Adjuvant Therapy for High-Risk Melanoma

Ahmad A. Tarhini, MD, PhD

Abstract

Patients with AJCC stages IIB-C/III/IV melanoma carry a high risk for melanoma recurrence and death from melanoma with surgical management alone. Systemic adjuvant therapy that targets melanoma micrometastases is indicated postoperatively where it may provide the greatest opportunity for cure before relapse into advanced inoperable stages. Multiple systemic therapeutic agents have been tested as adjuvant therapy for melanoma with durable benefits seen only with interferon (IFN)-alfa to date. In randomized clinical trials, IFN has been tested as part of regimens that vary by dosage, duration, route of administration, and formulation. Several randomized trials and 3 major meta-analyses have demonstrated a reproducible and significant impact on relapse-free survival. Overall survival benefit was seen only in 2 of the 3 ECOG and US Intergroup trials that tested the 1-year high-dose regimen (HDI) as compared with observation (E1684) and the GMK vaccine (E1694). CTLA4-blockade with ipilimumab is being tested in the adjuvant EORTC 18071 trial (stage III; ipilimumab 10 mg/kg compared with placebo),which recently reported significant improvements in relapse-free survival, and US Intergroup E1609 (stage III and IV; ipilimumab 10 mg/kg or 3 mg/kg compared with HDI). Ongoing adjuvant trials are also targeting patients with *BRAF*-mutant melanoma including vemurafenib (BRIM-8) and dabrafenib/trametinib (COMBI-AD). Adjuvant trials involving PD-1 blockade are in the planning stages, including S1404 that is designed to test the PD-1 antibody pembrolizumab versus HDI in resected stages III and IV melanoma. Here, we review melanoma adjuvant therapy trials and meta-analyses along with the major ongoing and planned randomized clinical trials. We also include a short discussion of the latest data on adjuvant radiation therapy for high-risk resected melanoma.

Introduction

High-risk resected melanoma signifies a group of patients that carries a risk of melanoma recurrence and death after initial surgical resection that may be defined as 35% to 40% or higher and includes patients with American Joint Committee on Cancer (AJCC) stages IIB, IIC, III, and IV. The development of local or regional recurrence after initial surgical management portends an even poorer prognosis.[1-3] In the Melanoma Surgical Trial, a local recurrence was associated with 5- and 10-year survival rates of 9% to 11% and 5%, respectively.[2] Residual micrometastasis is thought to be the source of future melanoma recurrence and death. This is where systemic adjuvant therapy may alter the course of this disease, presenting an opportunity for relapse-free survival (RFS) and overall survival (OS) benefits. Various therapeutic modalities, including immunotherapy, chemotherapy, biochemotherapy, and local radiation therapy, have been tested in the adjuvant setting over the past 3 decades.

Predictors of Risk in Operable Melanoma

The AJCC TNM staging system for melanoma divides patients into 4 stages based on the pathologic characteristics of the primary tumor, the status of the regional lymphatics, and the presence or absence of distant metastases. Stages I and II define localized melanoma that is restricted to the skin. Stage III is characterized by the presence of lymph node and/or in-transit metastases, while stage IV applies to distant metastatic spread.[2] The depth of the primary tumor (Breslow's tumor thickness) is the leading prognostic factor in stages I and II (absence of lymph node involvement) where the probability of survival declines as depth (measured in millimeters) increases. The presence of primary tumor ulceration proportionately lowers patient survival rates compared with those with nonulcerated tumors of the equivalent T category; survival rates are similar to patients with a nonulcerated melanoma of the subsequent T category. Increased mitotic rate (at least 1 mitosis/mm^2) is strongly correlated with diminished survival rates, and in the 7th AJCC staging edition it has replaced the Clark level of invasion as a complementary criterion to ulceration for differentiating T1a versus T1b primary tumor.[4]

Melanoma spread to *regional lymph nodes* or the presence of intralymphatic (satellite or in-transit) metastasis defines stage III. There is no minimum limit of tumor burden defining the presence of regional nodal metastases in the 7th AJCC staging edition. Lymph node tumors less than 0.2 mm that were ignored in the 2002 staging version were included. Even minute lymph node deposits (including detection by immunohistochemical staining) are felt to be relevant to melanoma recurrence and mortality and currently signify a positive lymph node. For the same T stage, the nodal subclassification N1a (micrometastasis) and N1b (macrometastasis) constitute stage IIIA and stage IIIB, respectively. In-transit lymphatic metastases without and with lymph node involvement correspond to N2c and N3, respectively.[2] It is noteworthy that this population of patients without distant spread of primary melanoma who are at high risk for recurrence and death is about 3 times the size of the population with metastatic disease.

