# The Adjuvant Treatment of Cutaneous Melanoma Just Became Interesting

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**Section 1: Abstract**

Until recently, melanoma was a very challenging cancer to treat. The only adjuvant therapy available for years was interferon, which was associated with significant toxicity. Advances in metastatic melanoma, namely the development of immunotherapies and targeted therapies, have rapidly changed the standard of care for patients with advanced or high risk local disease.

Ipilimumab was the first immunotherapy approved after demonstrating a relapse free survival (RFS) of 26.1 months compared to 17.1 months with placebo, and subsequently demonstrated a 10% difference in overall survival at 5 years, although with significant toxicity. Nivolumab and now pembrolizumab have also demonstrated prolonged RFS by about 10% at one year, with a hazard ratio for each around 0.55, each with much lower toxicity than ipilimumab. Targeted therapy combinations with the BRAF and MEK inhibitors dabrafenib and trametinib have shown a 20% improvement in median RFS at 18 months with hazard ratio of 0.47. The introduction of novel classes of therapy in the adjuvant setting has shown dramatic improvement in toxicity, tolerability, and survival. This has changed the standard of therapy for adjuvant melanoma and raised additional questions on overall patient management.


 

**Section 2: Introduction**

The number of new cases of melanoma has steadily increased over the past 35 years and melanoma now accounts for 5.3% of all new cancer cases. [1] Despite the substantial increase in the incidence of disease, the 5 year overall survival (OS) rate has remained fairly constant, attributed largely to early diagnosis and appropriate surgical management. The 5-year OS rate for those with "low risk" melanoma is 90-98% and comprises patients with stages IA through IIA disease[2] (Table 1.). Patients with stage IIB or IIC melanoma have an "intermediate risk" of recurrence and death and consist of those whose tumors are greater than 2mm with ulceration (T3b) or are greater than 4mm independent of ulceration status (T4a/T4b). The estimated 5 year OS for this population ranges from 65-92.8%.[3] Lastly, the" high risk" population includes patients with lymph node involvement, i.e. those with stage III disease, whose 5 year OS rate decreases to 41-71%.

| Stage | Tumor | Lymph Nodes | Metastasis |
|---|---|---|---|
| 0 | Tis | N0 | M0 |
| IA | T1a | N0 | M0 |
| IB | T1b-T2a | N0 | M0 |
| IIA | T2b-T3a | N0 | M0 |
| IIB | T3b-T4a | N0 | M0 |
| IIC | T4b | N0 | M0 |
| III | Any T | ≥N1 | M0 |
| IV | Any T | Any N | M1 |

Table 1: AJCC staging for cutaneous malignant melanoma. T=tumor, N=lymph nodes, M=metastasis, a=non-ulcerated, b=ulcerated.

Adjuvant treatment for melanoma is directed at reducing the risk of recurrence while minimizing long- and short-term toxicity. The first pivotal adjuvant therapy trial for melanoma was conducted in 1985 by the Eastern Cooperative Oncology Group in conjunction with the National Cancer Institute, known as E1684.[4] This study

included 287 patients with either stage IIC (T4a/T4b), or stage III (N1-3) disease and randomized them to high dose interferon versus observation. After a median follow-up of nearly 7 years there was improvement in median relapse free survival (RFS, 1.7 years vs 1.0 year) as well as median OS (3.8 years vs 2.8 years), favoring the interferon treated population. As a result of this study, the Food and Drug Administration (FDA) granted approval for the adjuvant use of interferon alfa-2b in 1996. This agent remained the only approved drug until 2011 when pegylated interferon (PEG-IFN) was approved after the EORTC 18991 study demonstrated benefit in the RFS rate, but not the OS rate.[5] Due to the marginal benefit of both of these agents relative to the substantial toxicities, their use as adjuvant therapy has remained controversial. Fortunately, recent advances in the treatment of metastatic melanoma have made their way to the adjuvant setting and promise improved outcomes with substantially less toxicity. These agents include immunotherapy with ipilimumab, nivolumab, and pembrolizumab as well as targeted therapies vemurafenib, dabrafenib, and trametinib.

