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MELANOMA (RJ SULLIVAN, SECTION EDITOR)

The Evolution of Adjuvant Therapy for Melanoma

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Abstract

Purpose of Review The past decade has been a time of remarkable advancement in the field of adjuvant therapy for patients with resected high-risk melanoma. Here, we review the data for adjuvant melanoma and raise questions about the best choice of therapy for an individual patient.

Recent Findings There have been several new adjuvant approvals including immunotherapy and targeted therapy approaches. Nivolumab is approved for patients with nodal involvement or metastatic disease after resection. Pembrolizumab is approved for patients with nodal involvement after resection. In addition, the combination of dabrafenib and trametinib is approved in patients' nodal involvement after resection whose tumors harbor $BRAF^{V600E/K}$ mutations.

Summary New therapeutic opportunities have provided promising options for patients with high-risk disease. These advances have significantly challenged the previous standard-of-care for this population of patients. Data is still forthcoming regarding durability of benefit and safety of these new treatments.

Keywords Melanoma · Adjuvant · Immunotherapy · BRAF

Introduction

The treatment paradigm for cancer is ever changing. Changes in therapeutic strategies typically first occur in the metastatic setting. Therapies with clear benefit in the metastatic setting quickly move to test in the high-risk adjuvant patients. However, such trials require longer follow-up to identify practical endpoints such as progression-free survival, time to disease recurrence, and even overall survival. Given the upsurge in approvals for metastatic melanoma over the past decade, it is not unforeseen that adjuvant options have also expanded. Responses and survival data in metastatic patients treated with targeted therapy and immunotherapy influence and challenge the treatment decisions in the adjuvant population.

Patients with resected stage III and stage IV melanoma have a high risk of distant recurrence and death from metastatic disease. A patient with stage III melanoma can have a 32–93% 5-year melanoma-specific survival despite complete surgical excision of their disease [1]. This population requires effective postoperative therapy [2, 3]. Promising results from the COMBI-AD trial, CheckMate 238, and Keynote 054. EORTC 1325 open new doors while simultaneously closing old ones. The changing landscape has also raised practical considerations for more clinical trials, highlighted treatment challenges, and continues to drive future research efforts. Long-term outcomes, future clinical trials, and biomarker research will ultimately help guide decision making for this patient population.

Adjuvant Advances

Until recently, options in the adjuvant setting were limited. For patients with a high risk of recurrence after surgery, interferon was the only standard of care option available. Many studies explored high-dose interferon alfa-2b (HDI) in the adjuvant setting for patients with high-risk, resected melanoma. The Eastern Cooperative Oncology Group (ECOG) E1684 trial, was the first study to demonstrate overall survival (OS) advantage compared HDI to observation and established HDI as the standard of care for adjuvant melanoma until 2011 [4]. Subsequent large meta-analyses have consistently

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demonstrated recurrence-free survival (RFS) with a less consistent OS benefit [5–8]. The most recent of those showed an OS advantage with a hazard ratio of 0.91 (95 CI 0.85 to 0.97; p value = 0.003) [5]. However, the use of interferon was not widely adapted due to the high toxicity and low benefit associated with it. There were many attempts to make interferon more tolerable including limiting the dosing to 1 or 3 months or using different formulations, such as pegylated interferon [9]. Pegylated interferon alpha was studied in a large phase III trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) and showed a RFS advantage but no OS benefit [10]. In addition to a modest benefit, HDI is associated with significant toxicities with at least 78% of patients experiencing grade 3 or higher toxicities in E1684 [4, 11]. Patients often experienced flu-like symptoms, which made it very difficult to complete a full year of therapy. While studies showed that patients were willing to tolerate toxicities with HDI for improvements in disease-free survival, better options were clearly needed [12, 13].

