07 to 2.88), while the median for those who received observation is 0.98 years (95% CI, 0.50 to 1.65). The overall median survival time is 3.82 years (95% CI, 2.34 to 7.08) for IFN recipients as opposed to 2.78 years (95% CI, 1.83 to 4.03) for those who received observation alone. Death occurred in 81 of 143 IFN patients and 90 of 137 observation patients.

The analysis of treatment impact on relapse-free survival in the efficacy sample is presented in Fig 2. The difference between treatment and observation groups is highly significant at $P = .0023$ (one-sided), adjusting for disease status at randomization. The estimated 5-year relapse-free survival rate on IFN is 37% (95% CI, 30% to 46%) versus 26% (95% CI, 19% to 34%) on observation. The outcome is further analyzed by hazards function for relapse in the treatment and observation arms of this trial. The hazards functions for relapse in the treated and observed groups are displayed for all analyzed patients in Fig 2B. The estimated hazard of relapse plotted in this figure shows a sustained effect difference between treatment and observation, with the greatest reduction of relapse hazard early during the first several months of treatment.

Analysis of this trial for the impact of treatment on overall survival is illustrated in Fig 3A. The difference between patients who received treatment and observation in terms of overall survival in the efficacy sample reached statistical significance ($P = .0237$, one-sided) in 1992. The estimated survival rate is 46% for patients treated with IFN at 5 years (95% CI, 39% to 55%), while on observation the 5-year estimated survival rate is 37% (95% CI, 30% to 46%). The impact of IFNα-2b on overall survival also has been sustained over the present median follow-up of nearly 7 years, with the greatest reduction in deaths early during active treatment, as observed for relapse-free survival; this is illustrated in the estimated hazards function for death in Fig 3B.

Stratification of accrual and analysis in this study was designed to assure balance in the distribution of disease burden between treatment groups, not specifically to make comparisons within the four subgroups.

The outcome of treatment on relapse-free interval for each stratification group is displayed in Figs 4 through 7. Analysis of the effects of treatment according to the four

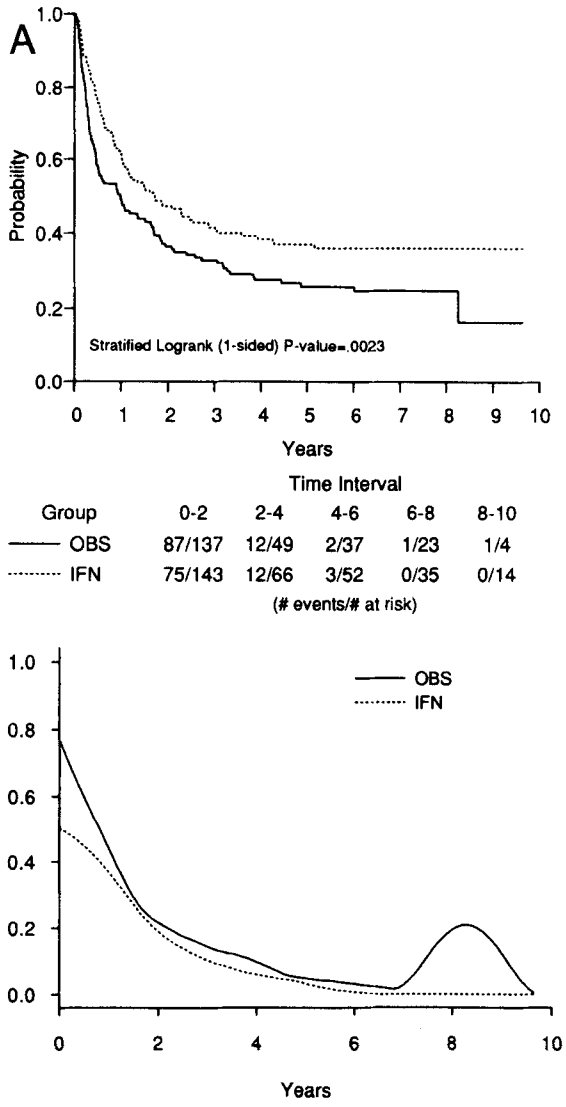


**Fig 2. Relapse-free survival of eligible patients (A) and estimated hazard of relapse over time for eligible patients participating in E1684 (B). OBS, observation.**

risk groups originally defined in this study shows differences in the impact of therapy on relapse-free survival among the four stage groups. Among the small number of CS1/PS1 patients (Fig 4), no impact of therapy is apparent. This group showed an imbalance in the presence of primary tumor ulceration that may bear on the outcome, and was too small to allow further analysis. In the pathologically proven microscopic node-positive group of 34 patients without clinically apparent evidence of regional lymphadenopathy, striking differences between the IFN-treated and observed groups were observed. The apparent difference in outcome between IFN and observa-

