Adjuvant therapy for resected high-risk melanoma
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Abstract
Melanoma is an aggressive cancer that arises from melanocytes that can both locally invade surrounding tissues as well as metastasize systemically. If detected early, melanoma can be curable with surgical resection. However, despite complete removal, high-risk resected melanomas have a significant rate of both local and distant recurrence. Curative treatment options are typically limited for patients who develop distant recurrence after resections of their primary melanoma. Therefore, adjuvant therapy is typically given after complete resection of high-risk melanomas to try and reduce the risk of recurrent disease. Adjuvant therapy for high-risk resected melanoma has changed considerably over the past couple of years due to the availability of new melanoma therapies that are active in the metastatic setting. Here, we review the new treatment options and ongoing clinical research for adjuvant therapy.

Interferon α
Interferon α was one of the first investigated adjuvant therapies for resected melanomas. This was based on early phase studies in the metastatic setting that showed modest activity, with higher response rates seen in patients with less disease burden.¹ High-dose interferon α was first approved by the Food and Drug Administration (FDA) in 1995 based on Eastern Cooperative Oncology Group (ECOG) 1684, which showed an increase in median recurrence-free survival (RFS) from 0.98 to 1.72 years (P = .023) and an increase in median overall survival (OS) from 2.78 to 3.82 years (P = .023) for patients with resected stage IIB-III or recurrent nodal disease.² Subsequent ECOG trials, E1690 and E1694, confirmed the RFS benefit of adjuvant interferon α for patients with resected melanomas; however, the benefit in OS was not consistent across all trials.³⁻⁴ A phase III trial comparing pegylated interferon to observation in this setting also showed a benefit in RFS without an increase in OS.⁵

Given the high toxicity of therapy and the inconsistent increase in OS, interferon was not uniformly adopted as the standard of care for patients with resected melanomas.

Granulocyte-macrophage colony-stimulating factor
Given the suggestion that the immune system could be leveraged to reduce the recurrence rates of resected melanoma suggested by the adjuvant interferon data, other more tolerable immune-directed therapies were studied in the adjuvant setting. One of these therapies was granulocyte-macrophage colony-stimulating factor (GM-CSF). A single-arm phase II trial in which patients with resected stage III and IV melanomas were given adjuvant GM-CSF showed a marked increase in RFS and OS compared with disease- and age-matched historical controls.⁶ Although this trial did not directly compare GM-CSF to placebo, given its tolerability, GM-CSF had some use as adjuvant therapy for melanoma. Unfortunately, the confirmatory phase III trial showed no statistical improvement in RFS or OS survival for GM-CSF compared with placebo.⁷

Vaccines
Another group of immune-directed adjuvant therapies for melanoma were antimeanoma vaccines. Multiple different types of tumor vaccines have been studied in clinical trials for patients with resected melanomas, including allogenic, ganglioside, and peptide vaccines. Two large phase III studies looking at patients with resected stage III and stage IV disease treated with an allogenic vaccine called Canvaxin were terminated early due to interim analysis showing no significant difference compared with the placebo-controlled arm.⁸ Two additional phase III studies looked at a ganglioside vaccine, GM2-KLH-QS21. Data from these trials showed the vaccine to be inferior to interferon α and suggested reduced OS as compared with placebo.⁹ The possibly inferior outcomes with vaccine therapy, as compared with placebo, may be due to chronic immune stimulation, leading to immune tolerance.

Ipilimumab
Ipilimumab was FDA approved for adjuvant treatment of resected melanomas in 2015 based on a trial of 951 patients with resected stage III melanoma. Ipilimumab was given at a 10 mg/kg dose every 3 weeks for 4 doses and then every 3 months for up to 3 years. It was shown to increase RFS at 5 years from 30.3% to 40.8% (P ≤ .0001) and increase the OS rate at 5 years from 54.4% to 65.4% (P = .001).¹⁰ This increase in RFS and OS came at the cost of significant toxicity, with a grade 3/4 adverse event rate of 23%.¹¹
event rate of 54.1\% and a death rate of 1.1\%. Despite the high toxicity rate, most of the adverse events were reversible with steroids and other immunosuppressive therapies.\textsuperscript{11}

Although ipilimumab has not yet been compared head-to-head with interferon, crosstrial comparison showed similar efficacy between interferon (5-year RFS of 37\%)\textsuperscript{3} and ipilimumab (5-year RFS of 40.8\%).\textsuperscript{10} Given the similar efficacy between these 2 therapies, clinicians were selecting either option based on the anticipated toxicity profile and personal preference without clear evidence showing superiority of one over the other. Results from an ongoing ECOG trial comparing ipilimumab to interferon is expected to be reported in 2018 (NCT01274338).