After the groundbreaking data with immune checkpoint inhibition in metastatic melanoma trials began in the adjuvant setting. In 2015, the Food and Drug Administration approved ipilimumab 10 mg/kg in the adjuvant setting based on results of EORTC 18071 [14]. This phase III, randomized, double-blind trial compared adjuvant ipilimumab 10 mg/kg versus placebo after complete resection of high-risk stage III melanoma. The trial revealed a RFS benefit in the patients who received ipilimumab. At a median follow-up of 2.74 years, median RFS was 26.1 months in the ipilimumab group versus 17.1 months in the placebo group (hazard ratio 0.75; 95% CI 0.64–0.90; p = 0.0013). The 3-year recurrence-free survival was 46.5% in the ipilimumab group versus 34.8% in the placebo group. And finally, at the most recent 5-year follow-up, RFS increased to 40.8% in the ipilimumab group compared with 30.3% in the placebo group and the OS in the patients who received ipilimumab was 65.4% versus 54.4% in the placebo group [15]. A 5-year follow-up in 2019 showed sustained improvement in RFS, distant metastasis-free survival, and OS [16•]. In this study, the dose of ipilimumab chosen was 10 mg/kg, which was higher than the approved metastatic dose of 3 mg/kg. The patients on this trial experienced a high rate of grade 3 or 4 adverse events with 41.6% having immune-related grade 3 or 4 events. There were also 5 deaths on the trial due to immune adverse events. Despite this high toxicity, there was still a reported benefit in a quality-of-life analysis [17].

Given the high rate of toxicity observed on EORTC 18071, E1609 compared ipilimumab 10 mg/kg or 3 mg/kg versus HDI [18]. Grade 3 or higher toxicities occurred in 57% of patients receiving ipilimumab 10 mg/kg versus 36.4% in patients who received ipilimumab 3 mg/kg. At the median follow-up of 3.1 years, an unplanned RFS analysis showed no difference between the two arms of ipilimumab 10 mg/kg and ipilimumab 3 mg/kg. Recent data from this trial demonstrated that adjuvant therapy with ipilimumab 3 mg/kg had an OS survival benefit over HDI [19]. Additional trials have explored a low-dose regimen in this setting [20].

Both ipilimumab and HDI have fallen out of favor as new adjuvant therapies with greater promise and less toxicity demonstrate benefit and are approved. The results of COMBI-AD, CheckMate 238, and EORTC 1325 have opened new and more tolerable adjuvant options for patients with resected melanoma.

Adjuvant Anti-PD1

The use of PD1 therapy for the treatment of melanoma in the metastatic setting has made dramatic changes in melanoma prognosis and survival. Exploration of these drugs in the adjuvant setting was a logical next step given their success and tolerability.

In 2017, Weber et al. [21••] published the results of the CheckMate 238 study. In this randomized, double-blind, phase III trial, patients with stage III or IVa resected melanoma were randomized to receive nivolumab every 2 weeks or FDA-approved ipilimumab 10 mg/kg. The 12-month rate of recurrence-free survival was 70.5% (95% CI, 66.1 to 74.5) in the nivolumab group and 60.8% (95% CI, 56.0 to 65.2) in the ipilimumab group. As expected, the rate of treatment-related adverse effects was far higher in the patients receiving ipilimumab (45.9% versus 14.4% in those receiving nivolumab), including two deaths related to toxic effects [22, 23]. These results lead to the approval of nivolumab for patients with resected stage III and IV melanoma.

More recently, Eggermont et al. [24••], published mature data from EORTC 1325 (Keynote 054), a phase III double-blind trial of pembrolizumab versus placebo in patients with resected stage III melanoma. At a median follow-up of 15 months, pembrolizumab was associated with prolonged RFS compared with the patients who received placebo. The one year rate of RFS was 75.4% in patients who received pembrolizumab versus 61% in patients who received placebo, (95% CI, 71.3 to 78.9 and 56.5 to 65.1), respectively. Adverse effects (grades 3–5) were reported in 14.7% of patients receiving pembrolizumab, including one treatment-related death from myositis. This was comparable to the adverse effects seen in the nivolumab arm of CheckMate 238.

Adjuvant Targeted Therapy

The other approach with huge benefit in the metastatic setting is targeted therapy for patients whose melanoma harbors a BRAF $^{V600E/K}$ mutation. However, there was some concern about this approach given the rapid progression that can occur at the time melanoma tumors develop resistance to therapy.