In stage IV disease with *distant metastases*, lactate dehydrogenase (LDH) blood levels are significantly prognostic. The 1-year survival rate of patients with M1c disease (visceral metastases or any distant metastasis with high LDH) is 33%, as compared with 62% for M1a (distant skin, subcutaneous, and lymph node metastases) and 53% for M1b melanomas (lung metastases).[2] Oligometastatic melanoma metastases that are amenable to surgical removal may derive survival benefits if chosen appropriately, and these patients may be candidates for systemic adjuvant therapy.[5,6]

Interferon-Alfa

The type I interferon (IFN) family includes IFN-alfa, IFN-beta, IFN-epsilon, IFN-kappa, and IFN-omega, whereas IFN-gamma constitutes the family of type II IFN. Among the IFNs, IFN alfa-2 has been the most widely studied clinically, and 3 commercially available subspecies exist including IFN alfa-2a (Roferon-A), IFN alfa-2b (Intron A), and IFN alfa-2c. Mechanistically, IFN-alfa has multiple effects shown in a variety of malignancies that range from potent immunomodulatory and differentiation-inducing, to antiproliferative, proapoptotic, and anti-angiogenic.[7] IFN-alfa promotes tumor immunogenicity and enhances dendritic cell (DC) response to the tumor, DC polarization or maturation, survival and antigen cross-presentation.[7-9] IFN-alfa promotes a Th1 shift in host immunity against tumors, enhancing cell-mediated cytotoxicity, and has a role in attracting Th1 lymphocyte traffic to the tumor.[10] Host type I IFNs were reported to be critical for the innate immune recognition of a growing tumor in vivo, leading to intratumor accumulation of CD8α+ DCs that promote tumor antigen-specific CD8+ T-cell responses.[11] As tested clinically in the neoadjuvant setting in melanoma, IFN-alfa has shown a significant impact on signal transducer and activator of transcription (STAT) signaling.[12]

IFN-Alfa in the Treatment of Stage IV Inoperable Melanoma

For stage IV inoperable melanoma, IFN-alfa was the first recombinant cytokine to be investigated clinically for the therapy of advanced metastatic melanoma. Initial phase 1 and 2 studies yielded overall response rates of about 16%, and about one-third of the responders were reported to have complete responses. Responses were observed as late as 6 months from initiation of therapy, and up to one-third of the responses were durable.[13,14] As an off-label systemic therapeutic option for stage IV inoperable melanoma, IFN-alfa has been used in the community for many years and continues to be used either as monotherapy or in combination as part of the biochemotherapy regimen (consisting of IFN-alfa, interleukin-2, dacarbazine, cisplatin, vinblastine).[15-18]

Adjuvant IFN-Alfa Trials

Adjuvant Regimens Testing High-Dose IFN-Alfa in Melanoma

Evidence of activity of IFN-alfa in metastatic disease led to its testing in the adjuvant setting. The North Central Cancer Treatment Group (NCCTG) trial[19] and the Eastern Cooperative Oncology Group (ECOG) trial E1684[20] were the first 2 adjuvant randomized controlled trials. Both trials tested a high-dose regimen of IFN-alfa (>10 million units (MU)/dosage).

ECOG E1684: This trial was initiated in 1984 and tested a high-dose regimen of IFN-alfa (HDI). HDI was administered intravenously (IV) at 20 MU/m^2 for 5 consecutive days a week for 4 weeks as the induction phase followed by subcutaneous (SC) administration at 10 MU/m^2 thrice weekly for 48 weeks as maintenance.[20] A total of 287 patients were randomized to either HDI or observation postoperatively. All patients underwent regional elective lymph node dissection (ELND), and the majority of patients enrolled in this study had bulky nodal or recurrent disease. At a median follow-up of 6.9 years, HDI demonstrated a statistically significant impact on RFS and OS as compared with observation. The estimated 5-year RFS in the treatment arm was 37% (95% confidence interval [CI], 30%-46%) versus 26% (95% CI, 19%-34%) in the control group. Median RFS was 1.72 versus 0.98 years (P = .0023), hazard ratio (HR) = 0.61 (P = .0013). The 5-year OS was 46% (95% CI, 39%-55%) versus 37% (95% CI, 30%-46%) in the treatment and observation arms, respectively. Median OS was 3.82 versus 2.78 years (P = .0237); HR = 0.67 (P = .01). The highest impact on survival was observed in patients with high tumor burden (node-positive disease). The outcomes of this trial led to the regulatory approval by the US Food and Drug Administration (FDA) in 1995.[7] The toxicity profile of HDI as observed in E1684 included a 67% incidence for grade 3 toxicity, 9% incidence for grade 4 toxicity, and 2 early therapy-related hepatotoxic deaths. This profile raised concerns about patient tolerance and motivated further testing of regimens that varied by dosage level, route of administration, or duration of IFN-alfa therapy.[21]

