

MELANOMA IN FOCUS

Current Developments in the Management of Melanoma

Section Editor: John M. Kirkwood, MD

Adjuvant Treatment For Patients With Surgically Resected Advanced-Stage Melanoma



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H&O What is the first step in treating patients with surgically resected advanced-stage melanoma?

KG The first step is to determine the risk of relapse and death for individual patients. Presently, the factors that guide our risk prediction are the presence or absence of a positive sentinel lymph node, the thickness of the tumor, the mitotic rate, and the presence or absence of ulceration. The current American Joint Committee on Cancer (AJCC) melanoma staging manual, published in 2009 by Balch and colleagues, is likely accurate for predicting relapse risk based on these variables, but the overall survival statistics have likely improved since this version was published owing to better treatments available to patients upon relapse. How big an impact modern therapy for stage IV disease has had on long-term survival of patients with stage III disease will be unknown until the next AJCC manual is published. We are in need of better biomarkers to identify patients at high risk for relapse. I think that this area is going to see a lot of growth in the upcoming years, with new tests becoming available soon.

H&O What is the standard adjuvant treatment for these patients?

KG At present, the best treatment option is a well-designed clinical trial. For patients who do not have access to a clinical trial, there are 2 treatments approved by the US Food and Drug Administration (FDA): high-dose interferon and pegylated interferon. Though not

specifically FDA-approved for this use, another option is biochemotherapy, which refers to the inpatient administration of cisplatin, vinblastine, dacarbazine, interleukin 2 (IL-2), and interferon.

Each of these therapies has its unique niche, and, in my opinion, should be part of the treatment-planning discussion for patients with high-risk resected melanoma.

H&O How effective are these treatments?

KG High-dose interferon is the only adjuvant treatment in stage III melanoma that has been shown to produce an overall survival benefit in a randomized controlled trial. The first of these studies was E1684 from the Eastern Cooperative Oncology Group (ECOG), a classic study that was published by Dr John Kirkwood and colleagues in 1996. Many review articles and pooled data summaries on interferon are available, including a Cochrane review by Dr Simone Mocellin and colleagues. The authors reviewed data on more than 10,000 patients with high-risk melanoma from 18 randomized controlled trials, and conducted a meta-analysis. The meta-analysis showed that interferon improved both disease-free survival (hazard ratio [HR], 0.83; 95% CI, 0.78-0.87; $P < .00001$) and overall survival (HR, 0.91; 95% CI, 0.85-0.97; $P = .003$).

Pegylated interferon has also been shown to improve disease-free survival. In a placebo-controlled study with more than 1200 patients by Eggermont and colleagues that was published in the *Lancet* in 2008, there was a statistically significant decrease in recurrence events (HR, 0.82; 95% CI, 0.71-0.96; $P = .01$) with pegylated

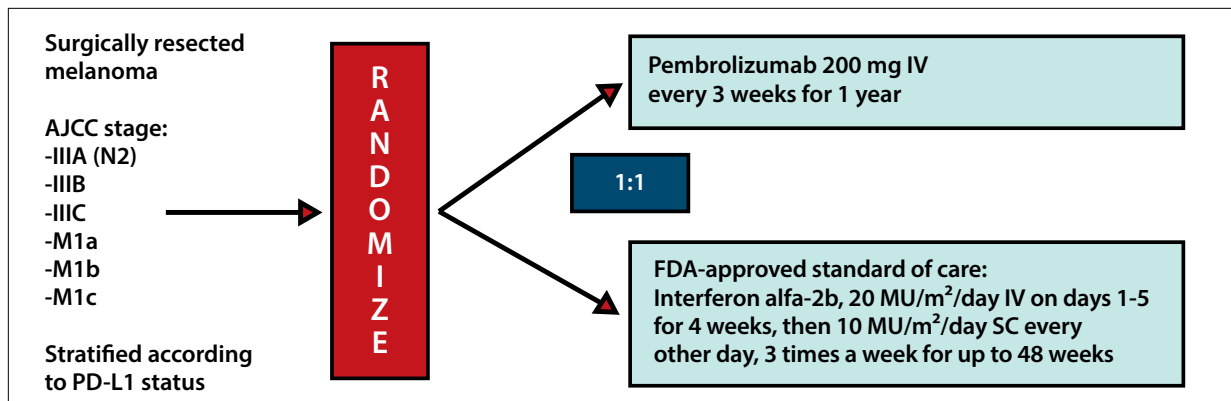


Figure. Design of the Southwest Oncology Group S1404 study.