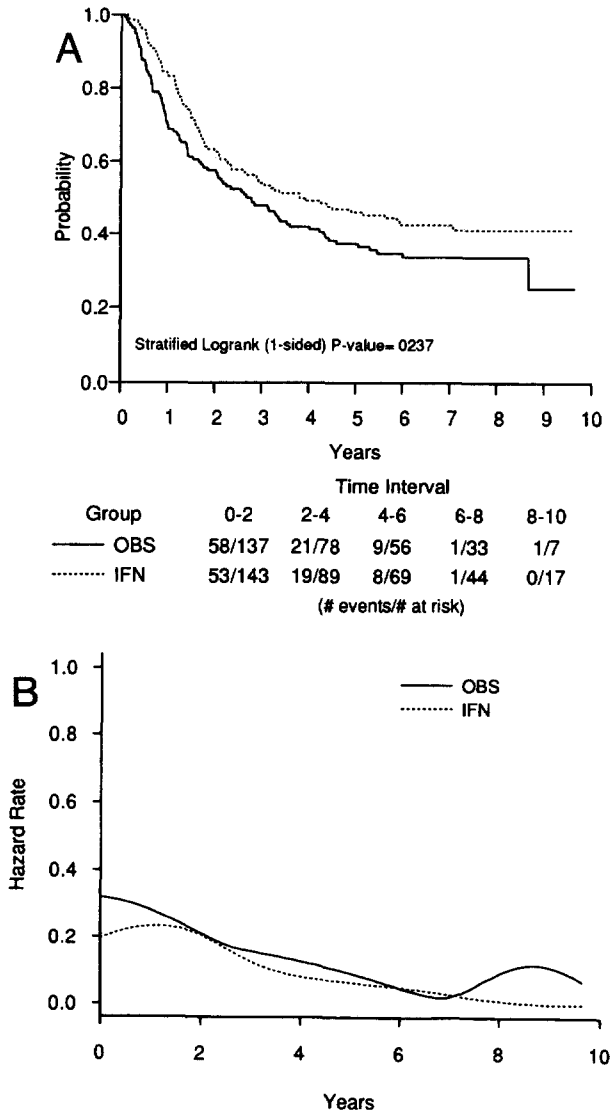


**Fig 3. Overall survival of eligible patients (A) and estimated hazard of death over time for eligible patients participating in E1684 (B).**

tion in this relatively small subgroup suggests that the effect of IFN treatment on microscopic metastatic disease may be worthy of further evaluation (Fig 5, CS1/PS2). The largest accrual to this trial occurred in the higher risk groups with clinically apparent nodal metastasis at presentation displayed in Fig 6, (n = 41) or at recurrence shown in Fig 7 (n = 174). The difference between relapses in treated and observed groups is accompanied by a suppression of the estimated hazards function for relapse in panel B for each subgroup in Figs 5 to 7. The hazards function for relapse demonstrates the largest reduction of the hazard of relapse in patients with microscopic involvement of regional lymph nodes detected during elective lymphadenectomy, and in patients treated at initial presentation with lymph node metastasis (CS1 PS2, Fig 5B; and CS2 PS2 Fig 6B). The right-hand tail of the hazards plots is subject to the diminishing population at risk, but the left-hand portion of these plots provides a useful estimation of the relative difference in the rates of relapse between the treatment arms.

All analyses performed for the noncancelled population of 280 patients were also performed on the entire population of randomized patients, minus one administratively cancelled patient, and show results that were not substantially different. The ITT analysis of overall survival verifies that exclusions due to cancellation do not alter the study conclusions. The treatment impact is significant at $P = .0273$, (one-sided, stratified log-rank test) in the larger sample. The Kaplan-Meier plot that illustrates this overall survival outcome for treatment and observation groups is presented in Fig 8.

A summary of the group sequential analyses of the differences between treatment and observation arms of this trial for disease-related events and for deaths is listed in Table 2 as they were conducted over time. The analyses performed in March 1990 to 1993 were based on the sample of eligible patients, with an ITT survival analysis performed in 1993. Differences between the two arms of this trial have been highly statistically significant in terms of relapse rates since 1990, with $P$ values that range from .0011 to .0049. Differences between the overall survival of patients who received treatment and observation reached nominal statistical significance in 1992, but were felt to warrant further follow-up evaluation by the data monitoring committee, due to the occurrence of fewer events than anticipated at that time. Results in the larger ITT population survival analysis of the data obtained to 1993 are significant at $P = .0234$ and a reanalysis of the data to May 1995 (Table 2) illustrates the consistency of these results over time. Since they were not part of the original group sequential design, there is no formal boundary value for these test results.