E1690: This ECOG and US Intergroup trial followed suit, utilizing the E1684 HDI regimen as well as a low-dose regimen of IFN alfa-2b (LDI) at 3 MU SC thrice weekly for 2 years both compared with observation.[22] Patient enrollment on E1690 lasted between 1991 and 1995, and at a median follow-up of 4.3 years, the 5-year estimated RFS rates were 44% for HDI, 40% for LDI, and 35% for the observation arm, respectively.[22] The effect of HDI on RFS alone was significant (P = .03). Neither HDI nor LDI was found to establish OS benefit compared with observation (52% high dose vs 53 % low dose vs 55% observation). However, improved OS in the E1690 observation arm was notable in comparison with E1684 observation arm (median, 6 years vs 2.8 years). Unlike E1684, E1690 did not require elective lymph node dissection, and a retrospective analysis showed evidence of crossover of 38 patients from the observation arm at regional nodal recurrence to IFN-alfa salvage therapy that may have impacted the survival analysis in E1690.

E1694: This trial conducted by the US Intergroup compared HDI with a ganglioside vaccine (GMK). The GMK vaccine consisted of purified ganglioside GM2 coupled to keyhole limpet hemocyanin (KLH) and combined with the QS-21 adjuvant.[23] Prior studies had shown evidence of immunogenicity and clinical activity. HDI showed improvement in RFS with HDI (HR =

TABLE 1. Summary of Adjuvant Phase III Studies of Interferon-Alfa in Melanoma

The studies are classified as high-dose, medium-dose, and low-dose based on the dosage levels tested in the trials.

Trial (PI)	Number of Patients	Stage	Regimens Tested	IFN Dosage and Schedule
High-Dose				
NCCTG 83-7052 (Creagan[19])	262	II-III (T2-4N0M0/TanyN+M0)	IFN-α2a vs observation	IFN IM 20 MU/m^2 3 times for 4 months
ECOG E1684 (Kirkwood[20])	287	II–III (T4N0M0/TanyN+M0)	HDI-α2b vs LDI vs observation	IFN IV 20 MU/m^2 5 days a week for 4 weeks and then SC 10 MU/m^2 3 days a week for 48 weeks
ECOG E1690 (Kirkwood[22])	642	II–III (T4N0M0/TanyN+M0)	HDI-α2b vs LDI vs observation	HDI: IFN IV 20 MU/m^2 5 days a week for 4 weeks and then SC 10 MU/m^2 3 days a week for 48 weeks LDI: IFN SC 3MU/m^2 2 days a week for 2 years
ECOG E1694 (Kirkwood[23])	774	II–III (T4N0M0/TanyN+M0)	HDI-α2b vs GMK vaccine	IFN IV 20 MU/m^2 5 days a week for 4 weeks and then SC 10 MU/m^2 3 days a week for 48 weeks
Italian Melanoma Intergroup (Chiarion-Sileni[27])	330	III (TanyN1-3M0)	Intensified IFN-α2b (IHDI) every other month vs HDI-α2b for 1 year	IHDI: IV 20 MU/m^2 5 days a week for 4 weeks every other month for 4 cycles Standard HDI: IV 20 MU/m^2 5 days a week for 4 weeks; then SC 10 MU/m^2 3 days a week for 48 weeks
Medium-Dose				
EORTC 18952 (Eggermont[35])	1388	II–III (T4N0M0/TanyN+M0)	IFN-α2b for 1 year vs 2 years vs observation	IFN IV 10 MU 5 days a week for 4 weeks and then: (a) SC 10 MU 3 days a week for 1 year or (b) IFN SC 5 MU 3 days a week for 2 years
EORTC 18991 (Eggermont[36])	1256	III (TanyN+M0)	PEG IFN-α2b vs observation	SC 6μg/kg a week for 8 weeks and then SC 3μg/kg a week for 5 years
Low-Dose				
Austrian Melanoma Cooperative Group (AMCG) (Pehamberger[39])	311	II (T2-4N0M0)	IFN-α2a vs observation	SC 3 MU 7 days a week for 3 weeks and then SC 3 MU 3 days a week for 1 year
French Melanoma Cooperative Group (FCGM) (Grob[37])	499	II (T2-4N0M0)	IFN-α2a vs observation	SC 3 MU 3 days a week for 3 years
WHO-16 (Cascinelli[31])	444	III (TanyN+M0)	IFN-α2a vs observation	SC 3 MU 3 days a week for 3 years
Scottish Melanoma Cooperative Group (Cameron[33])	96	II–III (T3-4N0M0/TanyN+M0)	IFN-α2a vs observation	SC 3 MU 3 days a week for 6 months
EORTC 18871/DKG-80 (Kleeberg[30])	728	II–III (T3-4N0M0/TanyN+M0)	IFN-α2b vs IFN-α vs ISCADOR M vs observation	IFN-α2b: SC 1 MU every other day for 12 months IFN-γ: SC 0.2 mg every other day for 12 months ISCADOR M
UKCCCR AIM-HIGH (Hancock[32])	674	II–III (T3-4N0M0/TanyN+M0)	IFN-α2a vs observation	IFN SC 3 MU 3 days a week for 2 years
DeCOG (Hauschild[34])	840	III (T3anyN+M0)	IFN-α2a for 18 months (A) vs 3 years (B)	IFN SC 3 MU 3 days a week for 18 months vs 3 years
DeCOG (Garbe[38])	441	III (TanyN+M0)	IFN-α2a (A) vs IFN-α2a + DTIC (B) vs observation (C)	IFN SC 3 MU 3 days a week for 24 months (A) vs IFN SC 3 MU 3 days a week for 24 months + DTIC 850 mg/m^2 every 4-8 weeks for 24 months (B) vs observation (C)

