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ORIGINAL REPORT

Phase III Randomized Study of 4 Weeks of High-Dose Interferon-α-2b in Stage T2bNO, T3a-bNO, T4a-bNO, and T1-4N1a-2a (microscopic) Melanoma: A Trial of the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network Cancer Research Group (E1697)

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ABSTRACT

Purpose
To test the efficacy of 4 weeks of intravenous (IV) induction with high-dose interferon (IFN) as part of the Eastern Cooperative Oncology Group regimen compared with observation (OBS) in patients with surgically resected intermediate-risk melanoma.

Patients and Methods
In this intergroup international trial, eligible patients had surgically resected cutaneous melanoma in the following categories: (1) T2bN0, (2) T3a-bN0, (3) T4a-bN0, and (4) T1-4N1a-2a (microscopic). Patients were randomly assigned to receive IFN α-2b at 20 MU/m^2/d IV for 5 days (Monday to Friday) every week for 4 weeks (IFN) or OBS. Stratification factors were pathologic lymph node status, lymph node staging procedure, Breslow depth, ulceration of the primary lesion, and disease stage. The primary end point was relapse-free survival. Secondary end points included overall survival, toxicity, and quality of life.

Results
A total of 1,150 patients were randomly assigned. At a median follow-up of 7 years, the 5-year relapse-free survival rate was 0.70 (95% CI, 0.66 to 0.74) for OBS and 0.70, (95% CI, 0.66 to 0.74) for IFN ($P = .964$). The 5-year overall survival rate was 0.83 (95% CI, 0.79 to 0.86) for OBS and 0.83 (95% CI, 0.80 to 0.86) for IFN ($P = .558$). Treatment-related grade 3 and higher toxicity was 4.6% versus 57.9% for OBS and IFN, respectively ($P < .001$). Quality of life was worse for the treated group.

Conclusion
Four weeks of IV induction as part of the Eastern Cooperative Oncology Group high-dose IFN regimen is not better than OBS alone for patients with intermediate-risk melanoma as defined in this trial.

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INTRODUCTION

Of the 76,380 new patients with melanoma projected for 2016 in the United States,[1] those with deeper primary lesions or regional lymph node involvement, classified in the 6th edition of the American Joint Committee on Cancer (AJCC) staging system as T3N0M0 (1.5 to 4 mm deep [IIA]) or T4N0M0 (> 4 mm deep [IIB]), will have 5-year survival rates diminishing from 75% to 66%, and those with regional nodal involvement (TxN1-2a-bM0 [IIIA-B-C]) will have 5-year survival rates diminishing from 59% to 40%.[2,3]

Interferon-α-2b (IFN-α-2b; Intron A, Merck, NJ) was the first agent approved for adjuvant therapy for patients with high-risk surgically resected melanoma (stages IIB and III) on the basis of the results of the Eastern Cooperative Oncology Group (ECOG) E1684 trial, which tested high-dose interferon (HDI; IFN-α-2b, 20 MU/m^2 intravenously [IV] for 5 of 7 days per week [Monday to Friday] for 4 weeks [induction], followed by

ASSOCIATED CONTENT

Appendix
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IFN-α-2b, 10 MU/m^2 three times per week [Monday, Wednesday, Friday, maintenance] for 11 months) versus observation (OBS). This trial showed statistically significant benefits of treatment for relapse-free survival (RFS; $P = .002$) and for overall survival (OS, $P = .024$).[4]

The Kaplan-Meier RFS and OS curves from E1684 showed early separation and sustained benefit throughout treatment and follow-up. It was hypothesized that the major source of benefit from the full HDI regimen may have been the initial IV induction treatment administered over 4 weeks. The current study (E1697) was proposed to test the impact of administering only 4 weeks of high-dose IFN-α-2b IV 5 of 7 days per week, as in the E1684 trial induction phase, compared with OBS for patients with resected melanoma in the following categories: (1) T2bN0, (2) T3a-bN0, (3) T4a-bN0 (> 4 mm), and (4) T1-4N1a-2a (microscopic). These patients were selected for study because they were considered to be at intermediate risk for recurrence and particularly likely to be motivated to pursue a shorter and potentially less toxic adjuvant therapy regimen with less disruption of quality of life (QOL).

PATIENTS AND METHODS

Eligibility

Eligibility criteria included completely resected, histologically confirmed cutaneous melanoma in the following categories: (1) T2bN0, (2) T3a-bN0, (3) T4a-bN0, and (4) T1-4N1a2a (microscopic). Participants also had to be > 10 years of age, have completed all primary surgical therapy (wide excision with or without lymphadenectomy) and be randomly assigned within 84 days of surgery, have an ECOG performance status of 0 to 1, have adequate hematologic and biochemical parameters, and have no major comorbidity or concurrent malignancy. The absence of regional or distant metastatic disease was required to be documented by physical examination and appropriate radiologic studies. Surgical staging of regional lymph nodes by sentinel node mapping was encouraged but not mandatory.

Treatment

The protocol (Data Supplement) was approved by the ethics committees at participating sites. All patients provided written informed consent. Patients were randomly assigned to OBS or IFN, stratified by pathologic lymph node status (known, unknown), lymph node staging procedures (sentinel lymph node procedure, elective lymph node dissection, no lymphadenectomy), Breslow depth (≤ 1.00 mm, 1.01 to 2.00 mm, 2.01 to 4.00 mm, > 4.00 mm), ulceration of the primary lesion (yes, no, unknown), and disease stage (lymph node positive [N1, N2a], lymph node negative [N0]; Fig 1).

