

# The Impact of Nonsteroidal Anti-Inflammatory Drugs, Beta Blockers, and Metformin on the Efficacy of Anti-PD-1 Therapy in Advanced Melanoma

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Disclosures of potential conflicts of interest may be found at the end of this article.

## ABSTRACT

Anti-programmed cell death protein-1 (anti-PD-1) therapy has greatly improved outcomes of patients with melanoma; however, many fail to respond. Although preclinical studies suggest a potentially synergistic relationship with anti-PD-1 therapy and certain concurrent medications, their clinical role remains unclear. Here, we retrospectively evaluated the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and other drugs in 330 patients with melanoma treated with anti-PD-1 therapy from four academic centers. In the cohort, 37% of patients used NSAIDs including aspirin (acetylsalicylic acid; ASA; 47%), cyclooxygenase (COX)-2 inhibitors (2%), and non-ASA/nonselective COX inhibitor NSAIDs (59%). The objective response rates (ORRs) were similar in patients with

NSAID (43.4%) and no NSAID (41.3%) use with no significant difference in overall survival (OS). There was a trend toward improved progression-free survival (PFS) in patients who took NSAIDs (median PFS: 8.5 vs. 5.2 months;  $p = .054$ ). Most patients (71.3%) took NSAIDs once daily or as needed. Multivariate analysis did not reveal an association with NSAID use with ORR, PFS, or OS. Concurrent use of metformin or beta blockers did not affect ORR, PFS, or OS. Our study found no conclusive association of concurrent NSAID or other medication use with improved outcomes in patients with melanoma treated with anti-PD-1 therapy. Larger and more systematic analysis is required to confirm these findings. *The Oncologist* 2020;25:e602–e605

## INTRODUCTION

Inflammation has been long recognized as a hallmark of cancer [1, 2]. Malignant tumors are often surrounded by immune cells with similarities to other inflammatory conditions [3]. Although an inflamed tumor suggests immune recognition of cancer neoantigens, cancers frequently evade the antitumor response through various escape mechanisms such as immune checkpoint upregulation or tumor-promoting inflammation (e.g., tumor-infiltrating macrophages). Although immune checkpoint inhibitors overcome some mechanisms of resistance, many tumors achieve immune evasion and fail to respond.

The use of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) is increasing in the U.S. population with recent estimates of 43 million and 29 million adults regularly

taking aspirin (acetylsalicylic acid; ASA) and NSAIDs, respectively [4–6]. Preclinical studies have demonstrated that a cyclooxygenase (COX)-dependent mechanism drives tumor growth and that inhibition of COX, when synergized with programmed cell death protein-1 (PD-1) blockade, leads to tumor suppression, suggesting that NSAIDs could improve the efficacy of anti-PD-1 therapies [7–9]. In addition, studies have suggested that other medications such as metformin and beta blockers may influence the outcomes of patients with advanced melanoma during treatment with PD-1 blockade or in other settings [10–15]. In this retrospective study, we evaluated the association of NSAIDs, beta blockers, and metformin with clinical outcomes in patients with advanced melanoma treated with anti-PD-1 therapy.