### *Multiple Cox Regression Model Analyses*

Factors that might contribute to relapse-free and overall survival were included in univariate and multivariate analysis of prognostic factors. Table 3 lists the univariate associations of relapse-free survival and overall survival. By log-rank test, age, time from diagnosis or first recurrence to study entry, and tumor ulceration were significantly associated with both relapse-free and overall survival ($P < .10$). Having an excisional biopsy was associated with

longer relapse-free survival time in the univariate test, but did not remain a significant predictor in the multivariate models. Table 4 lists the results of the multivariate Cox regression analysis. The primary aim is to adjust the estimate of the treatment effect for other factors also potentially associated with the outcome. Each factor identified in the univariate analysis as significant ($P \leq .10$) was estimated simultaneously in a model, and its association with the outcome was assessed after adjusting for all other factors included in the model. These factors, excluding excisional biopsy, remained independently significant in the multivariate setting. After including treatment, stage, age, time to randomization, and ulceration in the model, no other factor in Table 3 added significantly to the prediction of either outcome ($P < .05$). The model in Table 4 was arrived at after adding the one significant treatment interaction term, CS1/PS1 with IFN. The model for both relapse-free and overall survival estimates a $\geq$ 50% improvement due to IFN after adjusting for other factors that are also associated with the outcomes.

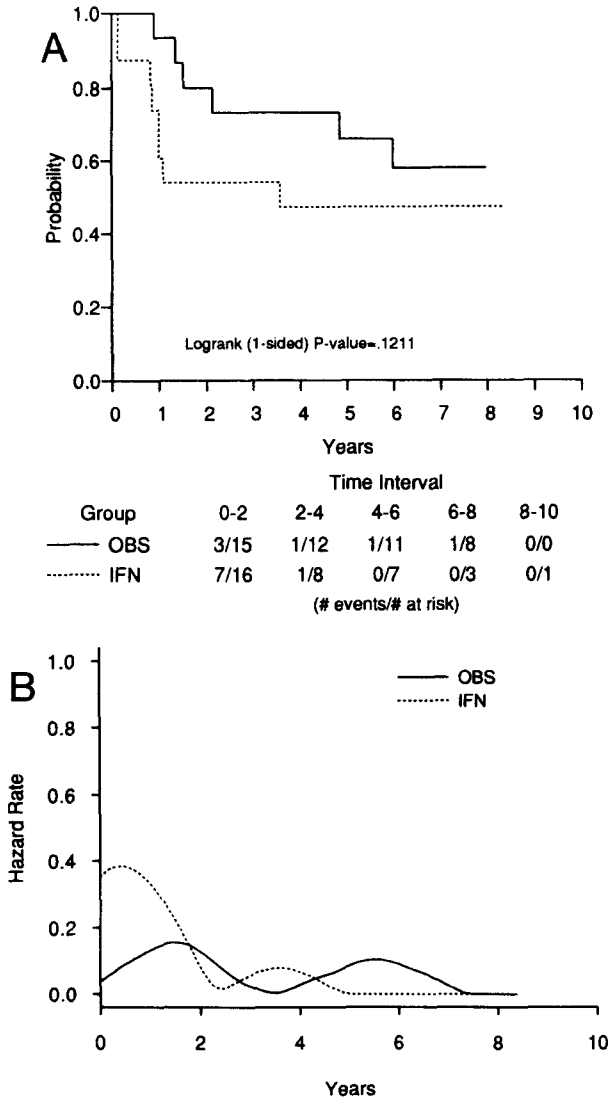


**Fig 4. Relapse-free survival and hazard of relapse over time for eligible patients stratified by stage of disease: CS1 PS1 (T4pN0M0, or AJCC IIB).**