Patients randomly assigned to the IFN group received IFN-α-2b at 20 MU/m^2/d IV for 5 of 7 days per week (Monday to Friday) for 4 weeks. Patients who experienced grade 3 or higher toxicity per National Cancer Institute Criteria for Adverse Events according to Common Terminology Criteria for Adverse Events (version 2.0) and protocol-specific criteria were specified to have treatment withheld or discontinued.

End Points

The primary objective was to compare RFS between IFN and OBS. Secondary objectives were to compare OS and assess toxicity and QOL. RFS was defined as time from randomization to first recurrence or death without recurrence. For censored patients, time from randomization to the last date of assessment was used. OS was defined as time from randomization to death from any cause. For censored patients, time from randomization to the last known date alive was used. Adverse events (AEs) were coded and graded according to the National Cancer Institute's Common Terminology for Criteria for Adverse Events (version 2.0). QOL data were collected longitudinally. Collection schedules, statistical analysis, and results are available in the Appendix and Table A1 (online only).

Statistical Design and Analysis

A cure rate model[5,6] was assumed when assessing power and sample size during the design stage of the trial. The model assumes that the target population is a mixture, with proportion p being those who would be cured and $1 - p$ being those who would fail according to an exponential distribution with rate λ. Thus, the survival function used to assess power

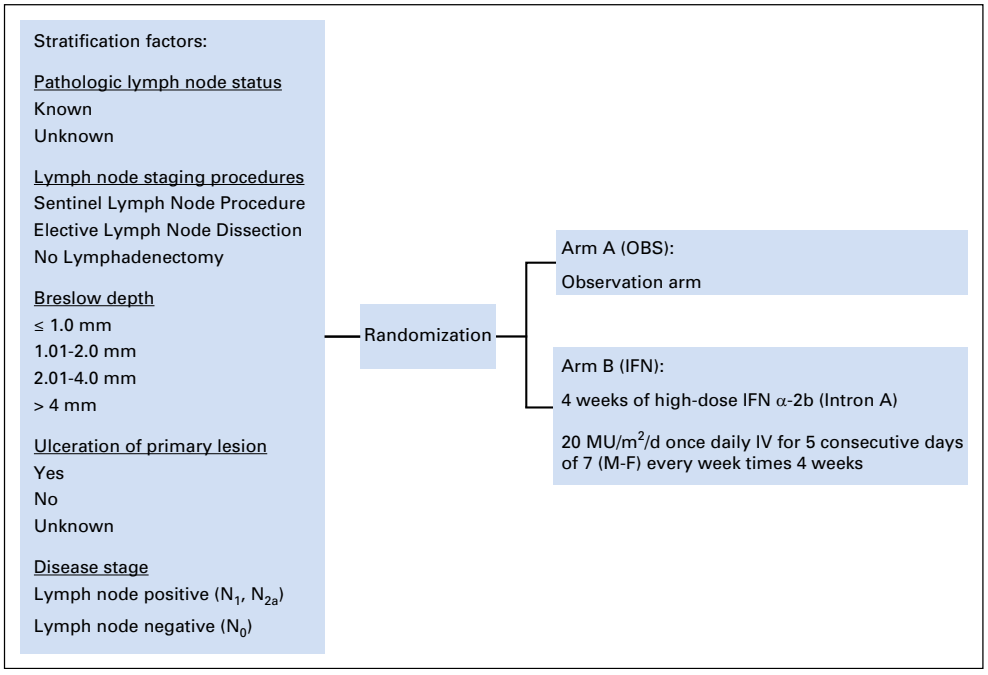

Fig 1. Study schema for the phase III randomized trial of 4 weeks of high-dose interferon-α-2b in patients with intermediate-risk melanoma. IFN, interferon group; IV, intravenously; M-F, Monday to Friday; OBS, observation group.

and sample size is expressed as $S(t) = p + (1 - p)\ exp(-\lambda t)$. It was assumed that IFN would provide a 15% relative increase in median time to event (from OBS RFS = 1.5 years, OS = 2.5 years) for those not cured and a 7.5% absolute increase in the cure rate (from OBS RFS = 65%, OS = 75%). This design required 1,420 total patients (with 1,278 eligible), 339 RFS events, and 186 deaths to achieve 88% power, and a two-sided type I error rate of 5% for each end point. Interim analyses were planned, starting at 25% information time. O'Brien-Fleming boundaries were used for efficacy and conditional power for futility monitoring.

All RFS and OS analyses were based on the intent-to-treat population. The distributions of RFS and OS were estimated using the Kaplan-Meier method,[7] with 95% CIs calculated using Greenwood's equation.[8] Differences in treatment effect were tested using stratified log rank tests. Stratified Cox proportional hazards models[9] were used to estimate hazard ratios (HRs) for the treatment effect for RFS and OS. Repeated CIs (RCIs)[10] were provided to adjust for interim analyses. Toxicity data were compared using Fisher's exact tests.[11] All reported *P* values were for two-sided tests, and the significance level was set at .05. Statistical analysis was conducted using SAS/STAT software (Version 9.2, SAS Institute, Cary, NC).

