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Updates in adjuvant systemic therapy for melanoma

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Abstract

There has been a rapid increase in adjuvant therapies approved for treatment following surgical resection of stage III/IV melanoma. We review current indications for adjuvant therapy, which currently includes a heterogeneous group of Stage III and IV melanoma patients. We describe several pivotal clinical trials of systemic immune therapies, targeted immune therapies, and adjuvant vaccine strategies. Finally, we discuss the evidence for selecting the most appropriate treatment regimen(s) for the individual patient.

Keywords

adjuvant therapy; melanoma

Introduction

Over the past several years, multiple new systemic therapies have demonstrated to be effective in patients with unresectable stage III and Stage IV melanoma.^{1,2} Subsequently these same treatments have been shown to improve recurrence free survival in the adjuvant treatment of high-risk, resected melanoma patients.^{1,3–8} The decision to recommend adjuvant therapy after surgery for melanoma is based on the relative risk of recurrence, specific tumor characteristics that impact drug selection (e.g. *BRAF V600E* or *V600K* mutation), risks associated with treatment, and patient related factors that affect ability to tolerate therapy. In this review, we will discuss indications for adjuvant therapy, key findings from landmark adjuvant therapy trials, preferred choices of adjuvant therapy, and future directions.⁹

Defining High Risk Populations for whom Adjuvant therapy is appropriate

The decision to recommend adjuvant therapy after surgery for melanoma is based on the risk of recurrence. Prior to surgery, some patients will have known AJCCv8 Stage IIIB or higher

disease including patients with clinically detected lymph nodes, or clinically detected Stage IV disease. In a large cohort study in an era preceding the liberal use of effective adjuvant therapy, only 32% with stage IIIB and 11% of patients with stage IIIC (AJCC v7) of patients were alive without recurrence at 5 years after surgical resection.¹⁰ Given the high rate of recurrence in these patients, all of the recent adjuvant trials included these types of stage III patients.^{3–5} The inclusion of Stage IV patients was limited to Checkmate 238. Prior to approval of multiple new effective therapies for unresectable stage III and stage IV melanoma, surgical resection remained a therapeutic option for many patients with Stage IV melanoma.¹¹ However in the current era, surgery should be considered only in selected cases of Stage IV disease given the improvements in systemic therapy.

Many patients are diagnosed with stage III melanoma after wide local excision and a positive sentinel lymph node biopsy (SLNB). In the final analysis of the multicenter selective lymphadenectomy trial I, SLNB positivity was associated with an increased risk of disease recurrence compared to SLNB negative patients with hazard ratio of 2.64 (1.92–3.64, $P < 0.001$).¹² However, patients with SLN positive disease are a heterogeneous group in regards to prognosis. For patients with a positive SLNB, the presence of non-sentinel lymph node (NSLN) involvement at completion lymph node dissection (CLND) is associated with increased melanoma-specific recurrence and mortality.^{18,19} Since CLND is no longer considered a part of standard oncologic surgical resection, the prognostic information of NSLN involvement cannot be used to further stratify patients at high risk of recurrence and death from melanoma.^{12,14}

Beyond NSLN involvement, the maximum tumor diameter in the SLN has been found to predict disease free survival and overall survival in melanoma patients.¹³ Patients with 1 mm or less tumor in the SLN have a 10 year melanoma specific mortality of less than 10%.¹⁴ In other studies, a cutoff of 1 mm of tumor in the SLN was shown to select patients with excellent survival.^{15,16} Thus, eligibility for many adjuvant trials included patients with 1mm of tumor in the SLN including EORTC 1325, EORTC 18071, SWOG 1404, COMBI-AD, and BRIM-8.^{5,6,8,17}

Even among patients with SLNB positive disease with greater than 1 mm of tumor, there remains heterogeneity in risk of recurrence. Both the tumor burden in the SLN and ulceration of the primary tumor have been explored by the Netherlands cancer institute group as another method to predict which benefits will benefit from adjuvant therapy and which patients need no additional therapy after a positive SLNB.²⁰ In their analyses, AJCC v8 staging plus SN tumor burden allowed more distinct risk stratification and was the best performing model at predicting recurrence.²⁰

While SLNB positivity and SLN tumor burden can identify patients at high risk or recurrence, a subset of patients with thin melanomas and/or a negative sentinel lymph node biopsy are at elevated risk of recurrence and mortality.¹² BRIM-8 was the only adjuvant trial to include patients with Stage IIC disease.^{3,4,8} Importantly, the expected 5- and 10-year melanoma specific survival of patients with American Joint Committee on Cancer (AJCC) v8 stage IIC is worse than that for stage IIIA (82 percent and 75 percent versus 93 percent and 88 percent, respectively).²¹ Patients with high-risk node-negative melanoma stage IIC

tumors (which include > 4 mm or > 2 mm and ulcerated) remain a group understudied in recent adjuvant therapy trials.