HDI, high-dose interferon; IFN, interferon; IM, intramuscular; IV, intravenous; LDI, low-dose interferon; MU, million units; NS, nonsignificant; OS, overall survival; PEG-IFN, pegylated interferon; PI, principal investigator; RFS, relapse-free survival; S, statistically significant clinical benefit reported; SC, subcutaneous.

Median Follow-up at Reporting (years)	RFS	OS
6.1	NS	NS
6.9, 12.1	S	S (S at 6.9 years median follow-up; NS at 12.1 years)
4.3, 6.6	S LDI: NS	NS
1.3, 2.1	S	S
5.0	NS	NS
4.65	NS	NS
3.8	S	NS
3.4 (mean)	S	NS
>3	S	+/-S (*P* = .059)
7.3	NS	NS
6.5	NS	NS
8.2	NS NS NS	NS NS NS
3.1	NS	NS
4.3	NS	NS
3.9	S NS	S NS

0.68; *P* = .0015) and OS (HR = 0.66; *P* = .009) in the eligible population. Similar benefits were seen in the intent-to-treat analysis for RFS (HR = 0.67) and OS (HR = 0.72).[21,23]

E2696: This was an ECOG-led randomized, phase 2 trial that enrolled 107 patients with surgically resected stage IIB, III, and IV melanoma. The trial was conducted between 1998 and 2000.[6] The primary objective was to test the immunogenicity of the GMK vaccine by measuring the anti-GM2 antibody response in the presence versus absence of HDI. The study compared 3 arms: arm A (GMK plus concurrent HDI), arm B (GMK plus sequential HDI), and arm C (GMK alone). The combination arms reduced the risk of relapse when compared with GMK alone (HR = 1.96 for C vs B, and HR = 1.75 for C vs A).

A pooled analysis of the 2 observation-controlled trials (E1684 and E1690) as updated through April 2001 showed that HDI maintained significant benefits in relapse at a median follow-up of 12.6 years for E1684 and 6.6 years for E1690.[24] This analysis did not include E1694 in which the GMK vaccine served as control. The pooled analysis did not show significant evidence of OS benefit, where the larger of the 2 observation-controlled trials (E1690) did not show an OS benefit for HDI. In addition, the median follow-up of 12.6 years in E1684 introduces the strong possibility that competing causes of death led to the erosion of the OS benefits originally seen in this trial at the mature median follow-up of 6.9 years.[20,22-24]

Trials Testing Varying Dosing Levels, Routes of Administration, and Durations of Therapy

Multiple trials have tested regimens that vary by dosing levels, routes of administration, duration of therapy, and formulation. Table 1 summarizes the completed major phase III trials of adjuvant IFN-alfa in melanoma.

The Sunbelt Melanoma Trial: This trial looked at lymph node dissection (LND) after a positive sentinel lymph node versus LND plus standard HDI.[25] This trial failed to detect an OS or disease-free survival (DFS) benefit for HDI, but can be criticized for not reaching target enrollment, and was therefore underpowered to detect clinically significant differences.[26] The Italian Melanoma Intergroup trial tested a shorter course of a more-intense IV dosing regimen versus HDI.[27] No statistically significant differences in outcome were seen.

