Original Study

The Association of Improved Overall Survival with NSAIDs in Non–Small Cell Lung Cancer Patients Receiving Immune Checkpoint Inhibitors

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Abstract

Response rates of immune checkpoint inhibitors (ICI) in advanced non-small cell lung cancer are suboptimal. In this retrospective cohort study of over 3,600 Veterans with advanced or metastatic non–small cell lung cancer, concomitant use of NSAIDs was associated with improved survival when given with ICI. This may indicate possibility of enhancing ICI efficacy using concomitant NSAIDs, although requires validation.

Background: Immune checkpoint inhibitors (ICI) are commonly used in the management of patients with advanced non-small cell lung cancer (NSCLC), but response is suboptimal. Preclinical data suggest ICI efficacy may be enhanced with concomitant nonsteroidal anti-inflammatory (NSAID) medications. **Patients and Methods:** In this retrospective study, the Veterans Health Administration Corporate Data Warehouse was queried for patients diagnosed with NSCLC and treated with ICI from 2010 to 2018. Concomitant NSAID use was defined as NSAID dispensation by a VA pharmacy within 90 days of the any ICI infusion. To mitigate immortal time bias, patients who started NSAIDs 60 or more days after ICI initiation were excluded from analysis. Survival was measured from start of ICI. **Results:** We identified 3634 patients with NSCLC receiving ICI; 2336 (64.3%) were exposed to concomitant NSAIDs. On multivariable analysis, NSAIDs were associated with better overall survival (HR = 0.90; 95% CI, 0.83-0.98; $P = .010$). When stratifying by NSAID type, diclofenac was the only NSAID with significant association with overall survival (HR = 0.75; 95% CI, 0.68-0.83; $P < .001$). Propensity score matching of the original cohort yielded 1251 patients per cohort balanced in characteristics. NSAIDs remained associated with improved overall survival (HR = 0.85; 95% CI, 0.78-0.92; $P < .001$). **Conclusion:** This study of Veterans with NSCLC treated with ICI demonstrated that concomitant NSAIDs are associated with longer OS. This may indicate that NSAIDs can enhance ICI-induced antitumor immunity and should prospectively validated.

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Introduction

Lung cancer remains the leading cause of cancer mortality in the United States and worldwide.[1] Immunotherapy, predominantly in the form of immune checkpoint inhibitors (ICIs), has brought substantial improvements in overall survival in patients with metastatic and locally advanced non–small cell lung cancer (NSCLC).[2,3] However, clinical response rates with ICIs are suboptimal and the majority of patients eventually have disease progression, possibly due to development of tumor resistance to further immune blockade.[4] Identification of clinical or pharmacologic factors that modify immunotherapy's efficacy may be useful in tailoring patient selection for treatment, predicting response, or augmenting response to therapy. There is preclinical data suggesting nonsteroidal anti-inflammatory drugs (NSAIDs) improve the efficacy of anti-PD-1

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therapies by abating COX-dependent tumor progression.[5,6] Given the potential immune-modulatory effects of NSAIDs, we sought to study the association of concomitant NSAIDs with overall survival in a real-world cohort of Veterans receiving ICI for advanced NSCLC.

Patients and Methods

The Veterans Health Administration (VHA) is the largest integrated health care system in the United States and serves nine million Veterans annually, approximately 50,000 with cancer. Clinical and administrative data are routinely collected on each VHA enrollee from over 150 VA hospitals and thousands of clinics into the Corporate Data Warehouse. We queried this resource for NSCLC diagnoses occurring from 2010, the first year ICIs were approved in the United States, through 2018, the most recent year for which cases would have 12 months of follow-up.

