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# **Is Ipilimumab an effective treatment in patients diagnosed with metastatic melanoma?**

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A Selective Evidence Based Medicine review

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
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## ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not ipilimumab is an effective treatment in patients diagnosed with metastatic melanoma.

Study Design: Review of three English primary studies published between 2009 and 2010.

Data Sources: Randomized, controlled, double-blind clinical studies comparing ipilimumab +/- gp100 peptide to a placebo +/- gp100. Studies were found using PubMed and Cochrane databases.

Outcomes Measured: Each of the studies measured outcomes of disease progression and overall survival. Response rate to treatment was also measured in two studies. Measurement of these outcomes was achieved utilizing the following classifications systems: [TNM] categorization, & Kaplan-Meier product-limit method of determining survival rates.

Results: In the Hodi et al. study the median overall survival was greater among patients receiving ipilimumab plus glycoprotein100 (gp100), as compared to patients receiving gp100 alone. In the Weber et al. study the median overall response rates were higher for those receiving ipilimumab 10 mg/kg alone, in comparison to ipilimumab 10 mg/kg with budesonide (blind). Subjects with more severe irAEs (immune related adverse events) experienced better disease control compared to those with less serious irAEs. A dose-dependent relationship was illustrated in the Wolchok et al. study; best overall response rate was notably higher for those receiving a higher dose of ipilimumab, opposed to a lower dose.

Conclusion: The results of all three of the reviewed RCT's and randomized double-blind studies demonstrated that ipilimumab shows activity in advanced melanoma. According to Hodi et al., ipilimumab may improve overall survival. The study done by Wolchock et al. provides evidence of a dose-dependent relationship on efficacy of ipilimumab, along with irAEs. In terms of safety, it was reported that most adverse events were manageable if not reversible with appropriate treatment, although serious & life-threatening effects were possible. Continued research is needed to determine the optimal dosing and regimen for reducing adverse effects and maximizing efficacy. Further research is desired, particularly at a dose of 10 mg/kg.

Key Words: melanoma, metastatic, skin cancer, treatment, ipilimumab, immunotherapy, CTL antigen-4

## INTRODUCTION

Skin cancer is the most common cancer in the United States, United Kingdom, and Australia.<sup>1</sup> Melanoma, by far, accounts for the greatest number of deaths due to skin disease.<sup>2</sup> In 2009, “58,094 cases of melanoma were diagnosed in the United States”, with 33,041 of those men and 25,053 cases in women. Melanoma makes up approximately 5% of all cancers. Tragically, one in four cases of melanoma occurs before the age of 40. There were a staggering 8,461 deaths in the U.S. in 2009 from melanoma alone. Metastatic melanoma, meaning the spread of cancer from the primary site to other areas of the body, occurs in 15–26% of stage I and stage II melanoma. The single most important prognostic factor is depth of tumor. Tumor thickness in millimeters, <1mm, 2–4 mm, and > 4 mm dictate ten year survival rates of 95%, 55%, and 30%, respectively (Figure 1). In the case of distant metastases, 5-year survival actually plummets to even less than 10%.<sup>1</sup> According to the *American Joint Committee on Cancer stage IV*, the median survival of patients with melanoma who have distant metastases is less than 1 year.<sup>3</sup>