RESULTS

This intergroup study was initiated by ECOG in 1998, with participation from the Southwest Oncology Group (SWOG), the National Cancer Institute of Canada, the CALGB (Cancer and Leukemia Group B), and the Sydney Melanoma Unit. At the third interim analysis, the data safety monitoring committee recommended that the trial be stopped early on the basis of futility analysis. The study was terminated in October 2010.

Total accrual was 1,150 patients. Baseline demographic and clinical characteristics are listed in Table 1. Randomization was well balanced between treatment groups for sex, race, age, lymph node status, and staging procedure, Breslow depth, Clark level, ulceration, disease stage, primary site, and ECOG performance status.

The data as of a cutoff date of January 2015 were used, with a median follow-up time of 7 years. There were 50 and 52 ineligible patients in the OBS and IFN groups, respectively. As shown in the

Table 1. Patient Characteristics (n = 1,150)

Variable	Level	OBS (n = 569) No. (%)	IFN (n = 581) No. (%)	Total (n = 1,150) No. (%)
Sex	Male	320 (56.2)	336 (57.8)	656 (57.0)
	Female	248 (43.6)	244 (42.0)	492 (42.8)
	Unknown/missing	1 (0.2)	1 (0.2)	2 (0.2)
Race	White	536 (94.2)	547 (94.1)	1083 (94.2)
	Hispanic	4 (0.7)	4 (0.7)	8 (0.7)
	African American	5 (0.9)	4 (0.7)	9 (0.8)
	Asian	2 (0.4)	0 (0.0)	2 (0.2)
	Native American	0 (0.0)	1 (0.2)	1 (0.1)
	Indian	0 (0.0)	1 (0.2)	1 (0.1)
	Other	0 (0.0)	1 (0.2)	1 (0.1)
	Unknown/unreported	22 (3.8)	23 (3.9)	45 (3.8)
Age (years)	Median	52	52	52
	Minimum	19	10	10
	Maximum	81	85	85
Lymph node status	Known	534 (93.8)	537 (92.4)	1071 (93.1)
	Unknown	35 (6.2)	44 (7.6)	79 (6.9)
Lymph node staging procedure	Sentinel	478 (84.0)	472 (81.2)	950 (82.6)
	Elective	59 (10.4)	72 (12.4)	131 (11.4)
	No lymphadenectomy	32 (5.6)	37 (6.4)	69 (6.0)
Breslow depth	≤ 1.00 mm	23 (4.0)	22 (3.8)	45 (3.9)
	1.01-2.00 mm	164 (28.8)	170 (29.2)	334 (29.0)
	2.01-4.00 mm	290 (51.0)	301 (51.8)	591 (51.4)
	> 4.00 mm	89 (15.7)	87 (15.0)	176 (15.3)
	Unknown/missing	3 (0.5)	1 (0.2)	4 (0.4)
Ulceration of primary lesion	Yes	193 (33.9)	201 (34.6)	394 (34.2)
	No	349 (61.3)	351 (60.4)	700 (60.9)
	Unknown/missing	27 (4.8)	29 (5.0)	56 (4.9)
Disease stage	Lymph node positive	108 (19.0)	102 (17.6)	210 (18.3)
	Lymph node negative	438 (77.0)	456 (78.4)	894 (77.7)
	Unknown/missing	23 (4.0)	23 (4.0)	46 (4)
Primary site	Head	81 (14.2)	98 (16.9)	179 (15.6)
	Neck	82 (14.4)	86 (14.8)	168 (14.6)
	Upper extremity	120 (21.1)	126 (21.7)	246 (21.4)
	Lower extremity	42 (7.4)	50 (8.6)	92 (8.0)
	Subungual	137 (24.1)	128 (22.0)	265 (23.0)
	Trunk	77 (13.5)	67 (11.5)	144 (12.5)
	Mucosal	15 (2.6)	13 (2.2)	28 (2.4)
	Other	14 (2.5)	12 (2.1)	26 (2.3)
	Unknown/missing	1 (0.2)	1 (0.2)	2 (0.2)

Abbreviations: IFN, interferon; OBS, observation.

CONSORT diagram (Fig 2), 17% of patients refused to start or withdrew consent after being randomly assigned, and 6.5% discontinued because of adverse events. Among the 581 patients randomly assigned to receive IFN, 12 never started treatment. The median duration of treatment was 26 days (range, 1 to 47 days).

Regardless of eligibility, an intent-to-treat analysis was conducted. Neither RFS nor OS was significantly different between the two arms of the study. There were a total of 367 RFS events (319 recurrences and 48 deaths without recurrences). The 5-year RFS rate was 0.70 (95% CI, 0.66 to 0.74) for OBS and 0.70 (95% CI, 0.66 to 0.74) for IFN ($P = .964$). Figure 3A displays the Kaplan-Meier plot of RFS. The HR for IFN versus OBS was 0.98, with a 95% RCI of 0.79 to 1.22.

There were a total of 241 deaths. The 5-year OS rate was 0.83 (95% CI, 0.79 to 0.86) for OBS and 0.83 (95% CI, 0.80 to 0.86) for IFN ($P = .558$). Figure 3B displays the Kaplan-Meier plots for OS. The HR for IFN versus OBS was 1.08, with a 95% RCI of 0.82 to 1.41. Figures 4A and 4B display the forest plot for the effect of IFN for RFS and OS in the subgroups. None of the subgroups indicated a significant treatment difference.