We conducted a nested cohort study of NSCLC patients receiving ICI. Utilization of ICI, date of ICI initiation, and duration of ICI therapy were ascertained from the VA Corporate Data Warehouse using a secure VA Informatics and Computing Infrastructure (VINCI) workspace, focusing on the 4 agents approved for use in NSCLC through 2018 (nivolumab, pembrolizumab, durvalumab, and atezolizumab). Similarly, NSAID exposure for the purpose of this analysis was defined as the Veteran having picked up a prescription for a systemic (oral or intravenous) NSAID within 90 days before or after any ICI administration. To mitigate the impact of immortal time bias, patients who initiated NSAID more than 60 days after start of ICI were excluded from analysis entirely. Patients were categorized *a priori* into groups for sociodemographic factors (age, race, gender, population density, employment status, and marital status), clinical characteristics (Elixhauser comorbidity index), cancer-specific features (histology, stage at diagnosis, and year of diagnosis), and treatment-related variables (time from diagnosis to ICI initiation, sequence of ICI with respect to chemotherapy). Pearson's χ^2 tests were used to assess the associations between variables and NSAID usage. We separately assessed the impact of any NSAID and of each NSAID agent. To isolate the impact of the most promising agents, pairwise comparisons were then performed between patients exposed to these specific agents and patients without any NSAID exposure.

The primary outcome evaluated was overall survival, measured from date of first ICI administration to date of last follow-up or death. Vital status was ascertained from Department of Defense data. Kaplan-Meier analysis without adjustment for covariates was initially used to compare survival between groups. Univariable Cox proportional hazards regression was then performed, with survival associations expressed as hazard ratios (HR) and corresponding 95% confidence intervals (95% CI), and HR > 1 indicating greater risk of mortality. Using backward elimination with an alpha level of removal of 0.05, multivariable Cox proportional hazards regression was then performed.

A generalized propensity score was estimated for each analysis by multinomial logistic regression treating the comparator groups (ie NSAID exposure) as the outcome and covariates as predictors. A generalized propensity score matching (PSM) algorithm was applied to create a pseudo-sample where all covariates of interest were balanced among the comparison groups. The covariate balance was checked before and after PSM by the standardized difference, with values <0.2 considered an acceptable imbalance. Associations with survival were then examined in the matched samples using the same tests as above. Statistical analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC). Tests were 2-sided with a level of significance of $P = .05$.

Results

We identified a total of 3634 Veterans with NSCLC treated with ICI, 2336 (64.3%) of whom were treated with NSAIDs (Table 1). Patients treated with NSAIDs were characterized by larger proportion of Black patients, higher comorbidity index, adenocarcinoma histology, more recent year of diagnosis, shorter duration between diagnosis and initiation of ICI, and more patients who received chemotherapy during or after ICI. Patients treated with NSAIDs were most commonly treated with 2 or more NSAIDs (40.2% of NSAID patients), aspirin (32.0%), ketorolac (10.3%), ibuprofen (6.3%), or diclofenac (4.3%).

On univariable analysis, receipt of NSAIDs was associated with better overall survival (HR = 0.87; 95% CI, 0.81-0.94; $P <$ .001), with median overall survival of 10 months versus 8 months (Figure 1). Other factors associated with improved overall survival included chemotherapy during or after ICI, older age, black race, lower comorbidity burden, adenocarcinoma histology, earlier disease stage, earlier year of diagnosis, and longer time from diagnosis to ICI. On multivariable analysis, receipt of NSAIDs remained associated with better overall survival (HR = 0.83; 95% CI, 0.76-0.89; $P <$ .001). Improved overall survival was also associated with chemotherapy during or after ICI, older age, black race, female sex, employed employment status, adenocarcinoma histology, earlier stage, earlier year of diagnosis, and longer duration from diagnosis to initiation of ICI (Table 2). On multivariable analysis stratifying by NSAID type, only diclofenac (HR = 0.60; 95% CI, 0.47-0.77; $P <$ .001) and 2 or more NSAIDs (HR = 0.75; 95% CI, 0.68-0.83; $P <$ .001) had a statistically significant association with overall survival (Supplemental Table 1).

After propensity score matching, there were 1251 patients in each cohort who were balanced in baseline characteristics (Supplemental Table 2). Receipt of NSAIDs remained associated with improved overall survival (HR = 0.85; 95% CI, 0.78-0.92; $P <$ .001) (Figure 2).