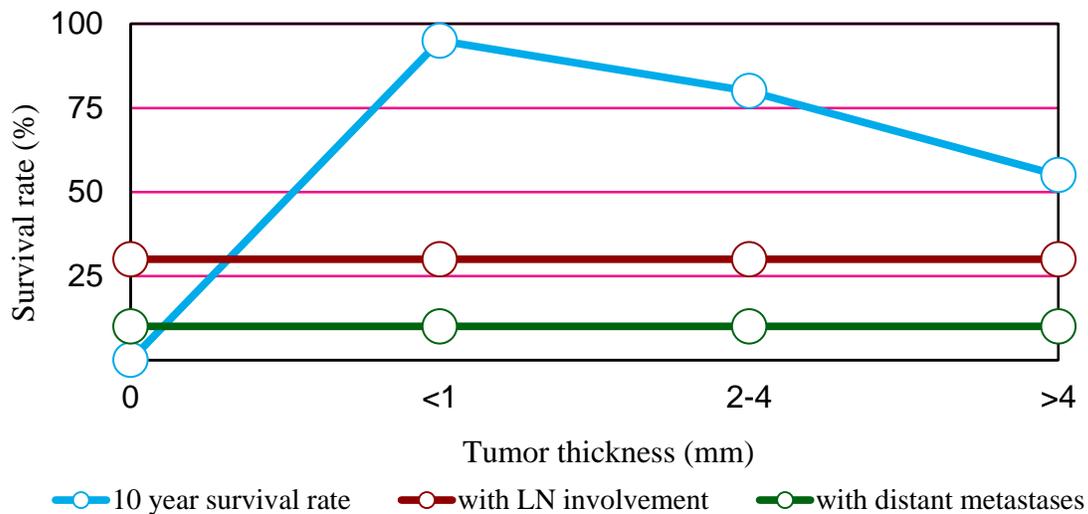


Figure 1. Survival rates of melanoma -- related to tumor thickness in millimeters<sup>1</sup>

The current treatment modality for melanoma is largely surgical excision with safety margins dictated by stage and tumor thickness, possibly including lymph node dissection. Metastatic melanoma, on the other hand, is essentially untreatable. No treatment is approved beyond the first-line therapy for metastatic melanoma. The standard of care being enrollment in a clinical trial.<sup>3</sup> Medical management of distant metastases is considered palliative, at best, considering the high incurability rate.<sup>1</sup> Unfortunately, melanoma often spreads to distant sites initially, including lymph nodes, skin and subcutaneous tissues. Palliative care consists of chemotherapeutic agents, radiation, and possibly a clinical trial medication. Dacarbazine is generally accepted as the most effective monotherapeutic agent. A chemotherapeutic treatment of stage IV melanoma that has been found disappointing, showing only a <20% response rate and absolutely no influence on overall survival.<sup>2</sup> The amount of resources required and costs of treatment increase considerably after evolution of metastases in individuals with melanoma. Mean health care costs increased from \$22,260 at baseline to \$113,940 per patient a year (p-value <0.01).<sup>4</sup> These statistics should be both relevant and concerning to the Physician Assistant (PA) professional, as accepted members of healthcare teams, PA's are working in specialties, inclusive of dermatology and surgery. Despite these exorbitant costs, up until this point, no treatment has proved effective in preventing or arresting progression of the disease.

Ipilimumab, also known as MDX-010 or MDX-101, is a human monoclonal antibody that blocks cytotoxic T-lymphocyte antigen 4. It is intended to be used as a drug to activate the immune system. Classified as a vaccine, ipilimumab works with the immune system to boost the body's response against melanoma cells. The mechanism of action to explain the drug's function is through blocking the negative feedback on T-cells, it more to attack melanoma cells. This type of immune therapy is the latest in attempts to halt progression of metastatic melanoma in

hopes of improving prognosis. Increasing overall survival among patients with metastatic melanoma has been an evasive goal. No therapy has proven effective in a phase 3, randomized, controlled trial to improve overall survival in individuals diagnosed with metastatic melanoma.<sup>3</sup> Ipilimumab is showing promising potential in this area. The precise efficacy and safety of ipilimumab in patients with advanced melanoma are not widely known.<sup>2</sup>

## OBJECTIVE

The objective of this systematic review is to determine whether or not ipilimumab is an effective treatment in patients diagnosed with metastatic melanoma.

## METHODS

All three randomized, double-blind studies selected met the criteria for subjects who were at least 16 years old with a medical diagnosis of unresectable stage III or IV melanoma, who had received prior treatment.<sup>3,5,6</sup> Two of the three studies limited the population to only 18 years and older.<sup>3,5</sup> Criteria for exclusion for participation in the study were concomitant treatment, or less than a four year life expectancy.