In summary, staging including SLNB can be useful tools in determining risk of recurrence and subsequent decision for adjuvant therapy. However, there are some shortcomings to histopathologic stage as the only risk stratification tool. For patients who may have prolonged recurrence free survival from surgery alone, the toxicities of adjuvant therapy may outweigh the benefits. There are ongoing efforts, such as those based on genetic profiling, aimed at providing additional tools for risk-stratification, though none have become part of standard practice.^{22–25}

Historical Adjuvant Therapy Trials

Over the past few years, several effective adjuvant agents have been approved for the treatment of patients with high-risk, resected melanoma. Table 1 listed specific details regarding the trials and Table 2 lists year of FDA approval. For more than 20 years prior to FDA approval of adjuvant ipilimumab in 2015, interferon- α 2b (IFN) was the only approved agent for adjuvant treatment of patients with high-risk cutaneous melanoma.^{26–28} High-dose interferon- α was found to have a marginal benefit (HR for disease recurrence with IFN- α vs observation, 0.82) in a large meta-analysis of randomized controlled trials (RCTs).²⁸ In 2012 pegylated interferon- α 2b was FDA approved based large European Organization for Research and Treatment of Cancer (EORTC) trial showing a statistically significant improvement in the relapse-free survival interval without an accompanying overall survival advantage in resected node positive melanoma patients.²⁶ However, the frequent and potentially serious side effects as well as the minimal clinical benefit, limited widespread use of both interferon- α 2b and peginterferon.^{29,30}

Adjuvant Modern Immune Therapy

Ipilimumab was the first immune checkpoint inhibitor to demonstrate efficacy in the unresectable stage III and stage IV melanoma setting and was subsequently explored in the adjuvant setting.³¹ EORTC 18071 was a phase 3 RCT of ipilimumab (10 mg/kg q3 weeks for 4 doses, then q3 months for up to 3 years) vs placebo in patients who had undergone complete resection of stage III cutaneous melanoma.³² To be eligible, patients had to have at least one node metastasis measuring > 1mm, or stage IIIB or IIIC (AJCC v7) melanoma exclusive of in-transit metastases and performance of complete regional lymphadenectomy following a positive SLN biopsy. In the ipilimumab group (n=475) overall survival (OS) at 5 years was 65.4% compared to 54.4% in the placebo (n=476) (p=0.001).⁶³² However, serious drug related adverse events (AEs) occurred in 41.6 % of patients in the ipilimumab group, only 13.4% of the patients completed the treatment period, and five patients (1.1%) in the ipilimumab group died from drug-related adverse events.

After the initial experience with adjuvant ipilimumab, different dosing regimens were explored in an effort to determine efficacy and decrease morbidity of the drug. US Intergroup E1609, a randomized study of adjuvant ipilimumab (3 or 10 mg/kg) versus high-dose interferon α -2b for resected high-risk melanoma patients, was designed to examine

different ipilimumab doses and compare the drug to interferon.³³ In the preliminary report, grade 3 AEs were noted in 58% of those in the 10 mg/kg group and 36.4% of those in the 3 mg/kg group. The relapse free survival did not appear to differ between the dosing groups. However, overall survival data are needed given the known significantly longer overall survival of the 10mg/kg ipilimumab dose compared to 3 mg/kg dose in the metastatic setting.³⁴ Given the rate of severe toxicity and emerging data on the improved efficacy and tolerability of programmed death cell protein 1 (PD-1) antibody therapy, the routine use of ipilimumab in the first line adjuvant setting is no longer recommended.

Programmed death cell protein 1 (PD-1) antibody therapy followed ipilimumab in the era of immune checkpoint inhibitor therapy and was first shown to have efficacy in the setting of unresectable stage III and stage IV melanoma before subsequently being applied to the adjuvant setting.¹ Checkmate 238 was a RCT of nivolumab (3 mg/kg every 2 weeks) vs ipilimumab (10 mg/kg every 3 weeks for four doses and then every 12 weeks) in patients with resected stage IIIB, IIIC, or IV (AJCC v7) resected melanoma.³ Complete regional lymphadenectomy was required. Randomization was stratified according to disease stage (stage IIIB or IIIC, stage IV M1a or M1b, or stage IV M1c, according to the AJCCv7 criteria) and status regarding PD-L1 (negative or intermediate vs. positive) on the basis of a 5% cutoff with PD-L1 staining only of tumor cells, preferably in the most recently resected lesion. Treatment was administered for up to 1 year or until disease recurrence, a report of unacceptable toxic effects, or withdrawal of consent. The primary endpoint was recurrence free survival in the intent-to-treat population. Although 507 events of recurrence-free survival were initially anticipated, the number was revised to 450 events of recurrence free survival event for the final analysis which provided power of 85% to detect a hazard ratio for disease recurrence or death of 0.75 with an overall two-sided type 1 error rate of 0.05.