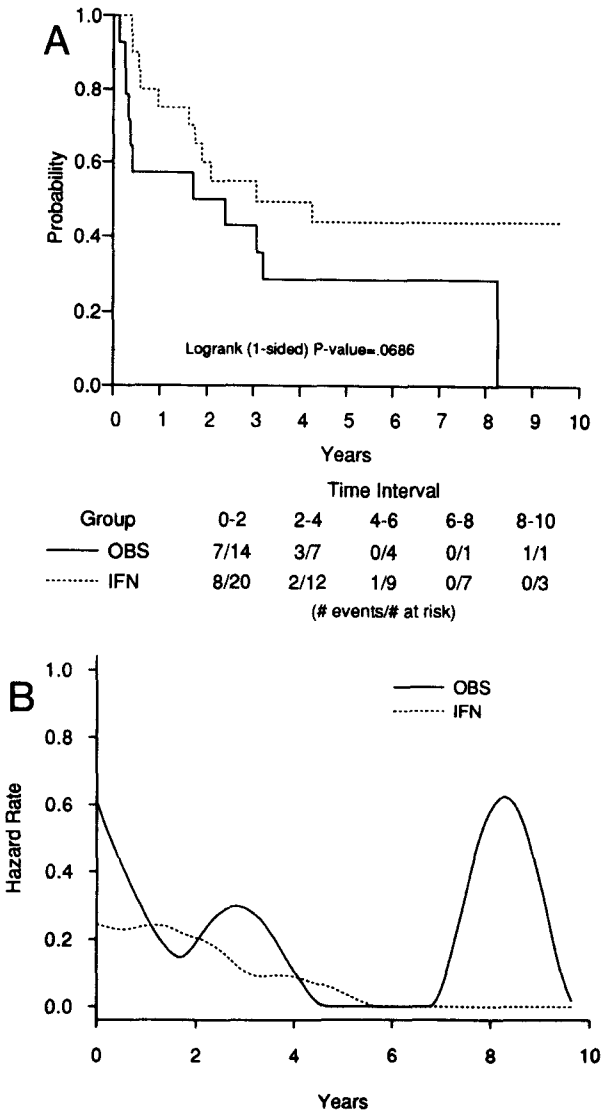


**Fig 5. Relapse-free survival and hazard of relapse over time for eligible patients stratified by stage of disease: CS1 PS2 (any TpN1M0, or AJCC III).**

*Toxicity*

Both treatment delays and dosage reductions were required during treatment; these are listed in Table 5 to

provide an index of the toxicity encountered on this trial. The percentages of patients who required dosing delays or dose reductions during the first month of IV induction therapy are tabulated separately from those required during months 2 through 12 of SC therapy for all 143 patients who received IFNα-2b. Dosing delays or reductions were required at least once for 50% of patients during the IV treatment phase and for 48% during the SC treatment phase for 48 weeks. Toxicity was significant, but tolerable, in the majority of participants with the dose interruptions and/or reductions specified in this protocol. The most prevalent toxicities encountered in the efficacy sample are listed in Table 6 according to grade. Constitutional, hematologic, and neurologic toxicities were noted most frequently. The myelosuppressive, hematologic, and biochemical hepatic toxicities incurred during this trial were largely reversible on interruption or attenuation of the dosage of IFN treatment.[11,12] The constitutional and neurologic toxicities were more problematic, in that these were occasionally persistent in sufficient magnitude to necessitate the discontinuation of treatment. The fraction of patients able to tolerate ≥ 80% of the target scheduled dosage of IFNα-2b therapy at five points in time is listed

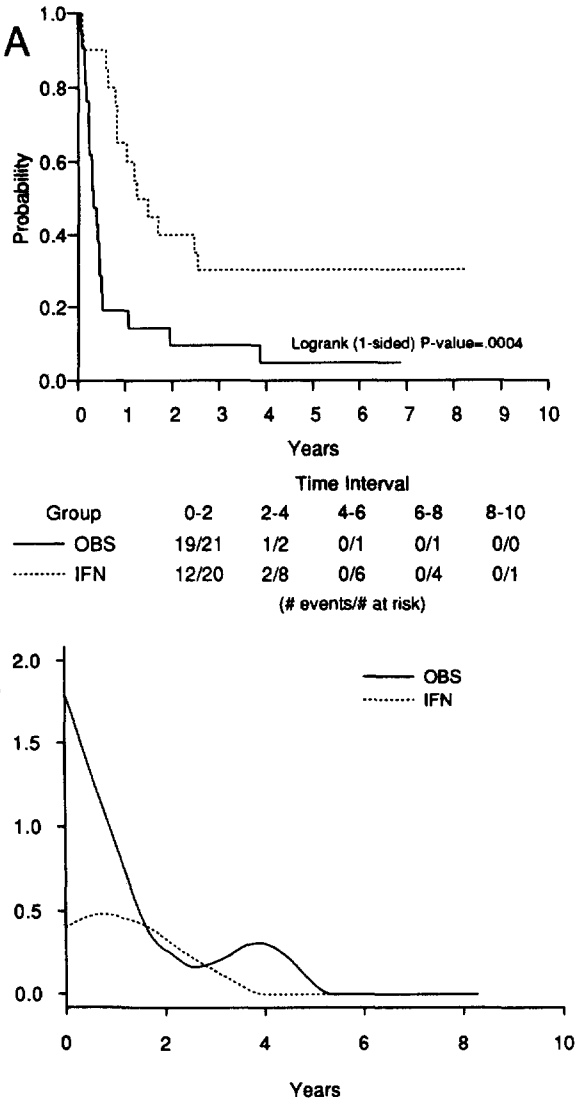


Fig 6. Relapse-free survival and hazard of relapse over time for eligible patients stratified by stage of disease: CS2 PS2 (any TcN1M0, or AJCC III).