Hellenic He 13A/98 trial: The Hellenic Cooperative Oncology Group tested a modified, less-intense dosing regimen of HDI.[28] Patients were randomized between 1998 and 2004 to an induction phase of 15 MU/m^2 only versus the same induction phase followed by a modified maintenance phase of 10 MU flat dose (not per m^2) thrice weekly for a year. At a median follow-up of 5.25 years and 182 patients per arm, there were no statistically significant differences in either RFS or OS. However, this study was also criticized for the relatively small sample size to allow the detection of clinically significant differences, in addition to the modified dosing regimen used.

E1697: The US Intergroup study E1697 targeted patients with resectable intermediate-risk melanoma (≥T3 or any thickness with microscopic nodal disease N1a-N2a).[29] The study recruited 1150 patients between 1998 and 2010, and randomized them

to 4 weeks of HDI (20 MU/m^2/day IV for 5 days weekly) versus observation. In 2010, a third interim analysis deemed the efficacy futile, leading to study closure. A subsequent presentation at the American Society of Clinical Oncology (ASCO) meeting in 2011 reported no impact on either RFS or OS with this 4-week regimen.

Several trials investigated less-intensive dosing regimens in terms of IFN-alfa. These included the very-low-dose (1 MU SC every other day) as in the European Organization for Research and Treatment of Cancer (EORTC) 18871 study (stage IIB, IIIA).[30] Low dose (≤3 MU SC thrice weekly) was tested in the WHO melanoma trial 16 (stage III),[31] the low-dose arm of E1690 (T4, N1),[22] the UKCCCR AIM-HIGH trial (stage IIB/III),[32] the Scottish trial (stage IIB, III),[33] and the 2010 German DeCOG study (T3anyN).[34] Intermediate-dose regimens (5-10 MU/m^2) were tested in the EORTC 18952 (T4 N1-2)[35] and EORTC 18991 (TxN1)[36] studies. Although these trials showed benefit in RFS for the IFN arms, this impact appeared to be lost with time. Support for this observation also comes from the French multicenter trial that indicated that the effect of IFN-alfa on RFS was lost on cessation of treatment.[37]

EORTC 18952: This trial enrolled 1388 patients with stage IIB/III melanoma between 1996 and 2000.[35] Patients were randomized to 4 weeks of induction IFN-alfa at 10 MU IV 5 times a week, followed by 1 of 2 maintenance regimens given SC at 10 MU 3 days a week for 1 year versus SC 5 MU 3 days a week for 2 years. Both were compared with a third observation control arm. At a median follow-up of 4.65 years , the study reported a distant metastasis-free interval of 47% and 43% versus 40%, and an OS of 53% and 48% versus 48% for 2-year and 1-year regimens versus observation, respectively. Therefore, an improvement in OS was observed only in patients treated for 25 months with 5 MU IFN-alfa and not in those treated for 13 months with 10 MU IFN-alfa. These results supported the hypothesis that the duration of therapy might be more important than dosage.

DeCOG: A randomized phase III trial by the Dermatologic Cooperative Group (DeCOG) tested the combination of low-dose IFN (LDI)/dacarbazine or LDI alone versus observation, randomizing 441 patients with stage III (T, any N+, M0) melanoma.[38] At a median follow-up of 4 years, the LDI group had a superior DFS (HR = 0.69) and OS (HR = 0.62). It is noteworthy that these results do not match with the earlier trials that tested LDI and showed no OS benefit, such as the Austrian (AMCG) trial[22] and French (FCGM) trial.[39]

Pegylated Interferon

EORTC 18991: The EORTC 18991 trial tested adjuvant therapy with peg-IFN alfa-2b versus observation for AJCC stage III melanoma, recruiting 1256 patients from 2000 to 2002.[36] The regimen consisted of an induction phase of peg-IFN given SC at 6 mcg/kg a week for 8 weeks followed by maintenance phase of once-weekly SC injections at 3 mcg/kg for up to 5 years. At a median follow-up of 7.6 years, the study showed an improvement in the primary endpoint of RFS (HR = 0.87; 95% CI, 0.76 -1.00; *P* = .05), but with no significant differences seen in OS or distant metastasis-free survival (DMFS) between observation and treatment. Subgroup analysis suggested that patients with microscopic nodal metastasis and ulcerated primary tumor derived the greatest benefit in terms of RFS, OS, and DMFS. The toxicity attrition rate during the study was 37%. Pegylated IFN-alfa was granted regulatory approval in the US as adjuvant therapy for high-risk resected melanoma with lymph node metastases.