A total of 906 patients underwent randomization and the minimum follow-up was 18 months. At publication, a total of 397 patients had completed 1 year of treatment: 60.8% in the nivolumab arm and 26.9% in the ipilimumab group. The median recurrence-free survival had not been reached in patients with stage III or IV disease in the nivolumab group. At 18 months, the recurrence-free survival was 66.4% (95% CI, 61.8 to 70.6) in the nivolumab group and 52.7% (95% CI, 47.8 to 57.4) in the ipilimumab group.³ Among the patients with stage IIIB or IIIC disease, the 12-month RFS was 72.3% (95% CI, 67.4 to 76.7) in the nivolumab group and 61.6% (95% CI, 56.3 to 66.5) in the ipilimumab group.³ The rate of recurrence appeared to be lower with nivolumab regardless of PD-L1 status. The rate of serious adverse events of any grade was 17.5% in the nivolumab group and 40.4% in the ipilimumab group. During the trial, adverse events led to discontinuation of nivolumab in 9.7% of patients. At recently reported follow-up, RFS continued to be significantly longer for nivolumab vs ipilimumab; the distant metastases free survival at 24 months was 70.5% for nivolumab vs 63.7% ipilimumab (HR 0.66, P <0.001).³⁵

Another PD-1 antibody, pembrolizumab, has also been studied in a randomized phase 3 double-blind adjuvant study. EORTC 1325 randomly assigned patients with completely resected stage III disease to 200 mg pembrolizumab every 3 weeks for 18 doses (1 year) or placebo.⁵ The patients had to have either AJCC version 7 stage IIIA melanoma (patients with stage N1a melanoma had to have at least one micro metastasis measuring >1 mm in

greatest diameter) or stage IIIB or IIIC disease with no in-transit metastases. A complete regional lymphadenectomy was also required. Randomization was stratified according to stage (stage IIIA, stage IIIB, stage IIIC with one to three positive nodes, or stage IIIC with four or more positive nodes) and geographic region (17 regions, each formed by 1 to 3 countries). The primary endpoint was recurrence free survival in the intention-to-treat population. A total of 409 events (recurrences or deaths without recurrences) would provide 92% power to detect a hazard ratio for recurrence or death of 0.70, corresponding to a 1-year recurrence-free survival rate of 58.3% in the placebo group versus 68.5% in the pembrolizumab group and a 3-year recurrence-free survival rate of 35.3% in the placebo group versus 48.3% in the pembrolizumab group, at a one-sided alpha level of 1.4%.

A total of 1019 patients underwent randomization. Among 509 patients who received pembrolizumab, 13.8% discontinued due to an adverse event compared to 2.2% of patients on placebo arm who discontinued due to adverse event. Adverse events of grades 3 to 5 that were related to the trial regimen were reported in 14.7% of the patients in the pembrolizumab group and in 3.4% of patients in the placebo group.⁵ The pembrolizumab group had a 1-year recurrence-free survival rate of 75.4% [95% confidence interval CI, 71.3 to 78.9] compared to 61.0% [95% CI, 56.5 to 65.1] in the placebo group. Recurrence-free survival was significantly longer in the pembrolizumab group than in the placebo group (hazard ratio for recurrence or death, 0.57; 98.4% CI, 0.43 to 0.74; $P < 0.001$). At 18 months, the rates of recurrence free survival were 71.4% [95% CI, 66.8 to 75.4] in the pembrolizumab arm compared to 53.2% [95% CI, 47.9 to 58.2] in the placebo group. Pembrolizumab was also effective in patients with PD-L1–negative tumors and in those with undetermined tumor PD-L1 expression⁵. Similar to Checkmate 238, this trial's secondary endpoint of overall survival (OS) is pending. Importantly, however, this trial allows crossover to pembrolizumab at progression, and it may help answer questions around the optimal timing of systemic therapy in this patient population.

Pembrolizumab as adjuvant therapy is also being studied in SWOG 1404, a randomized trial comparing IFN- α (amended to also allow ipilimumab) to pembrolizumab after resection of AJCC v7 Stages IIIA(N2), IIIB, IIIC and IV (M1a, b and c) melanoma.¹⁷ This trial has closed to accrual and results are pending. Although both adjuvant PD-1 trials using nivolumab or pembrolizumab reported RFS and not OS, the much lower toxicity profile and significantly longer RFS make PD-1 therapy the first line choice of immune adjuvant over IFN- α or ipilimumab.