AJCC, American Joint Committee on Cancer; FDA, US Food and Drug Administration; IV, intravenously; PD-L1; programmed death ligand 1; SC, subcutaneously.

interferon vs placebo. Unfortunately, no overall survival benefit has been seen with this therapy.

Biochemotherapy recently became the first treatment to improve upon the disease-free survival benefit seen with interferon. In the SWOG (Southwest Oncology Group) S0008 trial led by Dr Lawrence Flaherty, which randomly assigned patients to high-dose interferon or biochemotherapy, relapse-free survival was significantly better with biochemotherapy than with interferon (HR, 0.75; 95% CI, 0.58-0.97; $P=.015$). Unfortunately, the complexity, cost, and toxicity of this treatment have prevented it from becoming widely used in resected melanoma.

The therapeutic index—that is, the benefit relative to the toxicity—remains modest for all 3 of these treatment options, which makes the discussion of what therapy to select difficult for clinicians and patients alike. The data are complicated, and there is no clear front-runner among these options that is applicable to all clinical scenarios. In my practice, I have done my best to explain to patients the data behind each regimen, and let them decide among the options.

H&O Regarding the SWOG S1404 study that you will be conducting, what made you decide to study pembrolizumab (Keytruda, Merck) as a possible alternative to high-dose interferon?

KG We selected pembrolizumab as the experimental adjuvant treatment for the S1404 because of its low toxicity (<12% for grade 3 or 4 toxicity) and high response rate in stage IV disease (30%-40%). These benefits were apparent in the phase 1 research program that was conducted with pembrolizumab and published by Hamid and colleagues in 2013.

H&O Could you talk about the design of the S1404 study?

KG The study will be an open-label, randomized controlled trial comparing high-dose interferon vs pembrolizumab in up to 1378 patients with resected melanoma. The population will encompass resected melanoma ranging from stage IIIA (N2) to stage IV as long as all apparent disease is resected, and there is no history of central nervous system metastasis.

High-dose interferon treatment will consist of 20,000,000 U/m² per day intravenously on days 1 through 5 for 4 weeks, followed by 10,000,000 U/m² per day subcutaneously on Mondays, Wednesdays, and Fridays for the remainder of 1 year, provided that the patient tolerates treatment and does not relapse.

Pembrolizumab treatment will consist of a flat dose of 200 mg intravenously every 3 weeks for 1 year. As with high-dose interferon, the treatment will change if the patient develops intolerance to treatment or relapses.

H&O Is this study going to be looking at whether expression of programmed death ligand 1 (PD-L1) relates to the efficacy of anti-PD-1 therapy?

KG We will use an antibody made by Dako, which has been employed extensively in other pembrolizumab studies, to evaluate PD-L1 expression in all patients. The patients will be stratified based on the presence or absence of PD-L1 on staining. This will allow for a subgroup analysis at the end of the study where we can determine whether the benefits of treatment apply only to the PD-L1-positive subgroup, or whether all patients are likely to benefit from the treatment.

H&O What is the status of enrollment for this study?

KG Enrollment is scheduled to begin in late September 2015, and we expect to complete accrual in less than 2½ years. The first results may report as soon as study year 3, which is in the fall of 2018.

H&O Are other studies looking at the use of monoclonal antibodies as adjuvant treatment in these patients?

KG Yes, other studies are examining the use of monoclonal antibodies directed toward programmed death 1 (PD-1) in the adjuvant setting. For example, a study sponsored by the European Organisation for Research and Treatment of Cancer (EORTC) is comparing pembrolizumab vs placebo after complete resection of high-risk stage III melanoma (NCT02362594). This study is actively recruiting patients.

The CheckMate 238 (Checkpoint Pathway and Nivolumab Clinical Trial Evaluation 238) trial, which is sponsored by Bristol-Myers Squibb, also is recruiting patients. This is a placebo-controlled study comparing adjuvant use of the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor ipilimumab (Yervoy, Bristol-Myers Squibb) at 10 mg/kg for 4 doses vs nivolumab (Opdivo, Bristol-Myers Squibb) at 3 mg/kg every 2 weeks for 1 year (NCT02388906).