Given the association of diclofenac, specifically, with overall survival, a subset analysis was performed to specifically evaluate patients who received diclofenac versus those who did not receive NSAIDs. Compared to patients who did not receive any NSAIDs, patients who received diclofenac had statistically significant improved overall survival on univariate (HR = 0.65; 95% CI, 0.51-0.83; $P <$ .001) and multivariable analysis (HR = 0.62; 95% CI, 0.48-0.79; $P <$ .001) (Table 3). Additionally, improved overall survival was associated with older age, lower comorbidity index, earlier stage, earlier year of diagnosis, and chemotherapy during or after ICI. Propensity score matching yielded 98 patients in each cohort, well balanced in baseline characteristics (Supplemental Table 3). Receipt of diclofenac remained associated with improved overall

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Table 1 Descriptive Statistics of the Overall Cohort

Variable	Categories	NSAID				
		No		Yes		
		N = 1298		N = 2336		
		N	%	N	%	*P*
Age	≤65	343	26.4	608	26	.29
	66-70	382	29.4	752	32.2	
	71-75	320	24.6	564	24.1	
	>75	253	19.5	412	17.6	
Race	white	969	74.7	1683	72.1	.018
	black	236	18.2	510	21.8	
	other	15	1.2	108	1.5	
	unknown	78	6	12	4.6	
Gender	male	1266	97.5	2259	96.7	.16
	female	32	2.5	77	3.3	
Geography	urban	839	64.6	1560	66.8	.19
	rural	459	35.4	776	33.2	
Employment	employed	276	21.3	466	20	.54
	not employed	530	40.8	995	42.6	
	retired	454	35	795	34	
	unknown	38	2.9	80	3.4	
Marital Status	married	628	48.4	1078	46.2	.34
	not married	669	51.5	1254	53.7	
	unknown	1	0.1	4	0.2	
Elixhauser Comorbidity Index	0-4	443	34.1	589	25.2	<.001
	6-May	309	23.8	498	21.3	
	9-Jul	329	25.4	620	26.5	
	>9	217	16.7	629	26.9	
Histology	squamous cell carcinoma	557	42.9	768	32.9	<.001
	adenocarcinoma	532	41	1204	51.5	
	other	209	16.1	364	15.6	
Stage at Diagnosis	0	4	0.3	0	0	.069
	I	157	12.1	296	12.7	
	II	87	6.7	174	7.5	
	III	372	28.7	613	26.2	
	IV	520	40.1	967	41.4	
	unknown	158	12.2	286	12.2	
Year of Diagnosis	2010-2015	618	47.6	920	39.4	<.001
	2016-2018	680	52.4	1416	60.6	
Months from Diagnosis to ICI	0-4	262	20.2	610	26.1	<.001
	10-May	390	30.1	642	27.5	
	19-Nov	299	23	487	20.9	
	≥20	347	26.7	597	25.6	
Chemotherapy	none	178	13.7	302	12.9	<.001
	before ICI	757	58.3	1198	51.3	
	during ICI	339	26.1	769	32.9	
	after ICI	24	1.9	67	2.9	

Abbreviations: ICI = immune checkpoint inhibitor.

survival when compared to no NSAIDs (HR = 0.57; 95% CI, 0.41-0.79; $P < .001$) (Figure 3).

Given a proportion of patients had missing stage data, we conducted a sensitivity analysis excluding these patients. Receipt of NSAIDs was again associated with improved overall survival on multivariable analysis (HR = 0.84; 95% CI, 0.77-0.91; $P < .001$) and after propensity score matching (n = 1118 per cohort; HR = 0.85; 0.78-0.93; $P < .001$). When NSAIDs were stratified by specific drug, diclofenac was again the only individual NSAID drug to be associated with overall survival (HR = 0.62; 95% CI,

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Table 2 Cox Regression for Overall Survival in Entire ICI Cohort