For patients with unresectable Stage III and IV melanoma, the combination of ipilimumab and nivolumab has the highest clinical response rates compared to either drug alone, although toxicity of the combination is markedly increased.¹ To explore the combination in the adjuvant setting, a small pilot single-center study of forty patients with resected stage IIIC/IV AJCC v7 melanoma was conducted. Patients were treated with an induction regimen of 1 mg/kg of nivolumab plus 3 mg/kg of ipilimumab every 3 weeks for 4 doses ($n=20$), or an induction regimen of 3 mg/kg of nivolumab plus 1 mg/kg of ipilimumab every 3 weeks for 4 doses ($n=2$) followed by the same maintenance regimen for both groups, nivolumab at 3 mg/kg every 2 weeks for 2 years.³⁶ Among all 40 patients, the median RFS has not been reached yet at a median follow-up of 2.9 years.³⁶ However, the toxicity of the combination

appeared higher than in the metastatic setting.³⁶ In hopes of reducing toxicity, Checkmate 915, a RCT of adjuvant nivolumab and ipilimumab vs nivolumab monotherapy after complete resection of Stage IIIB/C/D or stage IV melanoma, was designed with dosing regimen of ipilimumab 1 mg/kg every 6 weeks and 240 mg of nivolumab every 2 weeks (NCT03068455). Accrual is closed and results are pending.

Adjuvant Targeted Therapy

In addition to immune therapy, adjuvant targeted therapy for the approximately 50% of melanoma patients whose melanomas harbor a *BRAF* V600E or V600K mutation has also been studied.^{4,8} In patients with unresectable stage III and stage IV melanoma, the combination of BRAF and MEK inhibition (BRAFi/MEKi) is associated with high initial response rates and a subset of patients achieving 3 years survival, although the development of resistance and disease progression can occur.^{4,37} The COMBI-AD trial was a phase 3 RCT of stage III resected melanoma patients with BRAF V600E or V600K mutation of oral dabrafenib 150 mg twice daily plus trametinib at a dose of 2 mg once daily or placebo for 12 months.⁴ Patients had undergone complete resection of Stage IIIA (limited to lymph-node metastasis of >1 mm), IIIB, or IIIC cutaneous melanoma (AJCC v7), and CLND was required for SLN-positive patients.⁴ Patients were stratified according to their BRAF mutation status (V600E or V600K) and disease stage (IIIA, IIIB, or IIIC). Patients were treated for 12 months in the absence of disease recurrence, unacceptable toxic effects, withdrawal of consent, or death. The primary end point was relapse free survival. An enrollment of 870 patients would result in relapse-free survival in approximately 410 patients by the analysis cutoff date (with a two-sided type I error rate of 5%) and would provide a power of more than 90% to detect a hazard ratio of 0.71 (corresponding to a median relapse-free survival of 21 months in the combination-therapy group and 15 months in the placebo group).

A total of 870 patients underwent randomization, and the median follow up time was 2.8 years. Of the 870 patients, 792 (91%) had a BRAF V600E mutation, and 78 (9%) had a BRAF V600K mutation. The most common reason drug was discontinued prior to 12 months was related to adverse events in 108 patients (25%) for dabrafenib and 104 patients (24%) for trametinib. In the placebo group, 175 patients (41%) discontinued placebo due to disease recurrence. At a median follow-up of 2.8 years, the estimated 3-year rate of relapse-free survival was 58% in the BRAFi/MEKi-therapy group and 39% in the placebo group (hazard ratio for relapse or death, 0.47; 95% confidence interval [CI], 0.39 to 0.58; $P < 0.001$). The 3-year overall survival rate was 86% in the BRAFi/MEKi-therapy group and 77% in the placebo group (hazard ratio for death, 0.57; 95% CI, 0.42 to 0.79; $P = 0.0006$), but this level was not considered significant per trial design. Serious adverse events occurred in 155 (36%) in the combination therapy group and 44 patients (10%) in the placebo group. One fatal serious adverse event occurred in the combination-therapy group.

BRIM8 is a RCT of oral vemurafenib 960 mg BID vs placebo for 52 weeks.⁸ Patients had fully resected Stage IIC-IIIA-IIIB (cohort 1) or stage IIIC (cohort 2) melanoma and underwent a CLND for node-positive disease.⁸ In cohort 2, median disease-free survival was 23.1 months (95% CI 18.6–26.5) in the vemurafenib group versus 15.4 months (11.1–35.9)

in the placebo group (hazard ratio [HR] 0.80, 95% CI 0.54–1.18; log-rank $p=0.26$).⁸ In cohort 1 (patients with stage IIC–IIIA–IIIB disease) median disease-free survival was not reached (95% CI not estimable) in the vemurafenib group versus 36.9 months (95% CI 21.4–not estimable) in the placebo group (HR 0.54 [95% CI 0.37–0.78]; log-rank $p=0.0010$).⁸ The results for cohort 1 were not considered significant because of the pre-specified analysis plan. Serious adverse events were reported in 40 (16%) of 247 patients in the vemurafenib group and 25 (10%) of 247 patients in the placebo group.⁸ While well tolerated and associated with clinical activity in cohort 1, adjuvant vemurafenib alone is no longer recommended given the results of COMBI-AD and the PD-1 trials.

