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Jacob L. Toscano

*Philadelphia College of Osteopathic Medicine*

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# **Is Combination Nivolumab And Ipilimumab Safe And Effective In Patients With Melanoma?**

Jacob L. Toscano, PA-S

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  
Philadelphia, Pennsylvania

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## **ABSTRACT**

**Objective:** The objective of this selective EBM review is to determine whether or not combination nivolumab and ipilimumab is safe and effective in patients with melanoma.

**Study design:** Review of two randomized controlled trials (RCTs) published in 2015, and one cohort study published in 2013.

**Data Sources:** All of the articles were published in English language, peer reviewed journals and were found using PubMed and Cochrane databases.

**Outcomes Measured:** The safety of combination nivolumab and ipilimumab was measured by treatment-related grade 3 or 4 adverse effects. The effectiveness was measured by progression-free survival, which is based on disease progression and death.

**Results:** Wolchok et al. (2013) conducted a cohort study and found that concurrent therapy with nivolumab and ipilimumab had a similar safety profile to previous studies with monotherapy (NNH = 3), and the adverse effects were generally reversible. In a randomized controlled trial, Larkin et al (2015) found that combination nivolumab and ipilimumab was more effective than nivolumab monotherapy in preventing death or disease progression (NNT = -3;  $p < 0.01$ ). Postow et al (2015) conducted a randomized controlled trial that found combination nivolumab and ipilimumab more effective than ipilimumab monotherapy in preventing death or disease progression (NNT = -3;  $p < 0.01$ ).

**Conclusions:** The cohort study conducted by Wolchok et al showed that nivolumab-plus-ipilimumab had an acceptable safety profile, as its safety was qualitatively similar to monotherapy and the effects were generally reversible. However, it is difficult to conclude that combination nivolumab and ipilimumab is safe in treatment of melanoma based on this one study. The two RCTs demonstrated that combining nivolumab and ipilimumab is effective at preventing death or disease progression of melanoma compared to using nivolumab or ipilimumab alone.

**Key Words:** Nivolumab, Ipilimumab, Melanoma

## Introduction

Melanoma is defined as a malignant tumor arising from melanocytes.<sup>1</sup> Although not the most common type of skin cancer, it is considered the most dangerous. Clinical features of pigmented lesions suspicious for melanoma are an irregular notched border where the pigment appears to be spreading into the normal surrounding skin, as well as color variegation, asymmetry, diameter greater than 6mm, and any evolution in existing lesions.<sup>2</sup> The exact cause of all melanomas remains unclear; however, the majority of melanomas are caused by ultraviolet rays.<sup>3</sup> Ultraviolet rays damage the DNA in skin cells, which leads to mutations in certain genes, which ultimately leads to uncontrolled skin cell growth and division.

Melanoma has a significant impact on the United States population. There were approximately 76,100 new melanoma cases diagnosed in 2014.<sup>2</sup> Also, each year in the United States, an estimated 9,710 deaths are caused by melanoma.<sup>2</sup> The annual medical costs related to melanoma in 2011 was \$8.1 billion.<sup>4</sup> There is no exact estimate available for the number of health care visits associated specifically with melanoma. However, 4.9 million people were treated for skin cancer in general in 2011.<sup>4</sup>

Currently, there are several treatment options for melanoma based on the severity of the disease. For more localized disease, surgical excision is the treatment of choice. Sentinel lymph node biopsy may also be done. For metastatic melanoma, there are a number of immunotherapies available, such as interleukin 2, ipilimumab, nivolumab, vemurafenib, dabrafenib, and trametinib. Chemotherapeutic agents, such as dacarbazine, temozolomide, paclitaxel, and carboplatin, may also be useful in metastatic melanoma. All of the aforementioned treatment options are important in the treatment of melanoma. However, there are shortcomings to these treatment options, as evidenced by the estimated 9,710 annual deaths due to melanoma. This

paper evaluates two randomized controlled trials and one cohort study comparing the safety and effectiveness of combination nivolumab and ipilimumab to monotherapy nivolumab or monotherapy ipilimumab.

### **Objective**

The objective of this selective EBM review is to determine whether or not combination nivolumab and ipilimumab is safe and effective in patients with melanoma.

### **Methods**

The two randomized controlled trials and one cohort study in this review were all conducted with patients greater than 18 years of age diagnosed with melanoma. The intervention used was combination nivolumab and ipilimumab. This intervention was compared to monotherapy nivolumab and monotherapy ipilimumab. The outcome measured in the cohort study was safety, which was determined by treatment-related grade 3 or 4 adverse effects. The outcome measured in the two randomized controlled trials was effectiveness, which was determined by progression free survival based on disease progression or death.