Variable	Categories			UVA				MVA			
		N	Deaths	HR	95% CI	*P*	*P*	HR	95% CI	*P*	*P*
NSAID	no	1298	1,048	-	-	-	<.001	-	-	-	.042
	yes	2336	1,737	0.83	0.77-0.90	<.001		0.83	0.76-0.89	<.001	
Age	≤65	951	742	1.21	1.08-1.35	.001	<.001	1.43	1.26-1.62	<.001	<.001
	66-70	1134	907	1.22	1.09-1.35	<.001		1.34	1.20-1.50	<.001	
	71-75	884	625	0.88	0.79-0.99	.038		0.92	0.82-1.04	.195	
	>75	665	511	-	-	-		-	-	-	
Race	white	2652	2,053	-	-	-	.009	-	-	-	.012
	black	746	545	0.86	0.79-0.95	.003		0.86	0.78-0.95	.003	
	other	50	37	1.02	0.73-1.41	.925		0.96	0.69-1.34	.818	
	unknown	186	150	1.06	0.89-1.25	.519		1.09	0.93-1.29	.294	
Gender	male	3525	2,712	-	-	-	.144	-	-	-	.016
	female	109	73	0.85	0.67-1.07	.159		0.75	0.59-0.95	.016	
Geography	urban	2399	1,821	-	-	-	.261				
	rural	1235	964	1.04	0.97-1.13	.275					
Employment	employed	742	544	-	-	-	.149	-	-	-	.002
	not employed	1525	1,165	1.08	0.97-1.20	.141		1.06	0.96-1.18	.268	
	retired	1249	988	1.12	1.01-1.24	.036		1.23	1.10-1.37	<.001	
	unknown	118	88	1.17	0.93-1.46	.176		1.12	0.89-1.41	.317	
Marital Status	married	1,706	1,301	-	-	-	.831				
	not married	1923	1,479	0.99	0.92-1.06	.755					
	unknown	5	5	1.24	0.52-2.99	.629					
Elixhauser Comorbidity Index	0-4	1032	754	-	-	-	<.001	-	-	-	<.001
	6-May	807	617	1.12	1.00-1.24	.042		1.15	1.03-1.28	.012	
	9-Jul	949	741	1.34	1.21-1.48	<.001		1.33	1.20-1.48	<.001	
	>9	846	673	1.24	1.12-1.37	<.001		1.25	1.13-1.39	<.001	
Histology	squamous cell carcinoma	1314	1,081	-	-	-	<.001	-	-	-	<.001
	adenocarcinoma	1712	1,268	0.83	0.77-0.90	<.001		0.83	0.77-0.91	<.001	
	other	567	436	0.96	0.86-1.07	.437		0.92	0.82-1.03	.16	
Stage at Diagnosis	0	4	2	0.43	0.11-1.70	.227	<.001	0.44	0.11-1.79	.254	<.001
	I	453	345	0.89	0.79-1.00	.054		0.99	0.87-1.13	.868	
	II	261	197	0.88	0.76-1.03	.105		0.96	0.81-1.12	.573	
	III	985	724	0.83	0.76-0.91	<.001		0.83	0.75-0.91	<.001	
	IV	1487	1,181	-	-	-		-	-	-	
	unknown	444	336	1.09	0.96-1.23	.183		1.14	1.00-1.28	.036	
Year of Diagnosis	2010-2015	1538	1,300	0.81	0.75-0.88	<.001	<.001	0.86	0.78-0.95	.002	.002
	2016-2018	2,096	1,485	-	-	-		-	-	-	
Months from Diagnosis to ICI	0-4	872	636	1.38	1.24-1.54	<.001	<.001	1.26	1.09-1.46	.002	.021
	10-May	1032	796	1.29	1.17-1.43	<.001		1.13	1.00-1.28	.057	
	19-Nov	786	624	1.16	1.05-1.30	.005		1.09	0.97-1.22	.147	
	>19	944	729	-	-	-		-	-	-	
Chemotherapy	none	480	364	1.06	0.95-1.19	.296	<.001	0.95	0.83-1.07	.395	<.001
	before ICI	1955	1,509	-	-	-		-	-	-	
	during ICI	1108	846	0.73	0.67-0.79	<.001		0.71	0.65-0.78	<.001	
	after ICI	91	66	0.6	0.48-0.79	<.001		0.58	0.45-0.74	<.001	