Meta-Analyses of Adjuvant IFN-Alfa Trials

From 2002 through 2010, at least 4 different meta-analyses of melanoma adjuvant trials have been published.[40-43] The largest was the 2010 meta-analysis by Mocellin et al.[42] This meta-analysis included 14 randomized controlled trials (RCTs) published between 1990 and 2008 including 8122 patients, of whom 4362 subjects had received IFN-alfa. IFN-alfa was tested against observation in 12 RCTs, and 17 different comparisons were established. Four out of 14 comparators revealed a statistically significant OS benefit with IFN-alfa. The review concluded that adjuvant IFN-alfa therapy demonstrated a statistically significant 18% risk reduction for recurrence (HR = 0.82; 95% CI, 0.77-0.87; *P* <.001) and 11% risk reduction for death (HR = 0.89; 95% CI, 0.83-0.96; *P* = .002). In this meta-analysis, no specific regimen, dosing, formulation, study design, or staging provided significant differences in overall HR estimates.

Adjuvant Biochemotherapy

S0008 was a SWOG-led intergroup phase III trial that tested a biochemotherapy (BCT) regimen administered over 9 weeks versus the standard 52-week HDI regimen.[44] The BCT regimen consisted of 3 cycles of cisplatin, vinblastine, dacarbazine combined with low doses of IL-2 and IFN-alfa. At 6 years median follow-up, there was significant improvement in RFS for BCT compared with HDI (median, 4.0 years vs 1.9 years), but no improvement in OS. A higher rate of grade III/IV toxicity was observed in the BCT group than in the HDI group (76% vs 64%). It was observed that patients on the HDI arm were more frequently followed during therapy as clinically indicated with IFN-alfa, while BCT patients were seen every 3 months following completion of the 9-week BCT regimen. It is not clear whether this imbalance of early follow-up between the HDI and BCT arms may have affected the RFS outcome.

Adjuvant Trials Testing Vaccines

These trials tested peptide vaccines, ganglioside vaccines, and whole cells/cell lysates. A phase 3 trial for resected stage III/IV melanoma tested the polyvalent vaccine Canvaxin versus BCG vaccination and reported that both DFS and OS were worse in the Canvaxin group.[45] The DERMA trial tested adjuvant therapy with MAGE-A3 protein in a randomized phase 3 study based on promising results from a previous study in metastatic melanoma.[46] A recent press release reported that this trial did not

TABLE 2. Summary of Ongoing Adjuvant Trials in High-Risk Melanoma

Study	Number of Patients	Stage	Regimens Tested	Dosage and Schedule	Primary End Point	ClinicalTrials.gov Identifier
EORTC 18071[49]	950	III (Tany, N+ except in-transit, M0)	Ipilimumab vs placebo	Ipilimumab IV, 10 mg/kg, 4x every 21 days, then starting from week 24 every 12 weeks until week 156 or progression, 3 years	RFS	NCT00636168
US Intergroup E1609[48]	1500	III (Tany, N+ except in-transit, M0)	Ipilimumab at 10 mg/kg (Arm A) or 3 mg/kg (Arm C) vs IFN-α (Arm B)	Ipilimumab IV, 10 mg/kg (A) or 3 mg/kg (C), 4x every 21 days, then starting from week 24 every 12 weeks 4x vs IFN-α IV 20 MU/m^2 5 days a week for 4 weeks, then SC 10 MU/m^2 3 days a week for 48 weeks (B)	RFS and OS	NCT01274338
DERMA[46]	1349	IIIB or IIIC (tumor expression of *MAGE-A3* gene)	GSK 2132231A (D1/3-MAGE-3-His fusion protein) vs placebo	GSK 2132231A IM solution, 13 injections over 27 months	DFS	NCT00796445
COMBI-AD	852	III *BRAF V600E/K* mutation-positive	Dabrafenib + trametinib vs placebo	Dabrafenib (150 mg twice daily) and trametinib (2 mg once daily) orally for 12 months	RFS	NCT01682083
BRIM 8	725	IIC, III *BRAF V600* mutation positive by Cobas test	Vemurafenib vs placebo	Vemurafenib 960 mg orally twice daily for 52 weeks	DFS	NCT01667419

DFS, disease-free survival; OS, overall survival; RFS, relapse-free survival.

reach its primary end point of RFS. However, it continues to be blinded in anticipation of the results of its second co-primary end point testing the vaccine's therapeutic predictive value for a proinflammatory tumor gene expression profile. The Melacine vaccine trial conducted in the US showed some promise initially, but failed to sustain it. Similarly, an Australian study using vaccinia viral lysates in high-risk subjects following resection failed to show a statistically significant increase in RFS.[47] The E1694 trial that tested GM2 with BCG and with KLH and a QS21 adjuvant (GMK) demonstrated no therapeutic impact for the vaccine.[23]