Toxicity is listed in Table 2. A total of 439 patients in the OBS group and 568 in the IFN group were included in the toxicity assessment. Treatment-related grade 3 and higher toxicities were seen in 4.6% of patients in the OBS group versus 57.9% of patients in the IFN group. This difference was significant ($P < .001$). The most common grade 3 or higher toxicities for patients receiving IFN were neutropenia (21%), fatigue (13%), elevated liver enzymes (13%), and headache (8%). The QOL analysis is provided in the Appendix.

DISCUSSION

Two decades after the first US Food and Drug Administration approval of an adjuvant therapy for high-risk melanoma (defined as AJCC stage IIB and III),[12] debate and controversy around the optimal clinical use of adjuvant IFN continues. The 1-year HDI regimen comprises a high-dose IV (induction) phase followed by a subcutaneous (maintenance) phase. On the basis of the results of trial E1684,[4] this regimen has been accepted as a standard in the United States and many other countries and has served as the control arm of most ECOG- and SWOG-led US intergroup randomized trials of adjuvant therapy, including E1609 and S0008. However, the toxicity associated with this regimen and the 12-month duration of treatment has been an impediment to its universal acceptance. The lack of an improvement in OS in one subsequent trial (E1690) has further fueled controversy.[13] In the absence of defined alternative treatment options, modifications of this regimen attempting to lower the dose or shorten the duration of therapy have been pursued.

Adjuvant trials have traditionally targeted patients at high risk. However, patients with melanoma of Breslow thickness between 1.5 and 4.0 mm without nodal metastases (stage IIA, 6th edition AJCC) account for 31% of new diagnoses, comprising approximately 25,000 patients per year.[14] These patients have a significant relapse rate of 30% at 5 years,[15,16] but have uniformly been excluded from prior cooperative group trials of adjuvant therapy.

At the time we designed E1697, information from two European trials for stage II patients were available. The Austrian

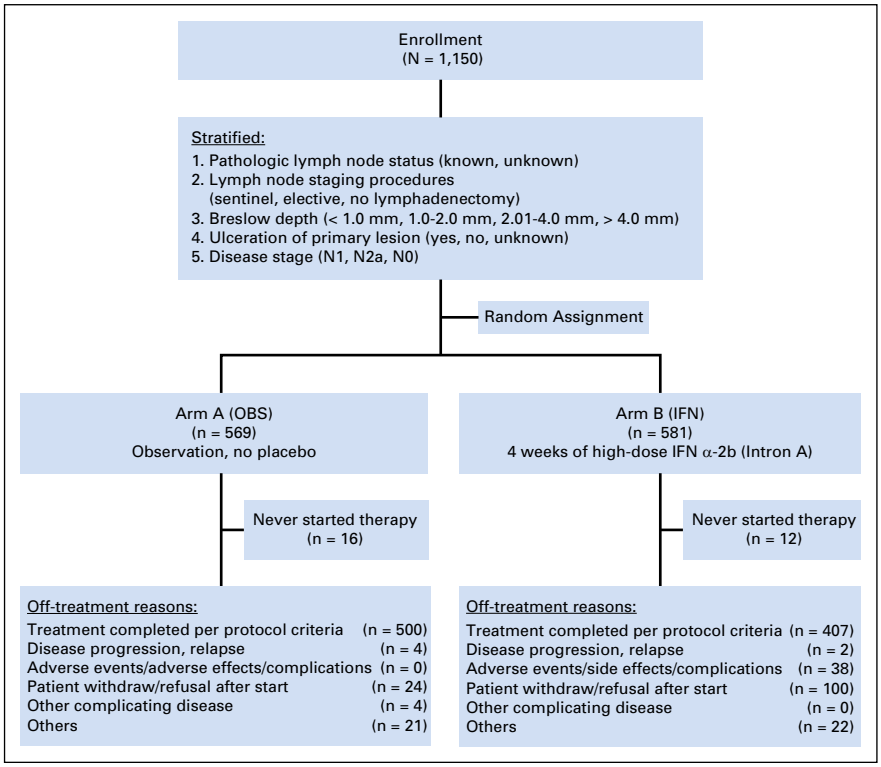

Fig 2. CONSORT diagram. Note that the patients in the observation (OBS) arm who refused participation were counted as never started assigned therapy. IFN, interferon arm.