Backward selection with an α of 0.05 was used. The following variables were removed from the model: geography and marital status.
Abbreviations: HR = hazard ratio; ICI = immune checkpoint inhibitor; MVA = multivariable analysis; UVA = univariable analysis; 95% CI, 95% confidence interval

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Figure 1 Kaplan-Meier curves for overall survival, comparing all patients who received NSAIDs and those who did not receive NSAIDs. Hazard ratio = 0.87; 95% CI 0.81 – 0.94; p < 0.001.

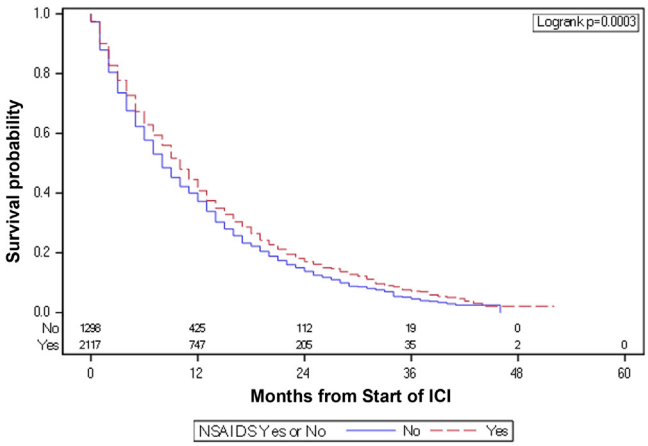
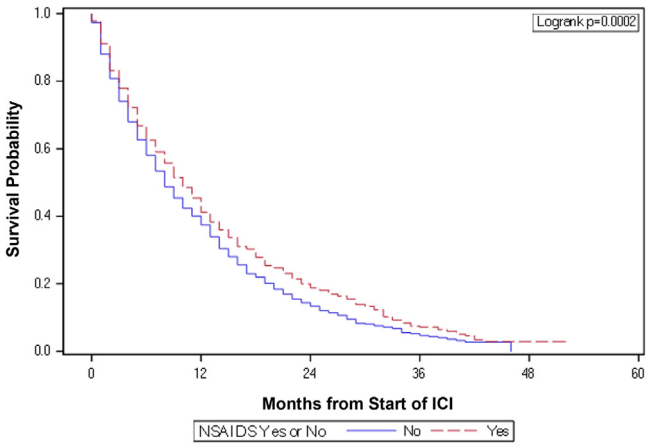


Figure 2 Kaplan-Meier curves for overall survival, comparing propensity-score matched patients who did and did not receive NSAIDs. Hazard ratio = 0.85; 95% CI 0.78 – 0.92; p < 0.001.



0.48-0.81; $P < .001$). When comparing patients who received diclofenac versus no NSAIDs (excluding patients who received other NSAIDs), diclofenac was associated with improved overall survival (HR = 0.64; 95% CI, 0.50-0.83; $P < .001$) on multivariable analysis.

Discussion

In this study of Veterans with NSCLC receiving ICIs, we identified an association of NSAIDs with improved overall survival. To our knowledge, this is the first study of a real world cohort that provides clinical evidence of an association between NSAIDs and concomitant immunotherapy with improved overall survival in NSCLC patients.

Preclinical studies suggest that cyclooxygenase-dependent pathways mediate tumor growth and evasion of immunity, blockade of which inhibits tumor growth in vivo.[5,7] This is potentially because Prostaglandin E2, a product of COX, is a key mediator of inflammation in the tumor microenvironment and attenuates antitumor immunity through a variety of mechanisms, including upregulation of T helper 2 response, inhibition of cytotoxic T cells, modulation of dendritic cell response, and induction of myeloid-derived suppressor cells.[8] COX-2, specifically, has been found to modulate PD-L1 expression, and its inhibition has resulted in suppression of tumor metastases in vivo in melanoma and breast cancer models.[9-13] The preferential expression of the COX-2 isoform in states of inflammation or malignancy makes it a potentially valuable target in cancer-directed therapies.[14]