Adjuvant Vaccine Strategies

Finally, adjuvant vaccine therapies have been explored although to date no melanoma vaccine trial has demonstrated clinical benefit.^{38–41} However there remains potential of vaccines to induce a tumor-antigen-targeted immune response with low overall toxicity such as a now approved vaccine in prostate cancer.³⁹ Various melanoma vaccine strategies are currently under investigation. Melanoma vaccines can be categorized based on the type of tumor-associated antigen involved: whole tumor cells, tumor lysates, peptides, DNA/RNA strands, and stimulated dendritic cells used for antigen presentation. The antigens may be shared across many melanomas (e.g.: cancer-testis antigens or melanocytic differentiation antigens), or they may be neoantigens that are uniquely expressed through malignant transformation. There is enhanced interest in targeting neoantigens that reflect somatic mutations in genes expressed uniquely in melanoma cells (mutated neoantigens).^{42,43} Other potential neoantigen strategies include phosphopeptides that reflect cancer-associated phosphoprotein targets.⁴⁴ These antigen strategies alone are generally not enough to elicit a strong, prolonged immune response and so are combined with “vaccine adjuvants”. Vaccine adjuvants are aimed at producing a more robust immune response by increasing antigen uptake and presentation, recruiting other immune cells, promoting antigen transport to lymph nodes, and forming a depot effect for sustained release of antigen at the site of injection.^{45–47}

One example of a melanoma vaccine that has shown promise in clinical trials of patients with melanoma is the 6-MHP (6-Melanoma Helper Peptide) vaccine.^{48–51} This antigen strategy synthetically combines six shared melanoma peptides derived from cancer-testis antigens and melanocytic differentiation proteins, which are presented in the context of a wide range of MHC Class II molecules. The vaccine adjuvants most used for this peptide antigen series are an incomplete Freund’s adjuvant (Montanide ISA-51), with or without GM-CSF or Toll-like receptor agonists. This vaccine has induced CD4 helper T cell responses in over 80% of patients and durable clinical responses or durable tumor control in over 20% of patients.⁵⁰ The T cell responses are Th1-dominant and are accompanied by CD8 T cell responses by epitope spreading.^{52,53} Improved survival was also observed in stage III and IV melanoma patients when early vaccine-specific T cell and/or antibody responses were detected.⁴⁹ When 6-MHP was administered to 40 patients with resected stage IV melanoma and compared to unvaccinated case-matched controls, median survival was significantly longer for vaccinated patients (5.4 vs 1.3 years, $p<0.001$).⁴⁸ Vaccines to induce helper T cells offer promise in part to create a memory response through Th1, but to

also elicit effector T-cell and dendritic cell responses, laying the groundwork for the secretion of cytokines to promote a stronger immune response.^{54–57}

An important breakthrough in vaccine development for stage III and IV melanoma patients is described in two recent papers published in the same issue of *Nature* in 2017.^{42,43} Both studies used neoantigen vaccines as a means of personalized vaccine development based on predicted immunopeptides from melanoma genome mutations. These predicted neoantigens were synthesized through complex algorithms to predict immunologic responses, comparing exome sequencing of matched tumor cells to normal cells. Both studies showed their predicted neoantigens allowed for an effective means of immunologic and therapeutic effectiveness against stage III melanoma after surgical resection during the short follow-up period of 12 to 25 months.^{42,43} However, results were more mixed for patients with stage IV disease and for patients that had signs of recurrence shortly after study inclusion. This method of personalized neoantigen vaccines still needs investigation to ensure its safety and effectiveness as it requires a significant amount of time and resources. There are other challenges to this approach, as well, since a wide array of neoantigen heterogeneity may be present in different sites of metastasis in the same patients.⁵⁸

As we gain more knowledge into these different vaccine strategies and how to best combine them with other immunotherapies, we advance our understanding of the interplay between the immune system and tumor biology to not only develop a therapeutic agent, but to also develop long-term efficacy against the progression of future disease.