**Section 3: Immunotherapy**

Melanoma has long been considered an immune-responsive tumor, with reports of patients developing spontaneous remissions; thus, it is not surprising that the early success of immune-oncologic drugs was first seen in patients with melanoma. The first FDA approved agent was ipilimumab, an anti-CTLA4 (cytotoxic T lymphocyte-associated antigen) monoclonal antibody that blocks the interaction of CTLA-4 and its ligands, B7.1 and B7.2, thereby enhancing the immunologic response and anti-tumor activity.[6]

In the adjuvant trial EORTC 18071, patients with resected stage IIIA to IIIC melanoma

were randomized to either ipilimumab at 10mg/kg intravenously every 3 weeks for four doses followed by the same dose administered every 12 weeks for up to 3 years or placebo.[7] The study enrolled 951 patients and met its primary endpoint of relapse free survival (RFS) in 2.7 years. The RFS for patients receiving ipilimumab was 26.1 months compared to 17.1 months in the placebo group (hazard ratio 0.75, 95% CI 0.64-0.90, p=0.0013)(Table 2). An updated report after 5.3 years of median follow-up confirms the improvement in RFS (40.8 versus 30.3%, HR 0.76) as well as in OS (65.4 versus 54.4%, HR 0.72). The FDA approved ipilimumab at 10mg/kg in 2011 for patients with stage III melanoma, however, this study has been criticized for the dose chosen. In the metastatic setting ipilimumab is administered at 3mg/kg, and the higher dose of 10mg/kg is associated with significantly more toxicity. In the EORTC 18071 study, 48.8% of patients discontinued therapy owing to drug-related adverse events. Grade 3 or 4 toxicities included diarrhea, colitis, hypophysitis, hypothyroidism, elevated levels of transaminases, and dermatologic issues (Table 3). The degree of toxicity raised the question as to whether the higher dose was required to achieve the advantage in survival. E1609 is a study that sought to address this question by randomizing patients with resected stage IIIB to IV disease to three different arms. Patients in Arm A received ipilimumab 10mg/kg intravenously every 3 weeks for four doses, followed by maintenance high-dose ipilimumab every 90 days for a maximum of four doses. Arm B received high-dose interferon alfa-2b for 1 month of induction, followed by maintenance subcutaneous injection three times per week for 48 weeks. Arm C received ipilimumab 3mg/kg on the same schedule as Arm A. E1609 accrued 1670 patients, 57% of patients in the higher

dose ipilimumab arm experienced Grade 3 or higher adverse event, thus, accrual to this arm was suspended early. In fact, treatment was discontinued during the first four doses in 53.8% of patients receiving 10mg/kg compared to 35.2% in those receiving lower dose ipilimumab. The median RFS at 3.1 years was not different between the two ipilimumab arms. Further survival data are expected to be reported later this year.

The toxicity and controversies related to ipilimumab may be inconsequential now with FDA approval of nivolumab in December 2017. Nivolumab is a human IgG4 monoclonal antibody against programmed death 1 (PD-1), a member of the CD28 superfamily that initiates inhibitory signals upon interaction with its ligand, PD-L.[8] PD-1 and its ligands play a range of immune-regulatory roles in T cell activation and tolerance. In a recent randomized double-blind phase 3 trial, patients with stage IIIB, IIIC, or completely resected stage IV melanoma were assigned to receive intravenous nivolumab 3mg/kg every 2 weeks or ipilimumab at 10mg/kg every 3 weeks for four doses then every 3 months for up to one year in both groups.[9] After 18 months of follow-up, the 1 year RFS was 70.5% in the nivolumab group compared to 60.8% in the ipilimumab arm (HR for disease recurrence or death 0.65, P<0.001). Furthermore, the discontinuance of therapy due to an adverse event strongly favored nivolumab, 9.7% compared to 42.6% with ipilimumab. Significant adverse events (Grade 3 or 4) were reported in 14.4% of patients receiving nivolumab and 45.9% in those receiving ipilimumab. Further trials are underway looking at combinations with both nivolumab and ipilimumab (CheckMate 915 trial [NCT03068455]).

Following the significant benefit reported with nivolumab, the data from a comparable trial with pembrolizumab, another anti-PD-1

antibody, was reported early on 351 of 409 planned events.[10] This trial included patients with stage IIIA, IIIB, and IIIC disease and all participants received 200mg of pembrolizumab every 3 weeks for one year. Follow-up data is limited due to the early reporting, but the primary endpoint of one year RFS was 75.4% versus 61% (HR: 0.57; 98.4% CI 0.43 to 0.74; $p<0.001$). Tolerance was similar to the nivolumab group with 13.8% stopping therapy due to a side effect.