Adjuvant Trials Testing Immune Checkpoint Inhibitors

Two ongoing trials (EORTC 18071 and US Intergroup E1609) are testing ipilimumab in the adjuvant high-risk setting. Ipilimumab is a fully humanized immunoglobulin G1 kappa monoclonal antibody that targets CTLA-4. Phase 3 trials in advanced inoperable melanoma have demonstrated significant OS benefits at the dosage level of 3 mg/kg versus the Gp100 peptide vaccine (MDX010-20 trial),[48] and at 10 mg/kg combined with dacarbazine versus dacarbazine alone (CA 184-024).[49] EORTC 18071 is testing ipilimumab at 10 mg/kg versus placebo in patients with surgically resected stage III melanoma except those with in-transit metastases. The trial's primary end point is RFS. At the 2014 ASCO Annual Meeting, Eggermont et al,[50] reported the first results at a median follow-up of 2.7 years and with 951 patients randomized. Overall, 46.5% and 34.8% (P = .0013) of patients were relapse-free in the ipilimumab and placebo treatment arms, respectively. Grade 3/4 adverse events (AEs) occurred in more patients receiving ipilimumab compared with placebo and included gastrointestinal (15.9% vs 0.8%), endocrine (8.5% vs 0%), and hepatic events (10.6% vs 0.2%). It is noteworthy that the dosage level of ipilimumab used in this trial is higher than the current dosage level (3 mg/kg) approved by the FDA for inoperable metastatic melanoma. E1609 is a randomized phase 3 trial that is testing ipilimumab at 10 mg/kg or 3 mg/kg versus the current standard for adjuvant therapy in the US, HDI. When first designed, this trial was planned as a 2-arm study testing ipilimumab at 10 mg/kg versus HDI. However, upon presentation of the MDX010-20 trial results and regulatory approval of this dosage level as the standard for metastatic disease, E1609 was revised to add the 3 mg/kg-arm assessment. The study has 2 co-primary endpoints of RFS and OS and will also allow the assessment of the safety of the 2 dosage levels of ipilimumab relative to HDI. Plans are under way to develop the next generation of adjuvant trials involving PD-1/PD-L1 immune checkpoint blockers based on the highly significant clinical results with these agents in metastatic disease. S1404, which is designed to test pembrolizumab

versus HDI in resected stage III and IV melanoma, is expected to begin in the last quarter of 2014.

AVAST-M Trial Testing Bevacizumab

The results of a preplanned interim analysis of the phase 3 AVAST-M trial were reported by Corrie et al[51] at the 2014 ASCO Annual Meeting. This trial tested adjuvant bevacizumab versus observation in patients with stage II/III resected melanoma (N = 1343). At a median follow-up of 25 months, OS and DMFS were similar between treatment arms. An improvement in the disease-free interval (DFI) was observed (HR = 0.83; 95% CI, 0.70–0.98; *P* = .03). Longer follow-up is needed to better assess the modest DFI benefit seen and to evaluate the effect on the primary end point of OS at 5 years.

Adjuvant Trials of Inhibitors of BRAF/MEK

Activating mutations of *BRAF* are found in about 40% to 50% of melanomas, where 80% to 90% are *V600E* mutations in which glutamic acid has substituted for valine at the V600 locus. BRAF phosphorylates regulatory serine residues on MEK1 and MEK2; hence, mutation of *BRAF* activates the RAS/RAF/MEK/ERK pathway leading to tumor proliferation. The BRAF inhibitors vemurafenib and dabrafenib have achieved regulatory approval based on significant phase 3 trial impacts on RFS and OS.[52] Recently, the BRAF/MEK inhibitor combination of dabrafenib and trametinib has also achieved regulatory approval based on significant phase 2 trial data.[53] COMBI-AD is an ongoing phase 3 trial that, according to ClinicalTrials.gov (NCT01682083), plans to randomize 852 patients with stage III *BRAF V600E/K* mutation-positive melanoma to combined adjuvant therapy with dabrafenib and trametinib versus placebo. The primary end point is RFS. In parallel, BRIM-8 plans to randomize 725 patients with stage IIC and III BRAF V600 mutation-positive melanoma to adjuvant vemurafenib versus placebo. Here too, the primary end point is DFS. **Table 2** summarizes the major ongoing adjuvant trials in high-risk melanoma.