The BRIM8 was a randomized, double-blind, placebo-controlled phase III trial of adjuvant vemurafenib in $BRAF^{V600}$-mutated patients [25]. Patients were eligible with stage IIC–IIIC resected melanoma. In patients with IIIC who received vemurafenib, median disease-free survival was 23.1 months (95% CI 18.6–26.5) compared to 15.4 months (11.1–35.9) in the placebo group (hazard ratio [HR] 0.80, 95% CI 0.54–1.18; log-rank $p = 0.26$). In patients with IIC–IIIB, median disease-survival was not reached at the time of publication for those randomized to vemurafenib. The median disease-free survival in the placebo group was 36.9 months 21.4-not estimable) (HR 0.54 [95% CI 0.37–0.78]; log-rank $p = 0.0010$). Fifty-seven percent of patients who received vemurafenib reported grades 3–4 adverse effects. While the study was designed prior to use of BRAF/MEK inhibitor combinations, the results still provide important insight. Specifically, the lack of disease-free survival benefit in patients with stage IIIC suggests that perhaps the patients who benefit from adjuvant targeted therapy are those with a lower residual disease burden.

In the COMBI-AD double-blind, placebo-controlled, phase III trial, patients with resected stage III melanoma with $BRAF^{V600E/K}$ were assigned to received dabrafenib and trametinib versus two matched placebos [26••]. The 3-year and 4-year rates of RFS were 59% (95% CI, 55 to 64%) and 54% (95% CI, 49 to 59%) in the combination group versus 40% (95% CI, 35 to 45%) and 38% (95% CI, 34 to 44%) in the placebo group [27]. Additionally, these patients had an improved rate of distant metastasis-free survival (HR, 0.53; 95% CI, 0.42 to 0.67). Patients who received targeted therapy had an estimated cure rate of 54% (95% CI, 49 to 59%) in the combination arm versus 37% (95% CI, 32% to 42%) in the placebo arm. Efficacy was also presented based on an updated AJCC 8 staging classification and showed a maintained RFS benefit when compared with the original AJCC 7 classification results [28]. The published results to date confirm a benefit with dabrafenib and trametinib in patients with resected BRAF-mutant melanoma.

COMBI-AD is the first study to examine the combination of BRAF and MEK inhibitors for adjuvant treatment in BRAF-mutated patients and this led to the FDA approval of dabrafenib and trametinib in patients with BRAF-mutated and -resected stage III melanoma. Toxicity remains a major barrier to successful completion of treatment. In the trial, 97% of patients reported at least one adverse effect. Twenty-six percent of patients required discontinuation, 38% required dose reduction, and 66% of patients required a dose interruption. Common adverse effects include increased risk of non-melanoma skin cancers, rash, pyrexia, and ocular toxicity. Health-related quality of life (HRQOL), however, does not appear to be negatively impacted during treatment or in follow up after adjuvant treatment with dabrafenib and trametinib [29].

In addition, those patients who progressed after targeted therapy were still able to undergo immunotherapy treatment and there were not many patients that progressed when the 1 year of treatment was complete. These findings were reassuring given concern for aggressive progression at the time of resistance or stopping therapy.

Consequences and Challenges of Adjuvant Treatment

The new adjuvant therapy approvals have already begun to have a wide range of impacts on patient care and healthcare. A larger population of patients is receiving immune checkpoint inhibition and targeted therapy with the potential for larger exposure to toxicity. Many consequences of the new adjuvant therapies will likely be addressed in the future through additional trials and research discovery. Survivorship studies will be critical as many of the long-term side effects of both targeted therapy and immune checkpoint inhibitors are unknown. Results may ultimately influence patient selection, monitoring, and long-term care. For example, patients on life-long prednisone for adrenal insufficiency will require vigilant bone surveillance. For younger patients on testosterone or other hormone replacement for hypogonadism, the effects on fertility are unknown. Furthermore, some irAEs can be severe and life threatening. Although severe morbidity or death from therapy is rare, the decision to start adjuvant treatment requires an in-depth discussion with patients.