**Anti-programmed cell death protein 1 antibodies**

The first trial comparing adjuvant nivolumab to ipilimumab was recently reported. A total of 906 patients with resected stage IIIB, IIIC, or IV melanoma were randomly assigned to receive nivolumab (given 3 mg/kg every 2 weeks) or ipilimumab (given 10 mg/kg every 3 weeks) for 4 doses, and then the same dosage every 12 weeks for up to 1 year. For all patients, nivolumab had a significant increase in RFS at 18 months compared with ipilimumab—66.4\% (95\% CI, 61.8\%-70.6\%) versus 52.7\% (95\% CI, 47.8\%-57.4\%).\textsuperscript{12} Subgroup analyses suggested that nivolumab was superior to ipilimumab in both patients who had programmed death-ligand 1 (PD-L1)-positive (>5\%) and PD-L1-negative tumors. When analyzed by stage, nivolumab was superior to ipilimumab for all included stages. In regard to toxicity, nivolumab was significantly less toxic than ipilimumab, with a grade 3/4 adverse event rate of 25.4\% versus 55.2\%. No OS survival data have been reported in this study; however, a recent analysis of 11 previously reported adjuvant studies suggests that an RFS hazard ratio of 0.77 or less predicts impact on OS.\textsuperscript{13} Hazard ratios for RFS in this study for patients with resected stage III and IV disease were 0.65 and 0.70, respectively, suggesting a likely benefit in OS.

Of note, this study is the only recent study to look at adjuvant therapy for patients with resected stage IV disease. Previous studies have shown benefit of metastastectomies for patients with oligometastatic stage IV disease. In a phase II single-arm trial from Southwest Oncology Group, the 1-year RFS for patients who underwent complete resection for stage IV disease was 31\% (95\% CI, 33\%-58\%).\textsuperscript{14} In subgroup analyses for patients with resected stage IV disease treated with either adjuvant nivolumab or ipilimumab, RFS at 1 year was 63.0\% for those treated with nivolumab and 57.5\% for those treated with ipilimumab. Although neither nivolumab nor ipilimumab have been compared to placebo in the adjuvant setting for resected stage IV melanomas, this comparison suggests that adjuvant therapy likely has benefit in this setting.

Pembrolizumab was recently compared to placebo for patients with resected stage IIIA-C melanoma.\textsuperscript{15} In this trial, patients were randomly assigned to receive pembrolizumab 200 mg every 3 weeks for up to 18 doses or placebo every 3 weeks for 1 year. Recurrence at 2 years was lower in the pembrolizumab group with a hazard ratio of 0.57. However, OS data from this trial have yet to mature and have not been reported. Another adjuvant trial comparing pembrolizumab to investigator’s choice—ipilimumab or interferon—for resected stage III and stage IV melanoma in the adjuvant setting has completed enrollment, and results have yet to be reported (NCT02506153). This trial is designed and powered to compare OS between the 2 arms. Results from this trial are expected in late 2018.

**Combination anti-PD-1 and anti-cytotoxic T-lymphocyte-associated protein 4 antibodies**

A phase 3 trial comparing nivolumab in combination with ipilimumab for patients with resected stage IIIB/C/D or stage IV melanoma (NCT03068455) as compared with single-agent nivolumab has recently completed accrual, with results expected in 2020.

**BRAF-Targeted therapies**

Combination BRAF and MEK inhibitors dabrafenib and trametinib (dab/tram) have recently been shown to have an OS benefit in BRAF-mutated metastatic melanoma.\textsuperscript{16} A phase 3 trial comparing up to 1 year of dab/tram to placebo for patients with resected stage III BRAF V600E- or V600K-mutated melanomas showed an increase in RFS at 3 years, 39\% for placebo and 58\% for dab/tram (P ≤ .001).\textsuperscript{17} The targeted-therapy arm also showed a trend towards increase in OS at 3 years, 88\% versus 77\% (P = .0006); however, this was not statistically significant because it did not meet the prespecified statistical boundary. Combination targeted therapy, although effective, was relatively toxic, with a grade 3/4 adverse event rate of 44\% and a drug discontinuation rate of 26\%.

Single-agent vemurafenib has also been evaluated in the adjuvant setting for patients with resected stage IIC-IIIC melanoma. Although results of this trial have yet to be reported in a peer-reviewed journal, these data have been presented in abstract form. Preliminary results show a hazard ratio for disease-free recurrence of 0.80 (95\% CI, 0.54-1.18) for those with resected stage IIIC melanoma, compared with observation. For patients with resected stage IIC-IIIB melanoma, vemurafenib resulted in a hazard ratio of 0.54 (0.37-0.78) for disease recurrence compared with placebo. However, based on the prespecified method of statistical analysis, it was not shown to be statistically significant.\textsuperscript{18}

**Conclusion**

Multiple new therapies have demonstrated reduction in the risk of recurrence, and in some cases increased OS, for patients with resected stage III and IV melanomas. Nivolumab, pembrolizumab, and dab/tram are effective options for adjuvant treatment for patients with resected stage III disease. Because the efficacy of anti-PD-1 antibodies and dab/tram appear to be similar, the decision between the two should be made at the
patient level, based on the unique side effect profiles of each regimen. For patients with completely resected stage IV disease without a B-RAF mutation, adjuvant nivolumab should be considered as the preferred option because it has the most data in this setting.

References


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