Both the nivolumab and pembrolizumab studies examined some important subgroups. The nivolumab study divided patients into two groups based on PDL-1 status: those expressing less than 5% or those expressing more than 5%. The majority of patients (approximately 61%) in both treatment groups fell into the less than 5% expression level. While all patients derived benefit from anti-PD-1 therapy, there was a higher probability of recurrence free survival at 12 months if the PDL-1 expression was greater than 5%. The pembrolizumab study used a different PD-1 antibody platform and scoring system that divided patients into at least 2% expression, and those with less than 2%. Again, there was a higher chance of one year RFS in the group with higher expression (77% v 62.6%) but both treatment subgroups had better responses than the placebo group. Both studies also examined whether patients had a BRAF mutation in their tumors and both showed patients derived benefit from the immunotherapy regardless of mutation status.

Table 2. Survival Outcomes for Adjuvant Therapies

| Study Drug | Stage | 1y RFS (%) | | (18 mo) or 3y RFS (%) | | Median RFS (months) | | Overall Survival | |
|---|---|---|---|---|---|---|---|---|---|
| Interferon v placebo | IIC-IIIC | NR | NR | NR | NR | 20.4 | 12.0 | 3.8 yr median | 2.8 yr |
| Ipilimumab v placebo | IIIA-C | NR | NR | 46.5 | 34.8 | 27.6 | 17.1 | 65.4% (at 5yr) | 54.4% (at 5yr) |
| Nivolumab v ipilimumab | IIIB- IV | 70.5 | 60.8 | (66.4) | (52.7) | NR | NR | NR | NR |
| Pembrolizumab v placebo | IIIA-C | 75.4 | 61.0 | (71.4) | (53.2) | NR | NR | NR | NR |
| Dabrafenib/ Trametinib v placebo | III- IV | 88 | 56 | 58 | 39 | NR | 16.6 | 86% (at 3y) | 77% (at 3y) |

**Section 4: Targeted Therapy**

BRAF-targeted therapy in melanoma has followed a similar and concurrent development pathway as immune therapy. BRAF is part of the mitogen activated protein kinase (MAPK) pathway involving RAS-RAF-MEK-ERK. The most common BRAF mutation in melanoma is the V600E substitution which results in constitutive activation of the MAPK pathway. Monotherapy with either BRAF or MEK inhibitors have shown benefit in the metastatic setting, while the combination of BRAF and MEK inhibition shows increased benefit over either agent alone.[11, 12] This combination has been studied in the adjuvant setting and on the basis of the COMBI-AD trial, the FDA approved dabrafenib (BRAF inhibitor) in combination with trametinib (MEK inhibitor) in April of 2018.[13] In this study investigators randomized 870 patients to active therapy versus placebo. Eligible patients had stage III completely resected melanoma with centrally confirmed BRAF V600E or

V600K mutation. Patients received standard doses of dabrafenib 150mg twice daily and 2mg trametinib once daily for one year. The trial met its primary endpoint of RFS with 37% of patients in the treatment arm having relapsed compared with 57% in the placebo arm (HR for relapse or death: 0.47; 95% confidence interval [CI], 0.39 to 0.58; P<0.001). The median RFS was 16.6 months in the placebo group and has not yet been reached in the treatment group. An interim OS analysis was conducted once the primary endpoint for RFS was met. There were 60 deaths in the treatment group versus 93 in the placebo group (HR: 0.57; 95% CI, 0.42 to 0.79; P=0.0006 [present significance boundary P=0.000019]). The study authors were careful to note that while the early data appears encouraging, this did not meet significance by the prespecified conservative significance boundaries, and longer follow up will be reported later. Patients had equal access to immune therapy after progression – with 16% of patients receiving this treatment in both arms. Notably, only 63% of patients completed the full year of intended therapy. There were 41% Grade 3 or 4 adverse events on the therapy arm versus 14% in the placebo group, similar to ipilimumab in percentage, although only 25% of all patients had to stop therapy due to these events. Secondary malignancies, a notable side effect of BRAF therapy, showed low incidence, but appeared similar across treatment groups for both cutaneous (squamous and basal cell carcinomas) and noncutaneous malignancies.

Early results have also been published for the BRAF inhibitor vemurafenib alone in the adjuvant setting (BRIM8 trial).[14] This trial included stage IIC through IIIC disease, however the primary endpoint of disease free survival was limited to the 184 patients in the IIIC group. With median RFS of 23.1 versus 15.4 months (HR 0.80, 95% CI 0.0.54-1.18), the trial did not meet its

primary endpoint. However, for the combined 384 patients in the other groups median disease-free survival was not reached in the investigational group versus 36.9 months (HR 0.54, 95% CI 0.37-0.78). Additional study and follow up will be needed in this setting before vemurafenib is approved.