Another issue of increasing significance is the cost of adjuvant treatment. Gerbasi et al. [30] analyzed the cost-effectiveness of adjuvant targeted therapy using data from the COMBI-AD study. They determined a cost-effective threshold of $100,000 per quality-adjusted life-years and calculated a probability that dabrafenib and trametinib were 92% cost-effective in patients with BRAF V600E/K mutations treated. Similar cost-effective analyses have been explored in patients treated with adjuvant immunotherapy. The average cost of a full treatment regimen with adjuvant ipilimumab is $1.77 million, without the 4.3% markup that Medicare reimburses to healthcare providers (which would total $1.85 million) [31]. The cost per recurrence-free life month (RFLM) and medical services costs were calculated from data from CheckMate 238 and EORTC 18071 [32]. Here, adjuvant nivolumab resulted in lower medical cost per RFLM in 1 year due to a longer time living without recurrence and savings in medical costs compared to placebo or ipilimumab. The cost of developing a severe irAE can also be very significant with many patients requiring hospitalization and lengthy treatments. Both the development of irAEs and cost-effective consequences of adjuvant therapy in melanoma prompt the need for clinical trials focusing on the length of treatment, comparing 1 year to 6 or 9 months [33].

Patients with stage IIIA melanoma represent a unique group of patients. COMBI-AD, EORTC 18071, and EORTC

1325 (Keynote-054) only included IIIA patients with > 1-mm focus in a lymph node [34]. CheckMate 238 did not include patients with IIIA. To complicate matters, with the introduction of the AJCC 8th edition in 2018, patients who may have been previously ineligible for these studies (eligibility by AJCC 7th edition) now meet eligibility for adjuvant treatment. The new staging system also removed many of the highest risk patients from the stage IIIA category, improving the melanoma-specific survival in these patients and complicating the conversation around adjuvant therapy in such a low-risk group. Furthermore, these adjuvant trials lacked the inclusion of patients with in-transit disease leading to another clinical dilemma in the post-surgical treatment of this specific population of patients.

Another confounding factor is the degree of lymph node removal. With the release of MSLT2 data, patients are no longer undergoing completion lymph node dissections given the lack of benefit. However, all patients in the above adjuvant trials had full lymph node dissections if they presented with a positive sentinel lymph node [35•]. This practice change both influences the patient population being treated and potentially complicates interpretation of treatment success in a patient with a local nodal recurrence. Ongoing and updated practice changes will continue to challenge the interpretation of the data from previous trials.

New adjuvant trials are taking many different approaches. In patients with very high-risk disease trials are investigating the combination of ipilimumab and nivolumab adjuvant setting [36, 37]. At the other end of the spectrum trials and trials in development are investigating the role of adjuvant therapy in lower risk patients with stage IIB and IIC disease (e.g., NCT03553836). There are also efforts to look at adding vaccines and other new agents in the adjuvant setting.

Translational Guidance for Decision Making

The use of biomarkers to guide treatment choice in melanoma therapy has been disappointing to date. While PD-L1 staining, tumor mutation burden (TMB) and other markers can predict which patient may do best on therapy in the metastatic setting; the frequent responses in those patients without these markers preclude their use in clinical care [38]. However, the need for better biomarkers in the adjuvant setting is even larger as it would allow for more selective administration of these toxic and expensive therapies.

Nivolumab or pembrolizumab is the clear choice over ipilimumab for immune checkpoint inhibition in adjuvant BRAF wildtype patients given the demonstration of fewer irAEs and prolonged recurrence-free survival. However, there is some skepticism about the efficacy of anti-PD1 within the microenvironment in patients with microscopic residual disease [39]. A small study examining PD-L1 expression in microscopically positive lymph nodes supports the use of adjuvant immune checkpoint inhibitors in patients with microscopic disease however there was at least 1–2 mm of tumor in these nodes [40]. With < 1 mm of melanoma in a node, there may not be enough PD-L1 expression for PD1 inhibitors to have an effect. This confirms the need for more sensitive biomarkers than PD-L1 to guide patient selection for adjuvant immunotherapy in the future.

Jacquelot et al. and others have explored peripheral blood cell markers in patients with stages III and IV melanoma [41, 42]. Results show an association with detectable CD137 on circulating $CD8^+$ T-cells in patients with resected stage III melanoma. Therefore, CD137 expression may be a predictor of long-term RFS mediated by the combination of immune checkpoint inhibitors in the adjuvant setting, however, it is unclear if this data will be similar for patients treated with anti-PD1 monotherapy.