Interventions included ipilimumab 3 mg/kg or 10 mg/kg compared to a control with or without glycoprotein 100 (gp100).<sup>3,5,6</sup> In the Hodi et al study, the treatment groups receiving ipilimumab at a dose of 3 mg per kilogram alone & those receiving ipilimumab with gp100 peptide vaccine were compared to a control group receiving a placebo with gp100. Treatment was administered once every 3 weeks for up to four treatments.<sup>3</sup> The Weber et al. study compared ipilimumab 10 mg/kg with budesonide to a control (ipilimumab 10 mg/kg), administered once every 3 weeks for four doses.<sup>5</sup> In the crossover study by Wolchok et al., ipilimumab was compared at different doses, 10 mg/kg and 3 mg/kg, administered intravenously once every 3 weeks for four cycles followed by maintenance therapy every 3 months.<sup>6</sup> Outcomes of interest included survival rate, progression of disease, and adverse events.

A detailed search for the studies was conducted December 2010 to February 2011 with the key words, “melanoma”, “metastatic”, “skin cancer”, “treatment”, “ipilimumab”, “immunotherapy”, and “CTL antigen-4”. The Cochrane Library and PubMed (U.S. National Library of Medicine) databases were utilized. Only English language articles published in peer-reviewed journals were selected. Articles were subsequently narrowed according to relevance and outcomes pertinent to patients. Inclusion criteria for the selection of articles involved randomized, controlled, published after 2009, and having patient oriented evidence which matters (POEMS). The only exclusion criteria were if they were published before 2007, due to a pre-existing meta-analysis reported at that time. The statistics reported included 95% confidence interval. The Wolchok et al study reported a p-value  $<0.05$  being statistically significant.<sup>6</sup> P-values for other studies were not statistically significant. Studies were evaluated for relative risk reduction (RRR), absolute risk reduction (ARR), and numbers needed to treat (NNT). Demographics of the final studies selections are presented in Table 1.<sup>3,5,6</sup>

Table 1: Demographics of included studies <sup>3,5,6</sup>

Study	Type	# ntc	Age	Inclusion	Exclusion	W/D	Intervention
Hodi 2010 <sup>3</sup>	Randomized double-blind, phase III study	403; 137	>18 yo	Patients at least 18 yo; diagnosis of unresectable stage III or IV melanoma & received a previous therapy containing: dacarbazine, temozolomide, fotemustine, carboplatin, or interleukin-2; positive HLA-A*0201; normal hematologic, hepatic, & renal fx; no systemic tx in the last 28 days; Life expectancy of at least 4 months; ECOG performance status of 0-1	<18 yo; primary ocular melanoma Any cancer patient is disease-free for less than 5 years; previous anti-CTLA-4 antibody or cancer vaccine; autoimmune disease; pregnant; concomitant tx with any nonstudy anticancer therapy or immunosuppressive agent; long-term of systemic immunosuppressive agent	380;131	Randomized to receive ipilimumab 3 mg/kg of body weight plus gp100 peptide vaccine; ipilimumab plus gp100 placebo -administered QD every 3 weeks for 4 treatments
Weber 2009 <sup>5</sup>	Randomized double-blind, placebo-controlled, multicentre, phase II trial	115	>18 yo	Patients at least 18 yo; histological diagnosis of unresectable & measurable stage III or IV melanoma; previous systemic therapy or untreated; Life expectancy at least 4 months; ECOG performance status of 0-1	<18 yo, ocular melanoma; Active untreated CNS metastases; malignancies had been disease-free for <5 years; Autoimmune disease; investigational drugs within 4 weeks; Previous tx with an anti-CTLA-4 antibody; immunosuppressive agent	N/A	Randomized to receive ipilimumab 10 mg/kg with daily blinded budesonide -administered every 3 weeks for four doses
Wolchok 2010 <sup>6</sup>	Randomized double-blind, multicentre parallel group study	217	>16 yo	Patients at least 16 yo; histological diagnosis of unresectable & measurable stage III or IV melanoma; at least 1 previous tx with antitumor regimen; progressed or failed response within 12 weeks or unable to tolerate regimen	<16 yo	3	Randomized to receive ipilimumab 10 mg/kg -administered every 3 weeks for 4 cycles (induction) followed by maintenance every 3 mo.