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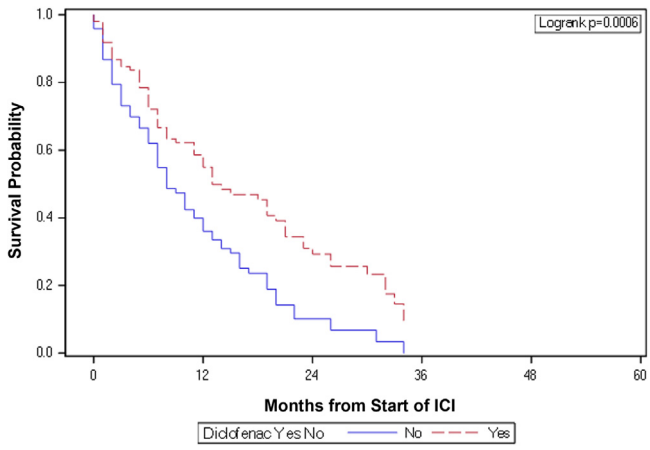
Table 3 Cox Regression for Overall Survival in subset analysis of patients who received diclofenac vs no NSAID

Variable	Categories			MVA			
		N	Deaths	HR	95% CI	*P*	*P*
Diclofenac	no	1298	1048	-	-	-	<.001
	yes	101	69	0.62	0.48-0.79	<.001	
Age	≤65	368	303	1.26	1.05-1.50	.011	<.001
	66-70	410	337	1.33	1.23-1.59	.001	
	71-75	345	262	0.95	0.79-1.15	.615	
	>75	276	215	-	-	-	
Elixhauser Comorbidity Index	0-4	469	362	-	-	-	.005
	6-May	339	279	1.17	1.00-1.37	.054	
	9-Jul	354	285	1.33	1.14-1.56	<.001	
	>9	237	191	1.1	0.92-1.32	.284	
Stage at Diagnosis	0	4	2	0.41	0.10-1.65	.21	.021
	I	167	127	0.87	0.71-1.06	.162	
	II	93	73	0.95	0.74-1.22	.676	
	III	408	321	0.84	0.72-0.97	.016	
	IV	560	463	-	-	-	
	unknown	167	131	1.16	0.95-1.41	.148	
Year of Diagnosis	2010-2015	657	571	0.83	0.73-0.94	.004	.004
	2016-2018	742	546	-	-	-	
Chemotherapy	none	198	153	0.99	0.82-1.19	.924	<.001
	before ICI	810	655	-	-	-	
	during ICI	367	291	0.67	0.59-0.77	<.001	
	after ICI	24	18	0.6	0.38-0.97	.036	

Backward selection with an α of 0.05 was used. The following variables were removed from the model: Emoloyment status, gender, geography, histology, marital status, month from diagnosis to initiation of ICI, and race.
Abbreviations: HR = hazard ratio; ICI = immune checkpoint inhibitor; MVA = multivariable analysis; 95% CI, 95% confidence interval.

Figure 3 Kaplan-Meier curves for overall survival, comparing propensity-score matched patients who received diclofenac vs no NSAIDs. Hazard ratio = 0.57; 95% CI 0.41 – 0.79; p < 0.001.



There is limited data regarding the potential effect of NSAIDs on ICI therapy. In a previous study evaluating various concomitant medications with ICI in advanced cancers, there was worse overall survival in NSCLC patients treated with ICI with NSAIDs.[15] Given this was a subset analysis in a group of patients with several types of advanced cancer, it is difficult to compare that study's findings to our current study of a large cohort of patients exclusively with NSCLC treated with ICI. In another study, NSAIDs were associated with higher likelihood of progression and death in a cohort of metastatic renal cell carcinoma.[16] Compared to the aforemen-