Cost of adjuvant therapy in melanoma

There are significant costs associated with systemic therapy for melanoma that should be considered when determining how these recommendations will be applied in the adjuvant setting. While there have been great advances in care and outcomes with the addition of targeted and immunotherapies, the new drugs are expensive, and their additional costs should be considered against the benefits they provide. To our knowledge no studies have been done specifically examining the costs of adjuvant therapy, but multiple analyses evaluating the costs of therapy in advanced melanoma have been completed. Although the costs between adjuvant and metastatic patients may differ, consideration of costs in the metastatic setting can presently inform estimates about costs in the adjuvant setting.

The costs of check point inhibitors have been an importance consideration in their use since they first became approved. A financial model published in 2017 examining patients with stage IV metastatic *BRAF* wild-type melanoma treated with six treatment strategies using different combinations and sequences of nivolumab, ipilimumab, pembrolizumab, carboplatin and paclitaxel, and dacarbazine found that first line pembrolizumab followed by second-line ipilimumab was the most cost-effective immune-based treatment.⁵⁹ Another financial model based on KEYNOTE-006 also supported the cost effectiveness of pembrolizumab over ipilimumab when taking into account quality-adjusted life-years, though its use was associated with a \$63,680 increase in cost per patient when compared to ipilimumab based on 2015 rates of \$4,316 per 100 mg for pembrolizumab and \$6,659.07 per 50 mg for ipilimumab.⁶⁰ A financial model based on CheckMate-067 trial data found

nivolumab monotherapy to be more cost-effective than nivolumab-ipilimumab combination therapy, which was in turn more cost-effective than ipilimumab monotherapy in patients with metastatic melanoma.⁶¹ Importantly, these analyses took into account costs of adverse events in addition to direct medical costs of the drugs.

Targeted therapies for melanoma are also associated with significant costs. In 2014, vemurafenib cost \$13,000 per month for a total of \$207,000 for a patient with median survival, while dabrafenib cost \$9,100 per month.⁶² A model published in 2016 compared costs of treatment for patients with *BRAF*-mutated metastatic melanoma with combination therapy with either nivolumab and ipilimumab or dabrafenib and trametinib, and found that the targeted therapy was associated with decreased financial cost as well as decreased patient time for similar gains in progression free survival (PFS) and overall response rate benefits.⁶³ The immunotherapy regimen cost \$22,843 per month of PFS, while dabrafenib and trametinib cost \$18,283 per month of PFS.⁶³ While this suggests a relatively decreased cost associated with the targeted therapies compared to combination immunotherapy, the cost remains significant. For both the targeted therapies and check point inhibitors, it is important to consider costs beyond that of the drugs themselves, including monitoring costs such as lab draws, delivery costs, as well as costs of adverse events that are results of the drugs. Cost can be another consideration in the decision for adjuvant therapy by the provider and the patient when deciding the cost benefit to risk ratio of proceeding with adjuvant therapy.

Applying Trial Results to Clinical Practice

Patients selected for therapy

The above reviewed RCTs suggest that patients treated with these adjuvant therapies will have a significant decrease in the rate of disease recurrence. PD-1 antibody therapy and BRAFi/MEKi targeted therapy in the adjuvant setting are now available for all resected Stage III patients including those with SLN metastasis > 1 mm (without CLND), those with clinically positive nodes and/or resected in-transit disease, and patients with resected Stage IV disease. However, the adjuvant trials to date have not included all these types of patients. Checkmate 238 excluded AJCC v7 IIIA patients (microscopic positive SLN involvement and no ulceration of primary tumor) and 93.2% of Stage III patients had LN involvement (6.8% unknown) which means patients with Stage III disease with IT- or satellite-only and no lymph node involvement were not studied. In COMBI-AD, 12% of patients had IT disease, Stage IIIA patients were included (18% of patients in the trial), but Stage IV patients were not studied. Some patients that are now being treated with adjuvant therapies have different disease patterns compared to patients included in the clinical trials. Given these differences, clinical outcomes for patients being treated outside the inclusion criteria of the RCTs should be monitored closely.

Changes to surgical practice

Given the data, our current surgical practice has evolved. A surgeon operating on a patient with known Stage III (in-transit, palpable nodal) or stage IV disease should order *BRAF* mutational status at the time of resection even if the primary tumor tested negative as there can be discordance in the mutational status from primary and metastatic lesions.⁶⁴

Additionally, if SLNB is discovered to have 1 mm foci of tumor, *BRAF* should be determined. Although more rapid immunohistochemical staining can be done, gold standard molecular analysis should be done.⁶⁵ Although PD-L1 expression may guide therapeutic decisions for unresectable stage III or metastatic melanoma patients, PD-L1 expression is presently not used for adjuvant therapy decision making outside of clinical trials.¹

An additional consideration for the surgeon is to perform SLNB for an in-transit or satellite lesion given our group has reported a 40% rate of SLNB positivity in those patients.⁶⁶ At the time of that publication, the only adjuvant therapy approval was for ipilimumab which required 1 mm of SLNB involvement. Given that both PD-1 antibody and targeted therapy BRAFi/MEKi are available after resection of IT disease only (no nodal disease required), SLNB of IT or recurrent subcutaneous disease should be considered only in selected circumstances where SLNB positivity may clarify the risk benefit ratio for adjuvant therapy.