## OUTCOMES MEASURED

The outcomes measured to determine response to therapy were survival rate and progression of disease. Methods employed to measure such outcomes were the WHO criteria in assessing lesions, the Tumor-Node-Metastasis [TNM] categorization for melanoma & Kaplan-Meier product-limit method.<sup>3,5,6</sup>

Each of the three studies measured outcomes of disease progression and overall survival. Response rate to treatment was also measured in two of the three studies, the Weber et al. study & Wolchok et al. study. All three studies applied the WHO criteria to ascertain overall response according to combined assessments of index & non-index lesions and the Kaplan-Meier product-limit method of determining survival rates. Measurement of outcomes in the Hodi et al study were also achieved utilizing the Tumor-Node-Metastasis [TNM] categorization of the American Joint Committee on Cancer, classification system.<sup>3,5,6</sup>

In addition, the Wolchok et al. study incorporated imaging in the form of CT or MRI, documenting a baseline which was compared at each tumor assessment. Cutaneous lesions were evaluated and recorded with digital photography. The primary objective in this study was overall response rate, simply defined by the proportion of patients with complete or partial responses according to the *World Health Organization* (WHO) criteria. Secondary objectives analyzing progression of the disease included: disease control rate and median overall survival.<sup>6</sup>

## RESULTS

The results assessing the efficacy pertaining to the primary outcome were presented as dichotomous data in all three studies. While 131 of participants in the experimental group withdrew from the Hodi et al. study, and 3 participants withdrew from the Wolchok et al. study, the efficacy analyses were presented as an intention to treat.<sup>3,5,6</sup> Hodi et al. demonstrated higher

rates of overall survival in the ipilimumab (experimental) group opposed to those receiving gp100 (control). (Table 2).<sup>3</sup>

Table 2: Efficacy of Ipilimumab in Treatment of Advanced Melanoma - NNT<sup>3,5,6</sup>

Study	experimental group (EER)	control group (CER)	p-value	RRR	ARR	NNT
Hodi, 2010	45.6%	43.6%	NS	5%	2%	50 pts
Weber, 2009	12.1%	15.8%	NS	0.23%	-3.7%	-27 pts*
Wolchok, 2010	11.1%	4.2%	p=0.0015	1.6%	6.9%	15 pts

RRR=Relative Risk Reduction ARR=Absolute Risk Reduction NNT=Numbers Need to Treat

*\* This negative value for NNT indicates that for every 27 patients treated with the experimental treatment (ipilimumab budesonide), 1 patient fewer had improved disease compared to the control.*

*NS = p-value not significant for the dichotomous data presented in the study.*

The median overall survival was approximately 10 months among patients receiving ipilimumab with or without gp100, as compared with 6.4 months among patients receiving gp100 alone.

Median overall survival proved greater among patients receiving ipilimumab plus glycoprotein100 (gp100), as compared to patients receiving gp100 alone. A greater reduction in risk of progression was seen with ipilimumab alone as compared with gp100 alone. The highest percentage of patients with an objective response to treatment or disease which remained stable was in the ipilimumab-alone group, this group had a best overall response rate of 10.9%.<sup>3</sup>

In the Weber et al. study the median overall response rates were higher for those receiving ipilimumab alone, in comparison to ipilimumab with budesonide (blind). The best overall response rates were 15.8% for those receiving ipilimumab, 12.1% receiving ipilimumab 10 mg/kg with budesonide, median overall survival of 19.3 and 17.7 months, respectively (Table

2). Patients with grade 3 to 4 irAEs (immune-related adverse events), experienced better disease rates as compared to patients with grade 0 to 2 irAEs. Even so, noteworthy clinical benefit was still experienced by many patients with grade 1 to 2 irAEs.<sup>5</sup>

The Wolchok et al. study utilized a cross-over study to compare a range of ipilimumab doses. The best overall response rates illustrated a dose-dependent relationship, “11.1% for 10 mg/kg, 4.2% for 3 mg/kg, and 0% for 0.3 mg/kg” (Table 3).<sup>6</sup> Immune-related adverse events of any grade became apparent in, “50 of 71, 46 of 71, and 19 of 72 patients at doses of 10 mg/kg, 3 mg/kg, and 0.3 mg/kg, respectively” (Table 4).<sup>6</sup>

Table 3: Efficacy of Ipilimumab as related to dosage<sup>6</sup>

Study	Low dose (3 mg/kg)	High dose (10 mg/kg)	p-value	CI
Wolchok, 2010	4.2% (0.9–11.7)	11.1% (4.9–20.7)	p=0.0015*	95%