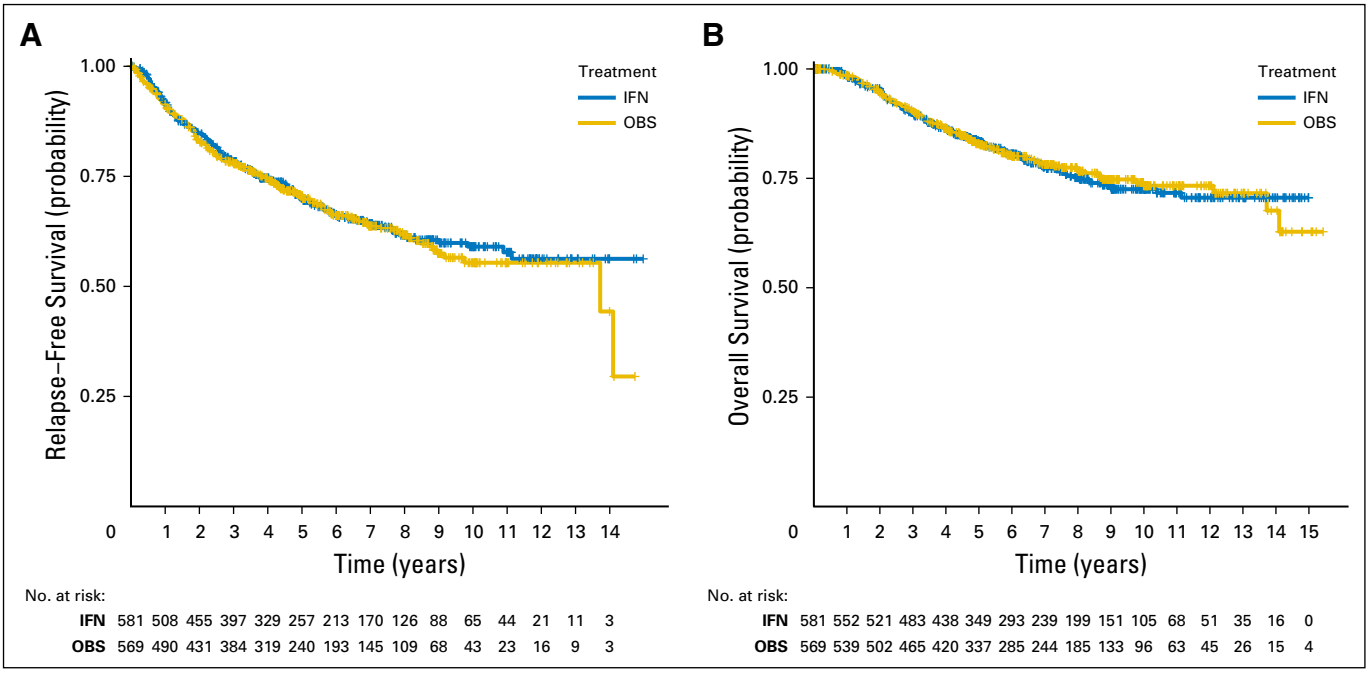

Fig 3. Kaplan-Meier plot of (A) relapse-free survival and (B) overall survival (OS) by treatment arm for patients with intermediate risk melanoma.

Melanoma Cooperative Group[17] and the French Cooperative Group on Melanoma[18] both tested lower doses of IFN-α (3 MU three times per week, termed low-dose IFN [LDI]) for varying durations compared with OBS. Both trials showed improvement in RFS that diminished over time without significant impact on OS, potentially implying transient benefits without a fraction of patients who are cured. The WHO trial No. 16 for patients with stage III disease tested the benefit of 3 years of LDI and showed no benefit in either RFS or OS.[19] Intergroup trial E 1690 tested HDI or LDI versus OBS for patients with stage IIB and III melanoma, showing no significant benefit for LDI in either RFS or OS.[20]

Analysis of the hazard functions observed in the HDI arm in E1684 showed maximal benefit early, during the IV induction phase, that was subsequently sustained.[4] This IV induction phase distinguished these trials from European trials of low- or intermediate-dosage IFN. We hypothesized that this induction phase might be necessary and sufficient for the benefit of the 1-year HDI regimen. In addition, toxicity in the E1684 trial showed two major adverse effects that influenced QOL for patients—namely, fatigue and depression—that were cumulative over the year of treatment. E1697 was designed to test the potential benefits of 1 month of high-dose IV IFN-α-2b alone in patients with intermediate-risk melanoma and defined this initially as T3N0 disease. Subsequently, eligibility was expanded to include patients with T4N0 and TanyN1a disease, as well.

The results of E1697 clearly show no impact of induction therapy alone in terms of either RFS or OS (*P* values of .964 and .558, and HRs for arm B versus arm A of 0.98 and 1.08, respectively). Subgroup and subset analyses on the basis of the various stratification factors, including T3, T4, and N1a disease as well as those with ulcerated primary lesions, also showed no differences between the treatment arms. QOL, not surprisingly, was worse for the patients who received treatment compared with OBS.

Other trials have attempted to address the issue of the value of IV induction therapy with IFN compared with the full year of treatment. The Hellenic Cooperative Oncology Group conducted trial 13A/98 to test the noninferiority of a modified IFN IV induction (15 MU/m^2 per day for 5 days per week for 4 weeks) compared with the same induction regimen followed by a modified maintenance phase (10 MU flat dose, three times per week for 48 weeks). This relatively small trial (364 patients) failed to show differences in RFS or OS between the two arms.[21] The modification of both the induction and the maintenance phases of this trial compared with the E1684 trial, and lack of a control arm, make interpretation difficult.[22] Payne et al[23] conducted a pilot trial with 194 patients with stage IIB-IIIC melanoma, randomly assigning a higher-risk population, among which 77% had gross nodal disease, to standard 1-year HDI or the induction phase alone using doses and schedules identical to E1684. The OS outcome for the induction-only arm was statistically inferior to the full year of HDI.