Choice of therapy based on efficacy

Ipilimumab was FDA approved in 2015 for adjuvant therapy in melanoma. However, following FDA approval of nivolumab (approval date December 20, 2017) and dabrafenib plus trametinib (approval date April 30, 2018) (only in patients with a BRAF V600 activating mutation) for adjuvant treatment of patients with melanoma, ipilimumab should no longer be considered first line therapy as monotherapy given the increased toxicity and lower efficacy.³ Comparing the efficacy of PD-1 therapy to BRAFi/MEKi is difficult because each RCT reviewed has slightly different patient populations, various primary endpoints, and unique statistics. Therefore, it is often difficult to directly compare trials. In Table 1, we have listed the 12-month recurrence-free survival for stage III patients for each trial in order to analyze the relative efficacies of these adjuvant therapy strategies. The 12 month RFS for Stage III melanoma patients in the treatment group in the following trials in order EORTC 18071, Checkmate 238, EORTC 1325, COMBI-AD are: 63.5% (ipilimumab), 72.3% (nivolumab), 75.4 % (pembrolizumab), 88% (Dabrafenib plus trametinib).³⁻⁶ As discussed, COMBI-AD and EORTC 1325 did include Stage IIIA patients while Checkmate 238 did not which confounds this comparison given the favorable prognosis of Stage IIIA patients.⁴

Other factors related to choice of adjuvant therapy

In addition to efficacy, the decision to recommend adjuvant therapy for patients after resection of stage III or IV melanoma, should also account for other logistical, safety, and cost issues. Targeted BRAFi/MEKi therapy is limited to the approximate 50% of patients with a *BRAF* activating mutation. PD-1 antibody therapy may be impacted or prohibited by a history of autoimmune disorders, transplant recipients, and poor performance status. The effects on fertility of both classes of agents are not well understood, though the development of immune related endocrinopathies may be of particular concern. A logistical advantage favoring targeted BRAFi/MEKi therapies is that patients who would need to travel a long distance for treatment with PD-1 antibody therapy, an IV formulation, could instead take an oral drug at home. Although the type and nature of toxicities associated with PD-1 antagonists and targeted BRAFi/MEKi therapies differ, the overall rates of adverse events are fairly similar. The risk of serious adverse events was 36% in COMBI-AD and 16% in

BRIM-8 including most commonly pyrexia, fatigue, and nausea while 26% of patients in COMBI-AD had adverse events leading to permanent discontinuation.⁴ By comparison Grade 3–5 adverse events occurred in 14.7% of patients in EORTC 1325/KEYNOTE 054 (pembrolizumab) consisting mostly of fatigue, diarrhea, and rashes. The rate of drug discontinuation due to any side effects was 9.7% in Checkmate 238. An important consideration is also that the specific toxicity of endocrinopathies after immune therapy may also not be reversible. The ability for a patient to safely comply and tolerate therapy should be a strong consideration.

Summary for choice of adjuvant therapy

Finally, for an otherwise healthy patient who is eligible for either PD-1 antibody or targeted BRAFi/MEKi therapy as adjuvant therapy, we can state with confidence that the 1-year risk of disease recurrence is lower with either therapy compared to observation. Depending on stage, recurrence-free survival may be slightly lower with targeted BRAFi/MEKi therapy, but whether there is a difference between PD-1 antibody and BRAF-targeted therapies with respect to overall survival is unclear. For the healthy patient with no preferences regarding toxicity profiles, we generally recommend adjuvant therapy with a PD-1 antagonist as first line, given concerns about targeted therapy resistance and long-term outcomes beyond 1 year.

Future Directions and Conclusion

As data from Checkmate 915, a RCT of adjuvant nivolumab and ipilimumab, ECOG1609 (NCT01274338), a RCT of low vs high-dose ipilimumab vs IFN- α , and adjuvant vaccine trials becomes available, it is likely the choices for adjuvant therapy will continue to expand. Given experience in the metastatic setting, adjuvant nivolumab and ipilimumab may result in the most efficacious risk reduction strategy but will likely come at the cost of toxicity. In future adjuvant therapy trials, it will be difficult to justify comparison to a placebo arm because of the effective approved adjuvant therapies now available. New therapies will have a higher standard to meet. Going forward, patients should also be encouraged to participate in clinical trials after resection of high risk melanoma especially when novel therapies might have a more acceptable safety profile.