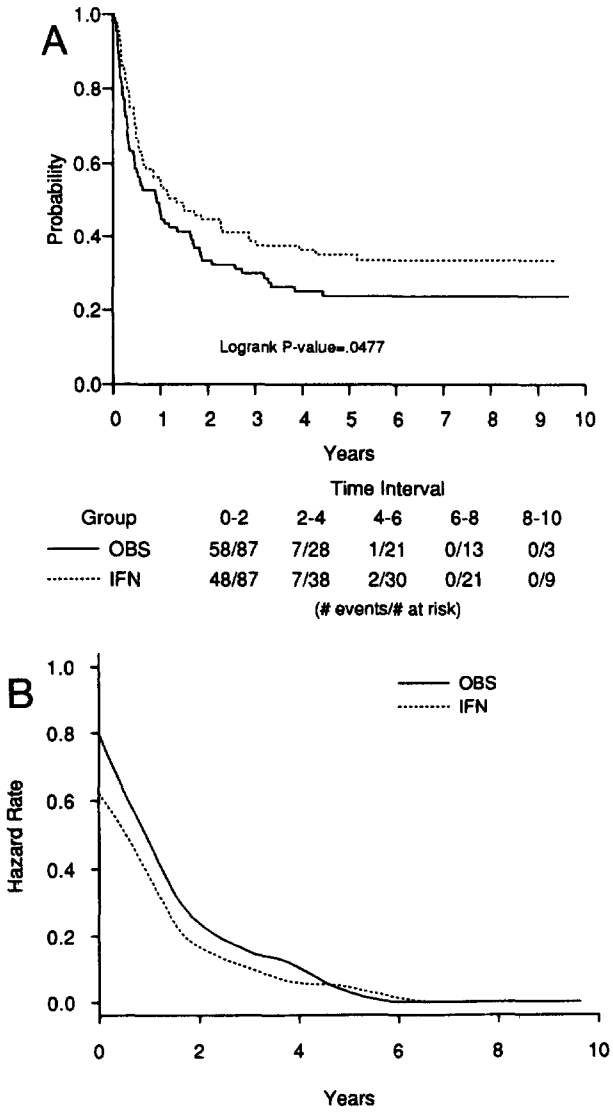


Fig 7. Relapse-free survival and hazard of relapse over time for eligible patients stratified by stage of disease: CS2 PS2 recurrent (TxrN1M0, or AJCC III).

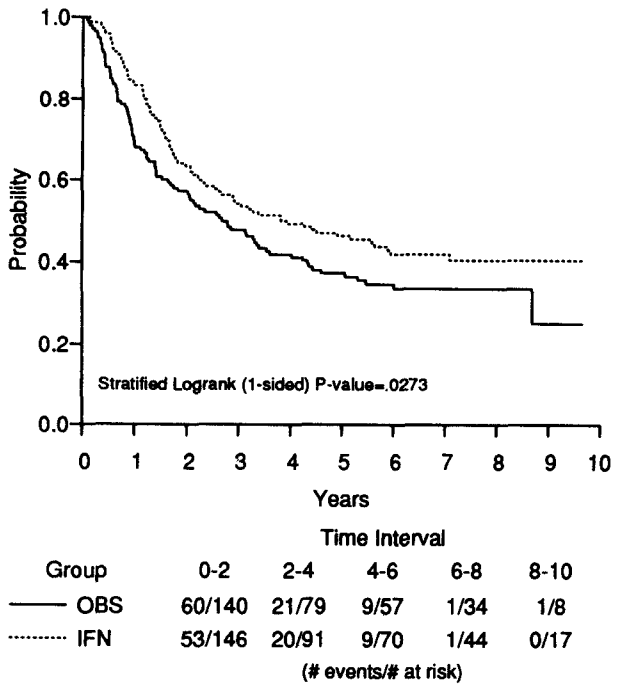


**Fig 8. Overall ITT analysis of survival for all randomized noncancelled (ineligible and eligible) patients.**

in Table 7. The majority of treatment withdrawals occurred in the first 4 months of treatment, after which discontinuation of therapy due to toxicity was unusual.

Fifty-nine percent of patients (72 of 143) were receiving at least ≥ 80% of the target dosage at the last induction dose (month 1). Of 110 patients who were still receiving IFN at 3 months, 79 (72%) were receiving at least 80% of the target dose. As Table 7 illustrates, although the number of patients still on treatment decreased over time, the proportion of patients receiving at least 80% of the target dose remained constant at ≈ 60%. Hepatotoxicity accompanied by liver failure and death was encountered in two patients who died early in the trial after 1 and 3 months of treatment. In both patients, there were historic suggestions of underlying antecedent liver disease, and the biochemical testing of liver function for treatment follow-up evaluation and dose modification as specified by the protocol had been omitted. Group notification of the importance of regular liver function testing during the follow-up period has prevented any further instances of life-threatening liver toxicity in the subsequent 5 years of the trial.