Other trials have tested the role of multiple courses of IV induction in patients with high-risk melanoma.[24,25] A trial from the Dermatologic Cooperative Oncology Group (DeCOG) randomly allocated 649 patients to either standard HDI or IV induction given three times every fourth month. No significant difference in survival was observed between the two arms of the study.[26] An Italian trial randomly assigned

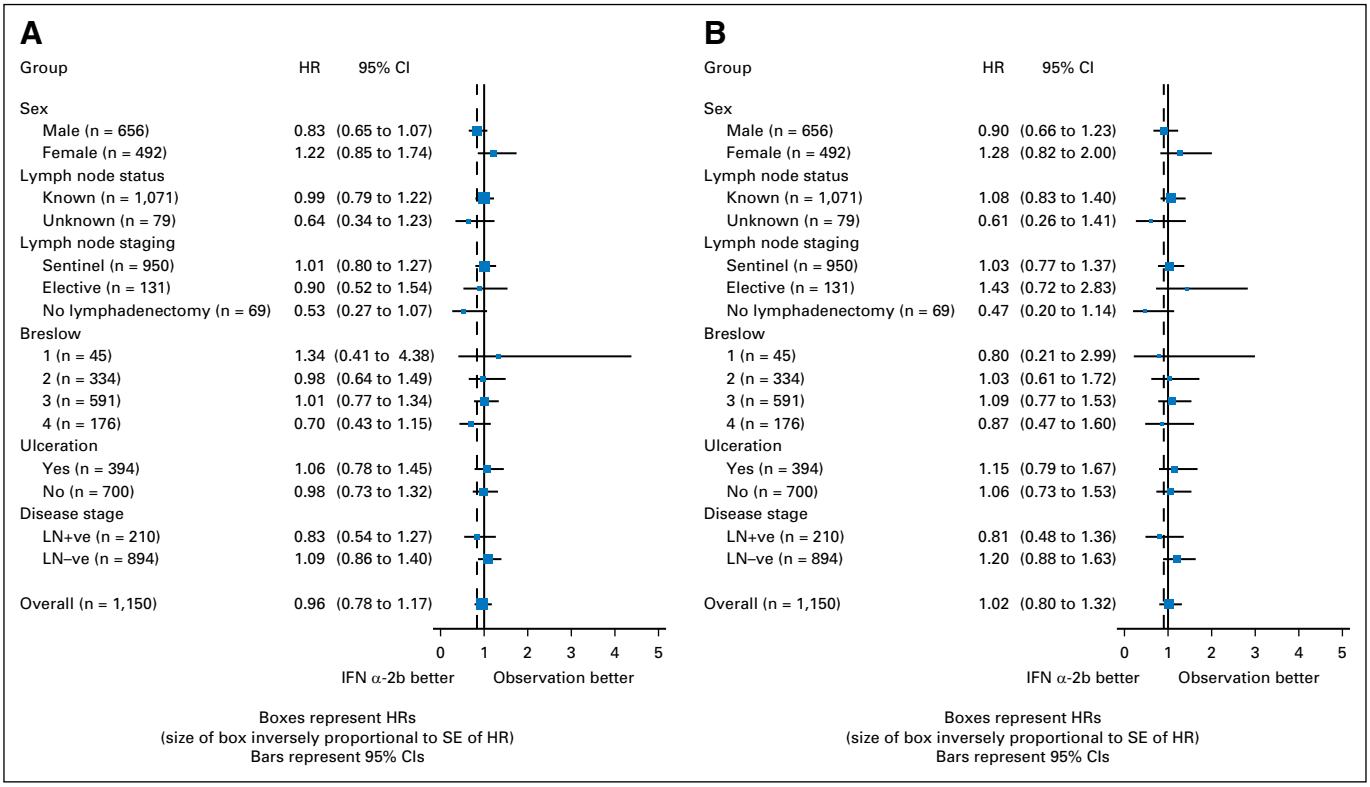

Fig 4. Forest plot for (A) relapse-free survival and (B) overall survival (with hazard ratios [HRs] for interferon [IFN] *v* observation [OBS]). Note that the CIs presented here are not recurrent CIs. SE, standard error; LN, lymph node; −ve, negative; +ve, positive.

336 patients in a similar design but with four courses of IV induction, once every third month. No significant differences were observed between the two arms of the trial.[27] Of note, both of these trials included only patients with stage III disease.

E1697 is the only trial to date to test the role of 1 month of IV induction versus OBS. The lack of any impact of this treatment on either RFS or OS in any subset of patients suggests that IV induction therapy does not, by itself, have a meaningful therapeutic role and that the overall benefit of the E1684 regimen requires additional IFN, either maintenance treatment of 11 months per the HDI regimen or possibly repeated courses of IV induction per the two European trials cited previously.

An alternate hypothesis regarding adjuvant IFN therapy is that treatment duration may be as important as dose intensity. A trial from the European Organization for the Research and Treatment of Cancer (EORTC 18991) tested the role of 5 years of pegylated interferon in 1,256 patients with stage III melanoma compared with OBS.[28] The difference in RFS between the treatment and the OBS groups (HR, 0.87; 95% CI, 0.76 to 1.00, $P = .05$) was statistically significant, but was not accompanied by any impact on OS. This regimen received regulatory approval in the United States for patients with resected stage III disease.

Taken in aggregate, a single IV induction course of IFN does not seem to benefit patients with intermediate- or high-risk melanoma when administered without the maintenance phase. For patients seeking additional options for adjuvant therapy with IFN, those with stage IIB and higher disease are eligible to receive standard HDI (IV induction followed by maintenance) and those with stage III disease unable or unwilling to pursue HDI may choose pegylated IFN for up to 5 years.