Adjuvant Radiation Therapy

The risk of local or regional relapse for stage III surgically resected melanoma is 15% to 20%. A higher risk (estimated 30% to 50%) is found in the presence of high-risk features that include positive margins, involvement of 4 or more nodes, extracapsular lymph node extension, bulky disease (exceeding 3 cm in size), cervical lymph node location and recurrent disease.[30] In these cases, adjuvant radiotherapy (RT) may be considered valuable for local disease control, although no OS benefit has been shown. Hypofractionation of radiation therapy appears to have a similar efficacy to standard radiation dosing regimens in melanoma.

A retrospective study from MD Anderson Cancer Center by Ballo et al[54] included 160 patients who had surgery for any nodal metastasis treated with lymph node dissection followed by RT (30 Gy in 6 Gy fractions 2 times per week). The study demonstrated 10-year local, regional, and locoregional control rates of 94%, 94%, and 91%, respectively. Another study from Roswell Park Cancer Center and MD Anderson Cancer Center by Agarwal et al[55] included 615 patients with clinically advanced, regional lymph node-metastatic disease. This study looked at surgery plus adjuvant radiotherapy versus surgery alone. A reduction in the regional recurrence rate was seen (10.2% vs 40.6%). Adjuvant radiotherapy was also significantly associated with 5-year regional disease control (*P* <.0001), DMFS (*P* = .0006), and disease-specific survival (*P* <.0001). A retrospective study by Strojan, et al[56] also showed improvement in the local relapse rate at 2 years by using adjuvant radiotherapy versus surgery alone (78% vs 56%; *P* = .015) among patients with regionally advanced melanoma to the neck and/or parotid.

The Australia New Zealand Melanoma Trial Group/Trans-Tasman Oncology Group (ANZMTG 01.01/TROG 02.01) recently reported results at a median follow-up of 40 months.[57] This study tested adjuvant radiotherapy (48 Gy in 20 fractions) versus observation in 217 patients with nodal metastases who had lymphadenectomy. The study enrolled a high-risk population based on the number of nodes involved, extranodal spread, and maximum size of involved nodes. The risk of lymph-node field relapse was improved in the adjuvant radiotherapy group (20 relapses in RT vs 34 in observation; HR = 0.56; 95% CI, 0.32-0.98; *P* = .041). However, there were no statistically significant differences in RFS or OS.[58-63]

Conclusion

HDI is unique in demonstrating significant improvements in the risk of recurrence (E1684, E1690, and E1694) and death as compared with observation (E1684) and the GMK vaccine (E1694). Peg-IFN as tested in the EORTC 18991 trial met its primary end point of RFS improvement in stage III disease and received regulatory approval as adjuvant therapy. In the most recent and largest meta-analysis of 14 adjuvant IFN-alfa trials, IFN-alfa was associated with significant risk reductions in relation to both disease relapse and mortality (based on E1684 versus observation, E1694 versus the GMK vaccine and the Mocellin meta-analysis).[23] Ongoing adjuvant trials are testing ipilimumab CTLA-4 blockade therapy (EORTC 18071 and US Intergroup E1609), BRAF inhibitors (BRIM-8 and COMBI-AD), and MAGE-A3 vaccine (DERMA). The RFS results of EORTC 18071 testing ipilimumab at 10 mg/kg are very encouraging, but there is a need to assess the adjuvant impact of the standard 3 mg/kg dosage level taking into account the toxicity profiles and the relative adjuvant impact of ipilimumab compared with HDI, which are being studied in E1609. The DERMA trial did not reach its primary end point of RFS but continues to be blinded relative to the therapeutic predictive value of a tumor gene expression signature. Future adjuvant trials to test anti-PD-1 antibody therapy are in the planning phases and are expected to be activated in the second half of 2014. Neoadjuvant studies with HDI and ipilimumab have added significant mechanistic insights and generated important preliminary biomarker

data.[64] Ongoing research nested within prior (E1697) or ongoing (E1609) adjuvant trials is focused on the development of biomarkers of disease-prognostic and therapy-predictive value, with the goals of individualizing patient therapy to those most likely to benefit, while saving others unwanted toxicities when agents are unlikely to work.

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Affiliation: Ahmad A. Tarhini, MD, PhD, is associate professor of Medicine and Translational Science at the University of Pittsburgh Cancer Institute, University of Pittsburgh School of Medicine, Clinical and Translational Science Institute, Pittsburgh, PA.
Address correspondence to: Ahmad A. Tarhini, MD, PhD, University of Pittsburgh Cancer Institute, UPMC Cancer Pavilion, 5150 Centre Avenue (555), Pittsburgh, PA 15232; phone: 412-648-6578; fax: 412-648-6579; e-mail: tarhiniaa@upmc.edu
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