**Table 2. Significance of Differences Between Treatment and Observation Over Time 1990 to 1995**

| Date | No. of Events (Observed/IFN) | No. of Patients | P (1-sided) Observed* | P (1-sided) Boundary |
|---|---|---|---|---|
| Relapse-free survival | | | | |
| 3/90 | 70/53 | 208 | .0011 | .0186 |
| 3/91 | 80/73 | 248 | .0101 | .0164 |
| 3/92 | 87/75 | 252 | .0030 | .0363 |
| 3/93† | 89/78 | 252 | .0049 | .0333 |
| 6/95† | 103/90 | 280 | .0023 | |
| Overall survival | | | | |
| 3/90 | 52/38 | 214 | .0222 | .0202 |
| 3/91 | 62/54 | 252 | .0301 | .0221 |
| 3/92 | 70/62 | 252 | .0227 | .0386 |
| 3/93† | 74/68 | 252 | .0424 | .0353 |
| 3/93‡ | 86/77 | 286 | .0234 | .0353 |
| 6/95† | 90/81 | 280 | .0237 | |

*From log-rank test stratified by disease burden.
†Unplanned.
‡Includes 286 randomized patients (ITT population).

**Table 3. Univariate Association of Patient Characteristics With Relapse-Free and Overall Survival**

| Factor | No. of Patients | Recurrence No. | Recurrence Median Interval (years) | Recurrence P* | Death No. | Death Median Interval (years) | Death P* |
|---|---|---|---|---|---|---|---|
| Age, years | | | | .1007 | | | .0676 |
| < 50 | 155 | 100 | 1.7 | | 86 | 4.4 | |
| ≥ 50 | 125 | 93 | 1.0 | | 85 | 2.6 | |
| Sex | | | | .8970 | | | .4819 |
| Male | 169 | 117 | 1.4 | | 107 | | |
| Female | 111 | 76 | 1.2 | | 64 | | |
| Performance status | | | | .7790 | | | .4162 |
| 0 | 249 | 171 | 1.5 | | 154 | 3.0 | |
| 1 | 31 | 22 | 1.0 | | 17 | 5.6 | |
| Clark level | | | | .1970 | | | .3306 |
| < 4 | 98 | 72 | 1.0 | | 63 | 2.8 | |
| ≥ 4 | 162 | 107 | 1.7 | | 95 | 3.8 | |
| NA | 20 | 14 | | | 13 | | |
| Breslow depth (mm) | | | | .9141 | | | .8330 |
| < 2 | 99 | 67 | 1.2 | | 57 | 3.4 | |
| 2-3 | 34 | 22 | 1.9 | | 20 | 3.4 | |
| 3-4 | 32 | 21 | 1.5 | | 21 | 2.4 | |
| ≥ 4 | 87 | 63 | 1.5 | | 55 | 3.3 | |
| NA | 28 | 12 | | | 18 | | |
| Time to Rand† (days) | | | | .0001 | | | .0034 |
| < 30 | 74 | 59 | 0.53 | | 53 | 1.6 | |
| 30-40 | 81 | 59 | 1.07 | | 50 | 2.9 | |
| ≥ 40 | 125 | 75 | 2.7 | | 68 | 4.9 | |
| Ulceration of primary tumor | | | | .0265 | | | .0032 |
| Yes | 46 | 38 | 1.0 | | 37 | 1.7 | |
| No | 217 | 143 | 1.7 | | 126 | 3.5 | |
| NA | 17 | 12 | | | 8 | | |
| Excisional biopsy | | | | .0855 | | | .3171 |
| Yes | 209 | 140 | 1.5 | | 125 | 3.3 | |
| No | 62 | 48 | 0.9 | | 42 | 2.5 | |
| NA | 9 | 5 | | | 4 | | |

*Log-rank.
†Time from diagnosis or first relapse to randomization.