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## MATERIALS AND METHODS

We evaluated all patients with advanced melanoma treated with anti-PD-1 therapy (nivolumab or pembrolizumab) at four academic centers ( $n = 330$ ) including Melanoma Institute Australia ( $n = 46$ ), MD Anderson Cancer Center ( $n = 109$ ), Westmead Hospital ( $n = 53$ ), and Vanderbilt University Medical Center ( $n = 121$ ) from October 2009 to January 2016, with institutional review board approval prior to the study. Waiver from patient's consent was approved because of the retrospective nature of this study. Baseline demographic, clinical, concurrent drug use, and treatment data were obtained from electronic medical records. The type of NSAIDs were divided into ASA; COX-2 inhibitors; and non-ASA, nonselective COX inhibitor NSAIDs (hereafter referred to as "other NSAIDs"). Patients were included if NSAIDs were started before anti-PD-1 therapy or within 6 weeks after anti-PD-1 treatment initiation. The use of other concurrent medications at baseline and within 6 weeks of anti-PD-1 treatment initiation, including beta blockers and metformin, was collected. Response was defined by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria by cross-sectional imaging and provided by medical oncologist at each collaborating institution. Progression-free survival (PFS) and overall survival (OS) were described using the Kaplan-Meier method and compared between groups using the log-rank test. Comparison of response between groups was performed using chi-square testing. Univariate and multivariable logistic regression models were used to test differences in response and survival with various concurrent medications controlled for age, gender, lactate dehydrogenase (LDH), number of prior therapies, center, stage, and body mass index (BMI). All statistical analyses were performed in R version 3.5.0.

## RESULTS

### Baseline Characteristics

A total of 330 patients were included; 209 (63%) were male with a median age of 60 years (range, 16–86), and 237 (72%) were American Joint Committee on Cancer stage IV M1c (Table 1). Among these patients, 122 (37%) reported any NSAID use, including ASA and COX-2 inhibitors. Of those patients who used NSAIDs ( $n = 122$ ), 52% were on other NSAIDs only, 39% were on ASA only, 7% were on both NSAID and ASA, and 2% were on COX-2 inhibitors only. Of the 72 patients who took other NSAIDs, 51 (71%) took ibuprofen and 15 (21%) took naproxen. Data on dosing were available in 37 patients with 28 (76%) patients on only as needed dosing and 9 (24%) patients on daily (or less frequent) dosing. Of patients on ASA, most (86%) received <100 mg daily.

In terms of timing of concurrent medication, 8 and 55 patients started ASA and NSAID, respectively, after initiation of anti-PD-1 therapy. Furthermore, metformin and beta blockers were started in six and five patients, respectively, after initiation of anti-PD-1 therapy. Notably, nine patients developed arthritis/arthralgia or rheumatoid arthritis flare while on therapy.

**Table 1.** Patient demographics

Characteristic	( $n = 330$ ), $n$ (%)
Mean age (range), years	60 (16–86)
Male gender	208 (63)
Mean BMI (range)	27.6 (16.4–50.5)
Academic center	
MDACC	109 (33)
MIA	46 (14)
Vanderbilt	121 (37)
WMH	53 (16)
Elevated LDH	113 (34)
Stage	
IIIC/M1a	42 (13)
M1b	50 (15)
M1c/d	234 (72)
NSAID use	122 (37)
NSAID only	63 (19)
ASA only	47 (14)
Both NSAID and ASA	10 (3)
COX inhibitors	2 (1)
Other drugs	
Metformin	34 (10)
Beta blocker	65 (20)

Abbreviations: ASA, acetylsalicylic acid (aspirin); BMI, body mass index; COX, cyclooxygenase; LDH, lactate dehydrogenase; MDACC, MD Anderson Cancer Center; MIA, Melanoma Institute Australia; NSAID, nonsteroidal anti-inflammatory drug; WMH, Westmead Hospital.