Table 3. Adverse Events in Adjuvant Therapy

| | **Any Grade (%)** | | **Grade 3/4 (%)** | | **Stopped due to AE (%)** | | **Stopped due to relapse (%)** | |
|---|---|---|---|---|---|---|---|---|
| Ipilimumab v placebo | 98.7 | 91.1 | 54.1 | 26.2 | 53.3 | 4.6 | 28.7 | 59.5 |
| Nivolumab v ipilimumab | 96.9 | 98.5 | 14.4 | 45.9 | 9.7 | 42.6 | 26.7 | 22.3 |
| Pembrolizumab v placebo | 77.8 | 66.1 | 14.7 | 3.4 | 13.8 | 2.2 | 21.4 | 35.7 |
| Dabrafenib/ Trametinib v placebo | 97 | 88 | 41 | 14 | 26 | 3 | 5 | 41 |

**Section 5: Discussion**

Adjuvant therapy for melanoma has evolved significantly in recent years, moving beyond interferon which required a very serious discussion with the patient weighing the toxicity of the treatment after a possibly curative surgery against the risk of relapse, at a time when there were few effective subsequent therapies. In contrast, the rapid development of immunotherapy and targeted therapy has shown dramatic improvements in both efficacy and tolerability. This has allowed adjuvant therapy to become widely adopted, but has also created a number of questions.

The first question that arises is how this impacts the initial diagnosis and staging of melanoma. At present, interferon remains the only FDA approved therapy for stage IIC patients, so in order to qualify for the

newer adjuvant therapies there must be adequate sentinel lymph node sampling. If the entire lesion is excised in a diagnostic biopsy, the draining dermal lymphatic channels are disrupted which can complicate identification of sentinel lymph nodes on subsequent procedures. For this reason the NCCN guidelines recommend only a punch biopsy to establish the diagnosis of melanoma, with definite resection by wide local excision and sentinel lymph node sampling to occurring separately.

The next question is how to appropriately manage patients identified as having nodal metastatic disease (stage III). The standard of care previously was to undergo full lymph node dissection, but recent studies have shown that in patients with stage IIIA disease (microscopic lymph node metastases) there was no survival benefit to full dissection. Another study showed only a local relapse benefit to nodal dissection, suggesting that surgical management may not improve survival.[15, 16] Now with effective adjuvant therapy, the role of full nodal dissection is unclear and will need further study.

The third question relates to the sequence of therapy in patients with BRAF mutations who would qualify for both targeted and immunotherapy. Importantly both trials of PD-1 immunotherapy examined the BRAF status of their patients and found that patients with BRAF mutations derived benefit from immunotherapy. Additionally, BRAF inhibitors in the metastatic setting show a limited duration of therapy before tumors develop one of a number of resistance mechanisms. It is unclear if such therapy given earlier in the disease course when tumor burden is lower would provide more durable benefit than that seen in the metastatic setting. It is also worth noting that only 14% of patients in the COMBI-AD trial received subsequent BRAF targeted therapy compared with 32% of the placebo

group. As such it is not known whether these patients would respond to re-challenge in the metastatic setting after prior exposure to BRAF therapy. Finally, BRAF therapy comes with a higher toxicity rate than immunotherapy and a small but known risk of secondary malignancy. For these reasons, our preference has been to treat with immunotherapy and reserve BRAF therapy for the metastatic setting except in patients have a contraindication to immune therapy.

Finally, in the era of responsible, cost-effective medicine the appropriate interval for routine scans in a population that has ideally received curative therapy has not been well defined. For clinical trial purposes, patients typically received scans every 3 months for the first 2 years, every 6 months out to 5 years, than annually thereafter. This follows a similar paradigm to what is used in colon cancer treatment. Another model could be adapted from breast cancer in which routine bloodwork and scans are done only if new symptoms guide further evaluation, except for routine screening mammography, in this case substituting appropriate dermatologic screening exams. The anticipated cure rate for melanoma is closer to that of colon cancer but as we get long term survival data, and a rising disease prevalence as melanoma patients live longer, this may be an area of future debate.

**Section 6: Conclusion**

Melanoma has seen dramatic improvements in survival with the development of novel agents utilizing immune therapy and specific BRAF targeted therapies. These agents have demonstrated impressive gains in survival in the adjuvant setting and should be considered the new standard of care. As more new agents are approved there will be a number of questions related to the appropriate treatment sequencing and ongoing management of these patients.

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