## DISCUSSION

We report that IFNα-2b administered at maximum-tolerated dosages IV daily for 5 days a week for 4 weeks, and SC three times weekly for 48 weeks, significantly

**Table 4. Cox Model Results Based on 280 Noncancelled Patients**

| Factor | Relapse-Free Survival Hazards Ratio | P | Overall Survival Hazards Ratio | P |
|---|---|---|---|---|
| Treatment with IFN | 0.61 | .0013 | 0.67 | .0115 |
| Stratum v CS2/PS2 | | | | |
| CS1/PS1 | 0.02 | .0004 | 0.22 | .0021 |
| CS1/PS2 | 0.58 | .0583 | 0.67 | .1680 |
| Recurrence | 0.64 | .0275 | 0.66 | .0573 |
| CS1/PS1 + IFN | 2.76 | .0727 | 2.97 | .0886 |
| Age > 50 years | 1.37 | .0333 | 1.39 | .0328 |
| Time from diagnosis to randomization v < 30 days | | | | |
| Days from diagnosis to randomization 30-40 | 0.68 | .0364 | 0.66 | .0379 |
| Days from diagnosis to randomization > 40 | 0.50 | .0002 | 0.54 | .0020 |
| Ulceration primary tumor | 1.44 | .0499 | 1.59 | .0148 |
| Ulceration data not available | 0.84 | .5762 | 0.65 | .2390 |

reduces the incidence of melanoma recurrence following operative therapy, with the most significant reduction early during the treatment period (Fig 2B). The significant impact of treatment on relapse-free survival of melanoma is evident in the analyses of efficacy sample of 280 patients ($P = .0023$, one-sided). Overall survival has also been prolonged in the efficacy sample ($P = .0237$, one-sided). Multivariable analyses using Cox multiple regression models show that IFNα-2b treatment is a significant predictor of both overall survival and relapse-free survival. Among the factors analyzed, treatment was the most significant predictor of relapse-free and overall survival ($P = .0011$) after stage of disease (CS1 PS1, $P = .002$), and interval from diagnosis or first recurrence to randomization ($P = .002$).

Toxicity of this therapy was significant but tolerable in the majority of patients. Constitutional and neuropsychiatric symptoms and laboratory findings of myelosuppression and hepatoxicity occurred in most patients. The severity and degree of the toxicity are evident in that 67% of all patients had severe (grade 3) toxicity at some point during the year of treatment, 9% had life-threatening toxicity, and two had lethal hepatic toxicity. The two deaths occurred early in the study, before the predictive value of changes in liver function was stressed to the group. Dose delays and/or reductions due to toxicity were required in 37% of patients during induction and 36% during maintenance. During the IV induction phase, at the last treatment, 67% of patients received at least 80% of the planned 20-MU/m$^2$ dosage, and during the SC maintenance phase, 59% of patients received at least 80% of the scheduled 10-MU/m$^2$ dosage per treatment. The toxicity of treatment with IFNα-2b as administered in this trial must be considered in assessing the benefits of IFNα-2b on relapse-free survival and overall survival of high-risk melanoma patients. Treatment required close attention to the need for dose modifications in a majority of patients, but with appropriate dose modification 74% of patients were able to continue treatment on protocol until 1 year (or relapse).

Stratification was performed to assure balance in the distribution of key risk factors among patients with differing levels of tumor burden, and to allow us to explore the hypothesis that treatment benefits may be greater in patients with early metastatic disease, such as in the CS1

**Table 6. Toxic Events by Type and Degree**

| Type | Grade (N = 143) 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Constitutional* | 18 | 53 | 64 | 5 | 0 |
| Myelosuppression | 37 | 57 | 34 | 0 | 0 |
| Hepatotoxicity | 30 | 39 | 20 | 0 | 2 |
| Neurologic | 31 | 47 | 33 | 7 | 0 |
| Worst grade/patient | 2 | 30 | 96 | 13 | 2 |

*Worst grade of any constitutional toxicity, including fever, chill, and flu-like symptoms: fatigue, malaise, diaphoresis.

**Table 5. Treatment Delays and Dose Reductions**

| Reason for Dose Modification | Patients With a Dose Delay No. | % | Patients With a Dose Reduction No. | % | Patients With Either Delay or Reduction No. | % |
|---|---|---|---|---|---|---|
| Induction treatment (n = 143) | | | | | | |
| Toxicity | 24 | 17 | 45 | 31 | 53 | 37 |
| Any reason | 49 | 34 | 51 | 36 | 72 | 50 |
| Maintenance treatment (n = 128) | | | | | | |
| Toxicity | 32 | 25 | 39 | 30 | 46 | 36 |
| Any reason | 52 | 41 | 45 | 35 | 61 | 48 |

**Table 7. Dose Received**

| Time Point From Date of Randomization | Patients Receiving > 80% of Target Dose/m$^2$/d (last dose) No. | % | Target Dose/m$^2$/d |
|---|---|---|---|
| Last dose (induction) | 96/143 | 67 | 20 |
| 3 months from randomization | 79/128 | 62 | 10 |
| 6 months from randomization | 51/128 | 40 | 10 |
| 9 months from randomization | 39/128 | 30 | 10 |
| 11 months from randomization | 32/128 | 25 | 10 |
| Last dose (maintenance) | 75/128 | 59 | 10 |

PS2 and CS2 PS2 patient groups. This is the only adjuvant trial of a systematic intervention in which the pathologic stage of regional lymph nodes has been established in all participants, permitting the evaluation of the effect of IFN$\alpha$-2b therapy on microscopic/subclinical regional lymph node disease. New techniques for lymphographic selection of sentinel regional draining lymph nodes may be expected to increase the detection of this category of disease, and may allow the more extensive evaluation of adjuvant therapy in this subset of patients.