Elevated blood neutrophil-to-lymphocyte ratio may be a potential biomarker associated with death in patients with high-risk, non-metastatic melanoma [43]. In a multivariate regression analysis, high neutrophil-to-lymphocyte (defined as ≥ 3) was an independent predictor of disease-specific death (HR 1.25, 95% CI 1.02–1.53; $p = 0.03$). The authors also noted high neutrophil-to-lymphocyte ratio to be associated with other poor prognostic factors including older age, male sex, thicker primaries, higher mitotic index, and more advanced nodal status. While this gives insight into the potential prognostic capabilities of the neutrophil-to-lymphocyte ratio, it is unclear whether it will influence adjuvant treatment decisions.

Circulating tumor DNA (ctDNA) may provide clues as to who will benefit from which treatments if they will benefit from any at all and provide markers to follow in patients on adjuvant therapy. Lee et al. [44] studied ctDNA in patients enrolled in the AVAST-M adjuvant trial [45, 46]. In this study, droplet digital polymerase chain reaction (ddPCR) detected BRAF and NRAS mutations in plasma of 161 patients with high-risk, pre-treated patients with stage II and stage III melanoma. The results showed detection of ctDNA (≥ 1 copy of mutant ctDNA) in 11% of BRAF mutant patient samples. Patients with detectable ctDNA had decreased disease-free interval and distant metastasis-free interval versus those patients with undetectable ctDNA. Additionally, 5-year OS rate for patients with detectable ctDNA (BRAF and NRAS) was 33% (95% CI 14–55%) versus 65% (95% CI 56–72%) for those with undetectable ctDNA. The results suggest that ctDNA might potentially predict relapse and survival in high-risk resected melanoma. A similar analysis in patients receiving adjuvant BRAF/MEK inhibitor combination would be the next step to determine if this method can predict patient selection and treatment response in melanoma patients.

Choosing Between Adjuvant Targeted Therapy and Immunotherapy

One of the biggest debates in melanoma these days is which adjuvant therapy should be used in patients with $BRAF^{V600E/K}$ mutations and high-risk disease. The degree of PFS benefit observed with anti-PD1 and BRAF/MEK targeted therapies was similar. Long-term data in this patient population will come with time but for now there is little to help guide the decision of which therapy should be started after surgery.

The argument for immunotherapy over targeted therapy is usually based around the tolerability of PD-1 inhibition and the durability of response traditionally observed with immunotherapy in the metastatic setting. The majority of patients who received PD-1 inhibitors on the trials did not experience severe irAEs with common more mild side effects being fatigue, rash, and thyroid issues. Others who prefer adjuvant immunotherapy point to the aggressive growth observed when metastatic tumors become resistant to BRAF/MEK inhibition. However, this concern is not supported by the data from the BRAF/MEK adjuvant trial.

Targeted therapy has previously been demonstrated to have the most benefit in patients with low tumor burden and normal LDH [47]. This finding suggests that the adjuvant setting would be the ideal place to use BRAF/MEK inhibition, as it is the best opportunity to use targeted therapy with a curative intent. The BRIM8 study supports this given a better response in patients with less risk of having residual disease. In those patients who subsequently fail targeted therapy, immunotherapy still has the potential for durable disease control. The largest challenge with targeted therapy has been the toxicity but those toxicities have the advantage of a quick resolution when medication is held without long-term consequences such as diabetes, adrenal insufficiency, or other irAEs seen with immune checkpoint inhibitors.

While different groups disagree on their preferred adjuvant therapy, there is no disagreement that more data is needed to make these decisions with confidence.

Conclusions

Despite the significant advances in the field of adjuvant therapy for resected melanoma, many challenges remain. The dilemma of treating BRAF mutant patients with targeted therapy versus immunotherapy is increasingly palpable as patients present at younger ages and trials expand to earlier stage disease. Furthermore, the optimal duration of therapy has not yet been fully explored and we may be over-treating patients at a high financial and toxicity burden. And finally, biomarkers have the potential to predict response to therapy but further data is needed in the adjuvant setting. Research is required to bring about a translational, biomarker-driven approach to minimize risk of toxicity and allow for effective treatment and monitoring of minimal residual disease.

Compliance with Ethical Standards

Conflict of Interest Justine V. Cohen has received compensation from Sanofi-Genzyme and Bristol-Myers Squibb for service as a consultant. Elizabeth I. Buchbinder has received compensation from Bristol-Myers Squibb, Trieza Therapeutics, and Novartis for service as a consultant.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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