Recent advances using checkpoint inhibitors in advanced melanoma have prompted investigation in the adjuvant arena. EORTC 18071 showed a statistically significant RFS and OS benefit in 951 patients randomly allocated to receive ipilimumab 10 mg/kg versus placebo once every 3 weeks for four doses and then every 3 months for up to 3 years. Adverse events led to discontinuation of ipilimumab in 52% of patients who started ipilimumab, including 39% during the initial induction phase of four doses.[29,30] Five patients (1%) died as a result of drug-related toxicity. Importantly, data related to distant metastasis–free survival and OS end points are still pending. This regimen has recently received regulatory approval in the United States for patients with stage III disease. The ECOG–American College of Radiology Imaging Network–led intergroup E1609 trial compared low-dose (3 mg/kg) and high-dose (10 mg/kg) ipilimumab with HDI and completed accrual in 2014, whereas the current SWOG-led intergroup S1404 tests the anti–programmed death-1 antibody pembrolizumab versus HDI or high-dose ipilimumab (10 mg/kg) in the adjuvant setting. Furthermore, CheckMate-238, testing nivolumab versus ipilimumab 10 mg/kg, completed accrual in 2015, and KEYNOTE-054, testing pembrolizumab

Table 2. Treatment-Related Toxicities

Toxicity Type	Treatment Arm: OBS (n = 439) Grade 3 No.	OBS Grade 4 No.	OBS Grade 5 No.	IFN (n = 568) Grade 3 No.	IFN Grade 4 No.	IFN Grade 5 No.
Allergic reaction	—	—	—	—	1	—
Inner ear/hearing	2	—	—	—	—	—
Hemoglobin	—	1	—	—	—	—
Leukocytes	—	—	—	37	1	—
Neutrophils	1	7	—	113	17	—
Platelets	—	—	—	3	—	—
Hematologic, other	—	—	—	1	—	—
Supraventricular arrhythmias	—	—	—	—	1	—
Vasovagal episode	—	—	—	1	—	—
Cardiac, ischemia	—	—	—	—	2	—
Cardiac, left ventricular function	—	—	—	1	—	—
Hypertension	2	—	—	5	—	—
Hypotension	—	—	—	1	—	—
Myocarditis	—	—	—	—	1	—
Thrombosis/embolism	—	—	—	1	—	—
Fatigue	—	—	—	68	2	—
Fever	—	—	—	4	—	—
Rigors/chills	—	—	—	1	—	—
Constitutional	—	—	—	—	1	—
Rash/desquamation	—	—	—	5	—	—
Anorexia	—	—	—	11	—	—
Constipation	—	—	—	4	—	—
Dehydration	—	—	—	1	—	—
Diarrhea	—	—	—	11	—	—
Nausea	—	—	—	28	—	—
Stomatitis	—	—	—	1	—	—
Vomiting	—	—	—	19	—	—
GI, other	—	—	—	2	—	—
Hematuria	—	—	—	1	—	—
Alkaline phosphatase	—	2	—	1	1	—
Bilirubin	1	—	—	3	1	—
GGT	—	—	—	2	—	—
AST	1	—	—	71	3	—
ALT	—	—	—	29	1	—
Catheter-related infection	—	—	—	1	—	—
Infection with grade 3 or 4 neutropenia	—	—	—	2	—	—
Infection with unknown ANC	—	—	—	2	—	—
Infection without neutropenia	—	—	—	1	1	—
Infection, other	—	—	—	2	—	—
Hyperglycemia	—	—	—	1	—	—
Hypertriglyceridemia	—	—	—	—	1	—
Hypocalcemia	—	—	—	1	—	—
Hypokalemia	—	—	—	1	—	—
Hyponatremia	—	—	—	—	1	—
Ataxia	—	—	—	—	1	—
Confusion	—	—	—	3	1	—
Depressed level of consciousness	—	—	—	3	—	—
Dizziness/lightheadedness	—	—	—	2	1	—
Insomnia	—	—	—	5	—	—
Memory loss	—	—	—	1	—	—
Anxiety/agitation	—	—	—	5	1	—
Depression	—	—	—	10	1	—
Neuropathy, cranial	—	—	—	1	—	—
Neuropathy, motor	—	—	—	3	—	—
Seizure	—	—	—	1	—	—
Speech impairment	—	—	—	1	1	—
Syncope	1	—	—	3	—	—
Vertigo	—	—	—	1	—	—
Neurologic, other	—	—	—	1	—	—
Abdominal pain	—	—	—	1	1	—
Arthralgia	—	—	—	6	1	—
Bone pain	—	—	—	2	—	—
Chest pain	—	—	—	1	—	—
Headache	—	—	—	42	—	—
Myalgia	—	—	—	12	1	—
Pain, other	—	—	—	1	—	—
Dyspnea	—	—	—	1	1	—
Hypoxia	—	—	—	1	—	—
Pleural effusion	—	—	—	1	—	—
Pneumonitis/pulmonary infiltrates	—	—	—	1	—	—
Creatinine	2	4	—	3	10	—
Urinary frequency/urgency	—	—	—	1	—	—
Worst degree	8	12	—	283	46	—

Abbreviations: ANC, absolute neutrophil count; GGT, gamma-gluatmyl transferase; IFN, interferon; OBS, observation.

versus placebo, are ongoing. Adjuvant trials testing molecularly targeted therapy with dabrafenib-trametinib versus placebo and vemurafenib versus placebo have also been completed and are pending analysis.