Analysis of the impact of treatment according to risk group shows a dramatic suppression of the hazard of relapse and death with IFN$\alpha$-2b treatment in all node-positive strata, including the group of patients treated with nonpalpable regional lymph node metastasis discovered at elective lymphadenectomy (CS1 PS2; Fig 5), and initial presentation with palpable regional lymph node metastasis (CS2 PS2; Fig 6). Patients who had nonpalpable but pathologically documented lymph node metastasis showed a reduction of the estimated hazard of relapse from approximately 60% to a rate of approximately 25% during the first year of treatment, while the reduction in the estimated hazard of relapse for patients who presented with palpable regional lymph nodes was even more pronounced. Thereafter, there was a sustained influence of IFN$\alpha$-2b therapy on relapse and death due to melanoma in these groups, as in the larger group of patients who were treated for regional lymph node recurrence.

The difference in continuous disease-free survival of treated compared with untreated patients at 5 years amounts to a 42% increment at a mature and stable plateau phase of follow-up (6.9 years median), which may represent a curative impact of IFN$\alpha$-2b pending further follow-up and corroboration.

The time dependence of the therapeutic effects of IFN$\alpha$-2b are important to consider in two regards. First, patients who entered this trial were treated less than 42 days after lymphadenectomy for recurrence, or 56 days after primary surgery and lymphadenectomy for initial presentation. Second, during treatment itself, the greatest impact of IFN$\alpha$-2b was manifest early in the first year of treatment, as demonstrated in the hazards plots for relapse in the overall trial and each substratum. These factors will also be important to consider in the development of future combinations of IFN$\alpha$-2b and other modalities such as vaccines. Specifically, they raise the issue of whether the initial first month of IV therapy used in E1684 was necessary or sufficient for the therapeutic benefit. The initial IV therapy using IFN$\alpha$-2b at 20 MU/m$^2$/d, designed to attain peak blood levels substantially higher than possible by other routes, may have been critical to the therapeutic benefit we have observed.

In summary, we report a trial of postoperative IFN$\alpha$-2b therapy in patients at high risk of relapse and death from melanoma, in which we have observed a highly significant prolongation of continuous relapse-free survival and a 50% increase in the fraction of relapse-free patients after surgery for high-risk deeply invasive or node-metastatic melanoma. The prolongation of overall survival in this trial amounts to approximately 1 year. Analysis of the impact of IFN$\alpha$-2b treatment on survival among 252 eligible patients as initially reported at a median follow-up time of 4.7 years[8] is borne out and enhanced in the larger analysis of 280 randomized patients at a median follow-up interval of 6.9 years. The greater statistical significance of the effects of IFN treatment on relapse compared with survival may be explained by the pursuit of surgical salvage, or other therapies including IFN$\alpha$-2b in patients after failure on the observation arm and removal from this trial.

The results of this study demonstrate that IFN$\alpha$-2b is capable of altering the natural history of melanoma and prolonging both relapse-free and overall survival by approximately 1 year. These results provide a strong rationale for the development of further regimens of IFN$\alpha$-2 therapy, building on either the initial 1 month of intensive IV therapy used for induction therapy in this trial, or the subsequent 1 year of SC therapy used in this trial. Whether one or the other of these elements is necessary, or sufficient, to achieve benefits observed in this trial remains to be determined. It is disappointing that a recent report of the results of treatment at lower dosages of 3 MU/d SC three times weekly for 3 years, as pursued by the World Health Organization Melanoma Program Trial no. 16 has been found to be ineffective.[13] The differing entry criteria and eligibility of patients with extracapsular lymph node disease excluded from E1684, as well as the differing dose, schedule, and species of IFN$\alpha$-2 used for this trial may have contributed to the lack of a survival or relapse-free interval benefit from this therapy. The Intergroup trial E1690 has tested a similar dosage of IFN$\alpha$-2b and will bear on this issue as well. There is a critical need for greater understanding of the immune and disease variables that may predict clinical benefit with IFN$\alpha$-2b. These issues are being evaluated in the context of the recently concluded Intergroup trial of IFN$\alpha$-2b, which may provide insight into the mechanism of therapeutic action for IFN$\alpha$-2b and permit the more precise identification of patients who are most likely to benefit from this therapy.

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