In addition, several studies have completed accrual and will begin reporting results as soon as the end of 2016. For example, the ECOG-led E1609 trial (A Phase III Randomized Study of Adjuvant Ipilimumab Anti-CTLA4 Therapy Versus High Dose Interferon α -2b for Resected High Risk Melanoma) is comparing high-dose interferon vs 2 doses of ipilimumab, 3 mg/kg and 10 mg/kg (NCT01274338). The ongoing COMBI-AD trial (A Study of the BRAF Inhibitor Dabrafenib in Combination With the MEK Inhibitor Trametinib in the Adjuvant Treatment of High-Risk BRAF V600 Mutation-Positive Melanoma After Surgical Resection), which is no longer enrolling patients, is comparing dabrafenib (Tafinlar, Novartis) plus trametinib (Mekinist, Novartis) vs a placebo for 1 year (NCT01682083). There is also the BRIM8 trial (A Study of Vemurafenib Adjuvant Therapy in Patients With Resected Cutaneous BRAF Mutant Melanoma), which is comparing vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) vs placebo (NCT01667419). I am hopeful that these trials will provide positive results, giving us improved treatment options in the adjuvant setting.

H&O Are there any other relevant studies you would like to mention?

KG Eggermont and colleagues published a study this year in *Lancet Oncology* that examined ipilimumab at 10 mg/kg every 3 weeks for 4 doses, and then every 3 months for up to 3 years. This study showed a significant

benefit from ipilimumab; median recurrence-free survival was 26.1 months with ipilimumab vs 17.1 months with placebo (HR, 0.75; 95% CI, 0.64-0.90; $P=.0013$). This result is similar to what has been shown when high-dose interferon has been compared with an inactive control arm. What is encouraging about this result is that checkpoint inhibition worked to reduce relapses in EORTC 18071 postoperatively, when tumor-infiltrating lymphocytes present in nodal metastases had been removed. The FDA is presently reviewing these data, and may approve ipilimumab at 10 mg/kg for adjuvant use in the late fall of 2015.

Unfortunately, this treatment has been associated with higher toxicity than was shown with the currently approved dosing for stage IV melanoma, which is 3 mg/kg. The concern is that some of the adverse events may result in permanent disability. Furthermore, there are no data available on the survival impact of this higher dose of ipilimumab, because EORTC 18071 did not achieve sufficient maturity to demonstrate whether there is an impact on overall survival. If the FDA does approve it, I will certainly discuss ipilimumab with my patients as an additional option for adjuvant treatment. Until more data are revealed from the E1609 trial, however—including overall survival data—I will continue to consider enrollment in a clinical trial to be a better option than adjuvant ipilimumab.

Suggested Readings

Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol*. 2009;27(36):6199-6206.

Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2015;16(5):522-530.

Eggermont AM, Suciu S, Santinami M, et al; EORTC Melanoma Group. Adjuvant therapy with pegylated interferon α -2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. *Lancet*. 2008;372(9633):117-126.

Flaherty LE, Othus M, Atkins MB, et al. Southwest Oncology Group S0008: a phase III trial of high-dose interferon α -2b versus cisplatin, vinblastine, and dacarbazine, plus interleukin-2 and interferon in patients with high-risk melanoma—an intergroup study of cancer and leukemia Group B, Children's Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *J Clin Oncol*. 2014;32(33):3771-3778.

Grossmann KF, Othus M, Tarhini AA, et al. SWOG S1404: A phase III randomized trial comparing high dose interferon to pembrolizumab in patients with high risk resected melanoma [ASCO abstract TPS9085]. *J Clin Oncol*. 2015;33(15)(suppl).

Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med*. 2013;369(2):134-144.

Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. Interferon α -2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. *J Clin Oncol*. 1996;14(1):7-17.

Mocellin S, Lens MB, Pasquali S, Pilati P, Chiarion Sileni V. Interferon α for the adjuvant treatment of cutaneous melanoma. *Cochrane Database Syst Rev*. 2013;6:CD008955.