To determine which articles to use in this review, keywords used were nivolumab, ipilimumab, and melanoma. All of the articles utilized were published in English and in peer reviewed journals. The articles were searched via PubMed and selected based on their relevance to the clinical question posed in this review and if they included patient oriented outcomes. Inclusion criteria included studies that were either randomized controlled trials or cohort studies. Exclusion criteria consisted of patients under the age of 18 years old. Statistics reported and used were numbers needed to treat (NNT), numbers needed to harm (NNH), and p-values.

**Table 1:** Demographics and Characteristics of included studies

Study	Type	# of pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Wolchok, 2013 <sup>5</sup>	Cohort	86	22-89	At least 18 years old, diagnosis of measurable, unresectable, stage III or IV melanoma, ECOG performance status of 0 or 1, adequate organ function, life expectancy of at least 4 months	Active, untreated central nervous system metastasis, history of autoimmune disease, previous therapy with T-cell modulating antibodies, HIV, hepatitis B or C	0	Escalating doses of IV nivolumab and ipilimumab administered concurrently every 3 weeks for 4 doses, followed by nivolumab alone every 3 weeks for 4 doses; combined treatment was subsequently continued every 12 weeks for up to 8 doses
Larkin, 2015 <sup>6</sup>	RCT	945	18-90	Histologically confirmed stage III or IV melanoma, at least 18 years old, ECOG performance status of 0 or 1, availability of tissue collected from metastatic or unresectable tumors, and known <i>BRAF</i> V600 mutation status	ECOG performance status score of 2 or higher, active brain metastases, ocular melanoma, autoimmune disease	0	Combination nivolumab and ipilimumab Vs. nivolumab monotherapy Vs. ipilimumab monotherapy
Postow, 2015 <sup>7</sup>	RCT	142	27-87	Histologically confirmed stage III or IV melanoma, known <i>BRAF</i> V600 mutation status, ECOG performance status of 0 or 1	Active brain metastases, uveal melanoma, serious autoimmune disease	0	Combination nivolumab and ipilimumab Vs. ipilimumab monotherapy

**Outcomes Measured:** The outcomes measured in this review were safety and effectiveness of combination nivolumab and ipilimumab. Wolchok et al, in their cohort study, determined safety of nivolumab-plus-ipilimumab by measuring treatment-related grade 3 or 4 adverse effects. Larkin et al, as well as Postow et al, determined effectiveness of nivolumab-plus-ipilimumab by measuring progression-free survival, which is based on disease progression and death.<sup>5,6,7</sup>

## Results

The two randomized controlled trials and one cohort study included in this review had similar inclusion and exclusion criteria, and no patients were withdrawn from the studies (Table 1). The cohort study examined the safety of combining nivolumab and ipilimumab for use in the treatment of melanoma. The two randomized controlled trials compared the effectiveness of combining nivolumab and ipilimumab to treatment with monotherapy nivolumab or monotherapy ipilimumab (Table 1).

In the cohort study conducted by Wolchok et al, 86 total patients were included. 53 patients were given concurrent therapy with nivolumab and ipilimumab, which meant that these patients were given intravenous doses of nivolumab-plus-ipilimumab every 3 weeks for 4 doses, followed by nivolumab alone every 3 weeks for 4 doses.<sup>5</sup> The other 33 patients were treated with a sequenced regimen, which meant that these patients were previously treated with ipilimumab and subsequently treated with nivolumab every 2 weeks for up to 48 doses.<sup>5</sup> Grade 3 or 4 adverse effects were measured in both of these groups. 53% of the concurrent-regimen group showed grade 3 or 4 adverse effects and 18% of the sequenced-regimen group showed grade 3 or 4 adverse effects (Table 2).<sup>5</sup> The NNH for the concurrent-regimen group was measured to be 3, with a relative risk increase of 1.94 and an absolute risk increase of 35 (Table 2).