These trials will provide further guidance for physicians and patients to help negotiate the complexity of choices that are available for the adjuvant therapy of high-risk melanoma. Meanwhile, standard HDI therapy is still a viable option. The results of E1697 presented here clarify that 1 month of IV induction is insufficient treatment and that the traditional 1-year HDI regimen should not be abbreviated or modified at this time.

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Disclosures provided by the authors are available with this article at jco.org.

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Phase III Randomized Study of 4 Weeks of High-Dose Interferon-α-2b in Stage T2bNO, T3a-bNO, T4a-bNO, and T1-4N1a-2a (microscopic) Melanoma: A Trial of the Eastern Cooperative Oncology Group–American College of Radiology Imaging Network Cancer Research Group (E1697)

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Appendix

Assessment of patients' quality of life (QOL) was one of the secondary end points for this study. This section summarizes the QOL analysis.

Statistical Analysis

The QOL was collected at the baseline, day 22, every 3 months after registration until 2 years, and then every 6 months until 5 years. The questions included: Main Activity (1 = work normally, 2 = need help, 3 = unable to work); Daily Living (1 = normal, 2 = need assistance, 3 = cannot manage personal care); Health (1 = feel well most of the time, 2 = feel well some of the time, 3 = feel lousy most of the time); Support (1 = strong support from family members, 2 = limited support, 3 = no support); and Outlook (1 = good, 2 = anxious and depressed at times, 3 = frightened and confused). The last question was a Patient Score of overall well-being over the past 2 weeks (0-100, with 0 being the worst possible health state and 100 being an excellent health state). To compare the QOL measurements between the two treatment arms, the χ^2 test was used for the first five questions (categorical measure) and the two-sample t test for the Patient Score (continuous measure) at each time point.

Because the patients in the treatment arm received only a single 4-week treatment of interferon-α-2b, it was hypothesized that the most pronounced changes of QOL would be between baseline and day 22.

For the patients with QOL measurements at baseline and day 22, a change in QOL score was estimated (by subtracting the baseline value from day 22 value). The difference in this change between the two treatment arms was compared. For the QOL measurements with the categorical variables (Main Activity, Daily Living, Health, Support, and Outlook) with values 1, 2, and 3 at each time point, this change could be -2, -1, 0, 1, and 2: negative measures indicating a change toward the better QOL at day 22, 0 indicating no change and positive measures indicating a change toward the worse QOL at day 22. This change was compared using the χ^2 test. The change in the Patient Score was compared using the two-sample t test. As exploratory analyses, the change in QOL measures between a later time point and baseline was evaluated in a similar manner.

All reported P values are for two-sided tests. Given the exploratory nature of this study, no adjustments were made for multiple testing.

Results

Of the 1,150 patients randomly assigned, 1,044 participated in the QOL study. Compliance rate varied over time, ranging from 93% (baseline) to 42% (5-year), using the number of patients reaching the specific time point as a denominator.

The primary analysis for QOL data were descriptive. First, QOL scores of Main Activity, Daily Living, Health, Support, and Outlook were compared at each time point between the two treatment arms. The QOL measures of Main Activity, Daily Living, Health, and Patient Score were significantly different between the two treatment arms at day 22 (each comparison with $P < .001$). No other comparisons were significantly different. For the Patient Score, only the measurement from day 22 comparison was significantly different between the two treatment arms ($P < .001$).

Comparing the change in QOL scores from baseline to day 22, only Main Activity, Daily Living, Health, and Patient Score were statistically significant, with P values $< .001$. The detailed results are presented in Table A1. No other comparisons from baseline to any other time points were significantly different.

Conclusion

QOL data suggest that patients experience lower QOL during the interferon-α-2b treatment.

Table A1. Comparison of the Change in QOL Measures Between Baseline and Day 22

Activity (differences)	OBS (n = 272) No. (%)	IFN (n = 281) No. (%)	*P*
Main activity			< .001
–2	4 (1.47)	5 (1.78)	
–1	10 (3.68)	4 (1.42)	
0	251 (92.28)	163 (58.01)	
1	4 (1.47)	67 (23.84)	
2	3 (1.10)	42 (14.95)	
Daily living			< .001
–1	7 (2.57)	2 (0.71)	
0	264 (97.06)	246 (87.54)	
1	1 (0.37)	33 (11.74)	
Health			< .001
–1	12 (4.41)	8 (2.85)	
0	247 (90.81)	107 (38.08)	
1	12 (4.41)	131 (46.62)	
2	1 (0.37)	35 (12.46)	
Support			.710
–1	5 (1.84)	6 (2.14)	
0	262 (96.32)	267 (95.02)	
1	5 (1.84)	8 (2.84)	
Outlook			.338
–1	11 (4.04)	14 (4.98)	
0	240 (88.24)	236 (83.99)	
1	21 (7.72)	31 (11.03)	
Patient score			< .001
	(n = 413)	(n = 456)	
Mean	0.51	−18.14	
95% CI	(−0.45, 1.45)	(−20.08, −16.20)	

Abbreviations: IFN, interferon; OBS, Observation group; QOL, quality of life.