There are several studies examining the role of neoadjuvant therapy in the setting of technically resectable disease that have shown some promising results that may change the paradigm for some patients.^{67–69} An entire separate review of the neoadjuvant approach appears in this Seminar by Michael Lowe and colleagues. In the decision regarding use of a neoadjuvant approach versus surgery followed by adjuvant therapy, again research and biomarkers to further characterize risk of recurrence may help individualize treatment plans. For patients who are candidates for complete resection of melanoma with minimal chance of recurrence, surgical resection may be all that is needed, and the risks of adjuvant therapy or neoadjuvant therapy can be avoided. For a patient at high risk of early systemic disease even after a minor surgery to make NED, or a patient facing a technically possible but morbid operation, surgery could be used as an adjuvant therapy as the primary treatment should be systemic therapy. The therapeutic options for patients with melanoma are rapidly evolving and we must continue to construct strategies to that will provide maximal benefit and

minimal risk to an individual patient. Surgical resection followed by adjuvant therapy will likely be a beneficial strategy for many patients going forward but there is much work to be done in appropriate patient selection, novel therapies with lower toxicities, and strategies regarding the role and timing of surgery combined with other types of the systemic treatments.

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Synopsis:

In this review, we discuss recent clinical trials of adjuvant therapy for melanoma and how these novel agents have been incorporated into clinical practice.

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Table 1:

Summary of Randomize Controlled Trials of Adjuvant Therapy for patients with cutaneous melanoma

Trial (year published)	Agents	Eligible Patients	Primary Endpoint And OS if reported	12-month RFS	Toxicity
EORTC 18071 (2015)	Ipilimumab vs Placebo	Complete resection Stage III	Median RFS (*): 26 mos Ipi 17 mos Plac 5 yr OS (*): 65.4% Ip 54.4% Pl	(*) 64% Ipi 56% Placebo	Gr 3/4 AE 54% Ipi 26% Plac 1% death from AE (Ipi)
Checkmate 238 (2017)	Nivolumab vs Ipilimumab	Complete resection Stage IIIB, IIIC, IV	12 month RFS (*): 71% Nivo 61% Ipi	(*) 71% Nivo 61% Ipi Stage III only (*): 72% Nivo 62% Ipi	Gr 3 /4 AE 14% Nivo 46% Ipi 0.4% death from AE (Ipi)
EORTC 1325 KEYNOTE-054(2018)	Pembrolizumab vs Placebo	Complete resection Stage III	12 month RFS (*): 75% Pembro 61% Plac	(*) 75.4% Pembro 61% Plac	Gr 3-5 AE 15% Pembro 3% Plac 1 death Pe
COMBI-AD (2017)	Dabrafenib+ Trametinib vs Placebo	Complete resection stage III	RFS 3 yr (*): 58% Da+Tr 39% Pl OS 3 yr 86% Da+Tr 77% Pl	(*) 88% Da+Tr 56% Pl	SAE 36% Da+Tr 10% placebo 1 death Da+Tr
BRIM8 (2018)	Vemurafenib vs Placebo	Complete resection stage IIC-IIIA/B cohort 1 and IIIC cohort 2	Primary: Median DFS Cohort 2 median DFS 23 mo Vem 15 mo Plac Cohort 1 median DFS NR Vem 37 mo Plac	Cohort 1 84 % Vem 66 % Plac Cohort 2 79% Vem 58 % Plac	Gr 3/4 AE 58% Ve 15% Pl SAE 16% Ve 2% Pl

Nivo=nivolumab, Ipi=ipilimumab, Pembro=pembrolizumab, Da=dabrafenib

Tr=trametinib, Vem=vemurafenib

Plac=placebo, AE=adverse event, Gr=grade

RFS= recurrence free survival, DFS=disease free survival, SAE=serious adverse event

*
= statistically significant

Table 2:

Adjuvant therapy FDA approval and indications

Drug Name	FDA approval	Indication	Trial leading to approval OR pivotal trial [*]
IFN alpha-2b	1996	High risk resected melanoma	ECOG 1684
ipilimumab	2015	Resected stage III melanoma	EORTC 18071
nivolumab	2017	Resected stage III or IV melanoma	Checkmate 238
dabrafenib+trametinib	2018	Resected stage III melanoma with BRAF V600 mutations	COMBI-AD
Pembrolizumab	Pending, supplemental Biologics License Application accepted by FDA	Resected stage III melanoma	EORTC 1325
Vemurafenib	Unknown status	Stage IIC-IIIB resected melanoma	BRIM8

^{*} If FDA has not approved therapy, the pivotal trial examining the drug is listed.