*\*Statistically significant p-value reported. P-values deemed significant if <0.05. Two-sided 95% CI, 0.5 significance level was reported for Wolchok et al. study in comparison of best overall response rate to low-dose vs. high does ipilimumab.*

Table 4: Incidences of Adverse Events as Related to Ipilimumab Dose<sup>6</sup>

Study	Ipilimumab (0.3 mg/kg)	Ipilimumab (3 mg/kg)	Ipilimumab (10 mg/kg)
Wolchok, 2010	26%	65%	70%

Noteworthy, is the positive correlation between increase in dose and seemingly efficacy; unfortunately this association comes with an increase in reported irAEs (Table 4). The most common immune-related adverse event (irAE) was diarrhea. Diarrhea was reported in as many as 31%, 35 %, 28% of the patients receiving ipilimumab for the studies Hodi et al., Weber et al., and Wolchok et al., respectively.<sup>3,5,6</sup> The majority experienced improvement of symptoms following administration of corticosteroids.<sup>3</sup>

## DISCUSSION

This selective EBM review of the Hodi, Weber, and Wolchok et al. studies sought to determine if ipilimumab is an effective treatment for metastatic melanoma. Ipilimumab, trade name, *Yervoy*, is a human monoclonal antibody intended to stimulate the immune system. The vaccine is administered as an intravenous infusion designed to interfere with activity of cytotoxic T-lymphocyte antigen 4. Essentially, the drug blocks the negative feedback on T-cells, which ultimately promotes more of these immune cells to attack melanoma cells.<sup>7</sup> Common adverse events to ipilimumab include nausea, diarrhea, rash, and fatigue.<sup>6</sup> There is a black box warning in effect for ipilimumab due to serious and potentially life-threatening side-effects of the drug including colitis, hepatitis, toxic epidermal necrolysis.<sup>7</sup> Ipilimumab shows an association with stimulation of immune response against advanced melanoma.<sup>3,5,6</sup> This radical form of immune therapy is the latest in attempts at preventing progression of metastatic or advanced melanoma.

The Hodi et al. study itself was designed to examine the role of gp100 in conjunction with ipilimumab. No additional therapeutic benefit was ascertained with inclusion of gp100. Although no difference in overall survival was detected between the experimental (ipilimumab) and control (ipilimumab plus gp100) groups; Ipilimumab, with or without a gp100 peptide vaccine, did improve overall survival in patients with previously treated metastatic melanoma.<sup>3</sup> Ipilimumab monotherapy showed a clear dose-dependent effect on biological and clinical variables in patients with advanced melanoma. The best overall response rate was associated significantly with increasing dose of ipilimumab.<sup>6</sup> The studies chosen for analysis had several limitations, including statistical significance, sample size, drop-out rate, biased of funding. Both the Hodi et al. and Weber et al. study lacking statistically significant p-values, limits the validity and accuracy of the data reported.<sup>3,5</sup> The small sample size of 113 in the Weber et al. research

and drop out rates as high as 40% in the Hodi et al. research restrict conclusions from data collected on this population.<sup>3</sup> A conflict of interest may be created by funding of all articles by Bristol-Myers Squibb, manufacturer of ipilimumab. In addition, each of the three studies attempted to measure progression or overall survival, but using different means for assessment resulting in an inconsistency and difficulty in comparison. Also lacking in continuity, were the experimental and control groups chosen, which varied in each study.

## CONCLUSIONS

The studies reviewed illustrate an association between ipilimumab and improvement in overall survival of patients with previously treated metastatic melanoma.<sup>3,5,6</sup> However, the data is not sufficient to prove statistical significance of ipilimumab as an effective treatment for advanced melanoma. The research is essentially inconclusive, without statistically significant p-values for all studies investigated, the most that can be confirmed is an association. Continued research is needed to determine statistically significant relationship between ipilimumab as a treatment for metastatic melanoma. Additionally, the optimal dosing and regimen for reducing adverse effects and maximizing efficacy, required further study. Future research is desirable, particularly at a dose of 10 mg/kg ipilimumab. Ideally, a systematic review able to compare multiple studies involving solely ipilimumab at optimal dosage to a control of a placebo consistent between all articles analyzed.

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