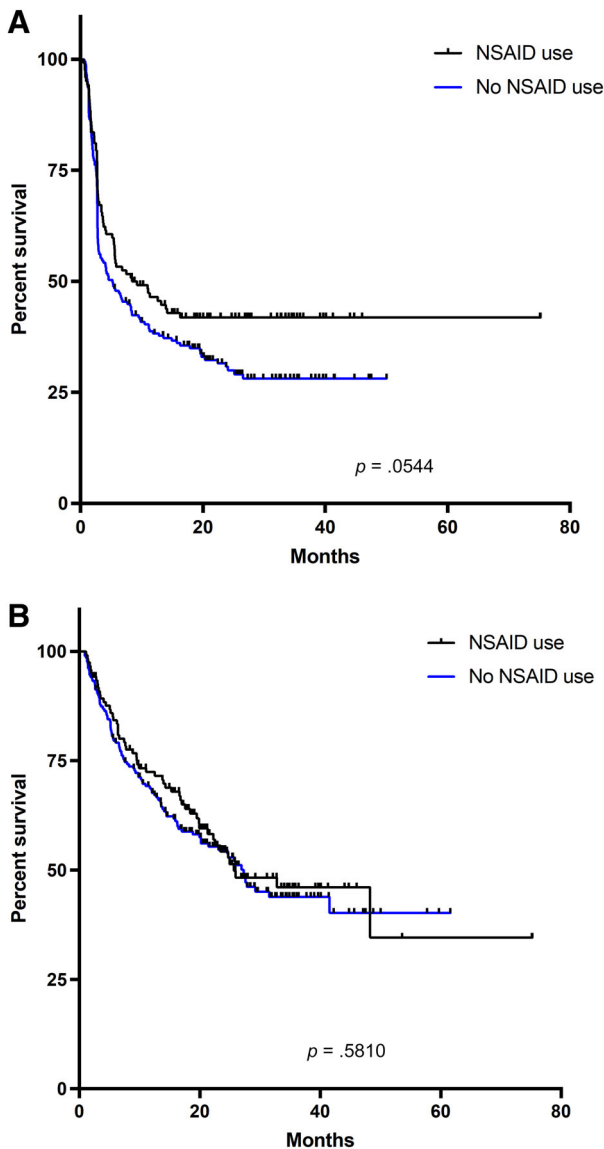
### NSAID Use and Efficacy

In the entire group, the objective response rate (ORR) was 42.1% (partial response, 26.7%; complete response, 15.5%). Median PFS and OS were 5.8 months (range, 0.5–75.2 months) and 26.9 months (range, 0.9–75.2 months), respectively. There was no significant difference in ORR (43.4% vs. 41.3%;  $p = .71$ ) in patients who used NSAIDs (including ASA and COX-2 inhibitors) versus those who did not. Patients who used NSAIDs had a nonsignificant trend toward improved PFS (median PFS: 8.5 vs. 5.2 months;  $p = .054$ ; hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.57–1.00; Fig. 1A), but there was no difference in OS (median OS: 25.7 vs. 27.3 months;  $p = .58$ ; HR, 0.91; 95% CI, 0.66–1.26; Fig. 1B).

Multivariable analysis adjusting for age, gender, stage LDH, prior therapies, aspirin dose, and BMI did not reveal an association between NSAID use with PFS (HR, 0.80; 95% CI, 0.59–1.09;  $p = .15$ ) or OS (HR, 0.84; 95% CI, 0.59–1.20;  $p = .34$ ). Furthermore, NSAID use did not lead to higher likelihood of response (HR, 1.08; 95% CI, 0.85–1.38;  $p = .76$ ). Similarly, aspirin use at higher doses ( $\geq 100$  mg) was not associated with improved PFS (HR, 2.19; 95% CI, 0.44–10.85;  $p = .34$ ) or OS (HR, 1.45; 95% CI, 0.22–9.8).

### Other Medications Use and Efficacy

Metformin and beta blocker use was also assessed. Among this cohort, only 34 (10.3%) patients used metformin. There



**Figure 1.** Progression-free and overall survival based on NSAID usage. **(A):** Progression-free survival based on NSAID usage. **(B):** Overall survival based on NSAID usage. Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

was no improvement in PFS (median 11.1 vs. 5.6 months;  $p = .36$ ; HR, 0.81; 95% CI, 0.54–1.23) or OS (median 27.6 vs. 26.0 month;  $p = .48$ ; HR, 0.82; 95% CI, 0.50–1.35) with the use of metformin. Beta blockers were used in 65 (19.8%) patients. These included atenolol (12.3%), bisoprolol (6.2%), carvedilol (15.4%), labetalol (1.5%), metoprolol (60%), nebivolol (3.1%), and solatol (3.1%). Again, there was no significant difference in either PFS (median 11.2 vs. 5.5 months;  $p = .40$ ; HR, 0.86; 95% CI, 0.62–1.20) or OS (median 27.8 vs. 25.8 months;  $p = .57$ ; HR, 0.89; 95% CI, 0.60–1.32) with beta blocker use.