**Table 2:** Concurrent-regimen of nivolumab-plus-ipilimumab vs. sequenced-regimen of nivolumab-plus-ipilimumab comparison of grade 3 or 4 adverse effects (Wolchok et al, 2013)<sup>5</sup>

Treatment-related grade 3 or 4 adverse effects		<b>Relative risk increase (RRI)</b>	<b>Absolute risk increase (ARI)</b>	<b>Number needed to harm (NNH)</b>
Sequenced-regimen (CER)	Concurrent-regimen (EER)	$\frac{\text{EER} - \text{CER}}{\text{CER}}$	EER - CER	1/ARI
18%	53%	1.94	0.35	3

Larkin et al conducted a randomized controlled trial comparing the effectiveness of nivolumab-plus-ipilimumab to nivolumab alone. To measure the effectiveness, the authors used progression-free survival by examining disease progression or death. Of the 314 patients in the nivolumab-plus-ipilimumab group, 23.6% had disease progression or death, and of the 316 patients in the nivolumab monotherapy group, 50.8% had disease progression or death ( $p < 0.01$ ). Compared to the nivolumab monotherapy group, the nivolumab-plus-ipilimumab experimental group was found to have a NNT = -3, showing that for every 3 patients treated with nivolumab-plus-ipilimumab, 1 fewer patient had disease progression or death compared to nivolumab alone. (Table 3).



**Table 3:** nivolumab-plus-ipilimumab vs. nivolumab monotherapy comparison of disease progression or death

Disease progression or death		Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)
nivolumab alone (CER)	nivolumab-plus-ipilimumab (EER)	$\frac{EER - CER}{CER}$	EER - CER	1/ARI
50.8%	23.6%	-0.535	-0.272	-3

Postow et al conducted a randomized controlled trial comparing the effectiveness of nivolumab-plus-ipilimumab to ipilimumab alone. As Larkin et al did, Postow et al. measured effectiveness by examining disease progression and death. Of the 72 patients treated with nivolumab-plus-ipilimumab, 30 patients had disease progression or death, and of 37 patients treated with ipilimumab alone, 25 patients had disease progression or death ( $p < 0.01$ ).<sup>7</sup> When comparing the nivolumab-plus-ipilimumab group to the ipilimumab monotherapy group, the nivolumab-plus-ipilimumab group was found to have a NNT = -3, suggesting that for every 3 patients treated with nivolumab-plus-ipilimumab, 1 fewer patient had disease progression or death compared to ipilimumab alone (Table 4).

**Table 4:** nivolumab-plus-ipilimumab vs. ipilimumab monotherapy comparison of disease progression or death

Disease progression or death		Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)
ipilimumab alone (CER)	nivolumab-plus-ipilimumab (EER)	$\frac{EER - CER}{CER}$	EER - CER	1/ARI
68%	42%	-0.62	-0.26	-3

## Discussion

The studies presented in this review examined the safety and effectiveness of nivolumab-plus-ipilimumab. Although these drugs in combination proved effective, a major obstacle is the price of these drugs. These drugs are available in the United States, but to treat a typical patient with combination nivolumab and ipilimumab, it is estimated to cost \$295,566.<sup>8</sup> Even with some insurance coverage, these drugs may prove to be too expensive for many melanoma patients to afford. Another problem with this combination treatment may be some fatal adverse effects. Although Wolchok et al. concluded in their cohort study that nivolumab-plus-ipilimumab had an appropriate safety profile with no reported adverse effect related deaths, nivolumab has been observed in the past to be associated, although rare, with fatal toxic epidermal necrolysis and adrenal insufficiency.<sup>9</sup> Despite these rare adverse effects, there are no contraindications listed for the use of nivolumab or ipilimumab.<sup>9</sup> Though ipilimumab has only been used in melanoma thus far, nivolumab has been studied and used for other cancers as well, such as lung and renal cell.<sup>9,10</sup>

Although the studies used in this review had very high validity, it may have been beneficial if this review itself could have included more than two randomized controlled trials. There also seemed to be a relatively large difference in the sample sizes used in the randomized controlled trials, as the Larkin et al study included 945 patients, whereas the Postow et al study only included 142 patients. Despite the difference in sample size, both studies were double blind, randomized controlled trials that proved to be valid.

## **Conclusion**

After examination of the three studies included in this review, it is difficult to conclude that combination nivolumab and ipilimumab is safe in patients with melanoma, as only one study focused on the safety of the regimen. However, it does appear that combination nivolumab and ipilimumab is effective in patients with melanoma. Combination nivolumab-plus-ipilimumab yielded lower disease progression and death compared to either nivolumab or ipilimumab alone. The only flaw to really consider with these studies is the smaller sample size in the Postow et al study. Since nivolumab is currently being used and studied in other cancers, further research into the addition of ipilimumab in these cancers may be warranted, as ipilimumab has only been used in melanoma treatment to this point and seems to be effective when combined with nivolumab.

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