## DISCUSSION

Although the use of PD-1 blockade has dramatically improved the clinical outcomes of patients with advanced

melanoma, most patients experience intrinsic or acquired therapeutic resistance. Preclinical studies support a mechanism for COX-2 inhibition to potentiate a response with PD-1 blockade; however, our study did not show any significant improvement in response or survival with the concurrent use of NSAIDs in a real-world population. Additionally, the use of other concurrent medications including metformin and beta blockers did not affect efficacy. Despite the largely negative statistical findings, we noted a trend toward improvement in PFS with NSAID use that may suggest a signal of efficacy and may need to be further explored in a larger prospective study.

Interestingly, preclinical models suggest COX-2 inhibition leads to a significant reduction in distant metastasis along with inhibition of tumor growth, suggesting a benefit in the adjuvant setting after curative therapy [16–18]. With the approval of anti-PD-1 therapy in the adjuvant setting for melanoma, further studies in this setting are needed to assess its role in preventing recurrence along with anti-PD-1 therapy. In addition, the rising obesity epidemic in the U.S. has led to increase use of NSAIDs and other medications, which has important implications in the outcomes of patients with melanoma. A study from our groups demonstrated a significant survival benefit for obese men who were treated with immunotherapy and targeted therapy, which perhaps could be confounded by concurrent medication [19]. However, we did not observe a clear contributor to such an association in this study.

The limitations of this study include small numbers of patients, potential underreporting of medication use and frequency, and retrospective data collection. In particular, the dose and type of NSAIDs were quite heterogeneous, with many patients taking intermittent or low doses of NSAIDs that may not potentiate antitumor immunity. Studies in melanoma xenografted mice showed tumor shrinkage with chronic daily aspirin administration, suggesting a dose-dependent mechanism, which needs to be further explored [13]. Along with pharmacodynamics studies of the drugs, further molecular studies of the tumors would help elucidate any prognostic biomarkers of response with these concurrent medications. Inherent issues with the variability in scan frequency and measurement techniques used at each site may also affect response and survival assessment. Additionally, 2.7% of patients developed inflammatory arthritis, which may have additionally confounded the survival results, although this relationship needs to be confirmed prospectively. However, the percentage of cases seems in line with the reported 1% to 7% seen in clinical trials [20].

In conclusion, we observed that routine use of NSAIDs, beta blockers, and/or metformin did not significantly improve response or survival in a modest-sized cohort of melanoma patients treated with anti-PD-1 therapy. These findings need to be confirmed with larger and more systematic analysis.

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#### DISCLOSURES

**Jennifer L. McQuade:** Merck, Bristol-Myers Squibb (C/A); **Georgina V. Long:** Aduro, Amgen, Array, Bristol-Myers Squibb, Merck Sharp Dohme, Novartis, Pierre-Fabre, Oncosec, Roche (C/A); **Matteo S. Carlino:** Merck Sharp Dohme, Bristol-Myers Squibb, Amgen,

Novartis, Roche, IDEAYA (SAB); **Alexander M. Menzies:** BMD, Merck Sharp Dohme, Novartis, Roche, Pierre-Fabre (C/A); **Michael A. Davies:** Bristol-Myers Squibb, Novartis, Array, Roche/Genentech, GlaxoSmithKline (C/A), Bristol-Myers Squibb, Roche/Genentech, GlaxoSmithKline (RF); **Douglas B. Johnson:** Array, Bristol-Myers Squibb, Incyte, Merck, Novartis (C/A), Bristol-Myers Squibb, Incyte (RF). The other authors indicated no financial relationships.

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