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tioned 2 studies, it is possible the larger patient numbers in our study and ability to account for more confounders better mitigated selection bias associated with patient's taking NSAIDs for comorbid conditions. A separate meta-analysis evaluating the effect of concomitant analgesics on prognosis in patients with multiple types of cancer treated with ICIs found overall no significant difference in progression-free survival or overall survival in patients receiving NSAIDs; it did, however, find an association with better PFS in a subgroup of patients who received anti-PD-1 therapy.[17] A prior study of 330 patients with advanced melanoma did not identify a significant association between NSAID use and improvement in overall survival or progression-free survival in patients who received anti-PD-1 therapy.[18] The study contained a minority of patients who received NSAIDs, in comparison to our much larger study which perhaps affords greater power to detect statistically significant differences in overall survival. Additionally, it is unclear how many patients in that study received diclofenac, which our study specifically identified has the strongest association to improved outcomes. Another study did not show a benefit of aspirin with checkpoint inhibitors in a single-institution cohort. The study included heterogeneous cancer types and only a small number of patients who received aspirin. Also, its analysis included CTLA-4 inhibitors, which were not evaluated in our study and do not have the same extent of association to COX modulation as PD-L1.[19]

The strength of the association of diclofenac with improved overall survival raises the possibility that diclofenac may modulate a unique mechanistic pathway independent of COX. Diclofenac, unlike other NSAIDs, has been shown to decrease lactate secretion of tumor cells through inhibition of lactate transporters monocarboxylate transporter 1 and 4.[20] Although lactate has complex immunomodulatory effects on different subtypes of immune cells, it is generally immunosuppressive.[21] Studies suggest that the metabolic effect of diclofenac causes increase in intratumoral lactate and corresponding decrease in the tumor microenvironment, resulting in enhanced local antitumor immune response.[22] Preclinical data suggests administration of diclofenac enhances the effect of checkpoint inhibitors through pH-dependent upregulation of IFNγ, IL-2, and PD-1 expression; this effect is unique to diclofenac and not seen with aspirin administration.[20] Diclofenac has also been shown to have direct antitumor effects as well,[23] such as through downregulation of VEFG via increased arginase activity in tumor stroma,[24] downregulation of c-Myc expression,[25] and induction of apoptotic pathways.[26] It is possible that the effects of diclofenac are unique among NSAIDs in enhancing antitumor response when combined with ICIs.

The data presented here should be interpreted cautiously given our study's retrospective design, which entails several limitations that are worth noting. Given that overall survival was the only available endpoint for analysis, we were not able to analyze the potential impact of NSAIDs on progression, patterns of failure, or lung cancer-specific survival. It is possible that the overall survival benefit may in part be due to selection bias, despite the use of propensity score matching to mitigate the effect of identifiable confounding variables. The analyzed cohort consisted of a heterogeneous group with regard to several key variables including disease stage, year of diagnosis, and timing of chemotherapy. Although this was accounted for in regression and propensity score matching, it is difficult to account for all of the potential treatments these patients received (eg surgery, radiation, chemotherapy type, and duration) and the impact of these treatments on survival. Additionally, given that NSAID use was defined by the presence of an active prescription, it is difficult to account for variability in use (eg oral vs. parenteral, as-needed vs. scheduled regimens, inconsistent adherence, variable dosing, differences in duration). Along these lines, we are unable to account for patients who may have taken NSAIDs over the counter. As a proportion of patients in the cohort without NSAIDs may have received such over the counter medications, it is possible that exposure misclassification may be lowering the measured magnitude of effect of NSAIDs (both as a group and on an individual basis) on overall survival. Finally, although we noted a unique statistically significant association of survival with diclofenac, it should be emphasized that our study lacks the statistical power to evaluate individual NSAIDs, some of which comprised a very small proportion of NSAIDs.

In summary, we identified an association of improved overall survival with ICI and NSAID use. This may indicate that NSAIDs can enhance ICI-induced antitumor immunity, potentially through COX inhibition or distinct antitumor pathways. These findings merit prospective study.

Clinical Practice Points

Immune checkpoint inhibitor (ICI) response is suboptimal in advanced non–small cell lung cancer (NSCLC) and strategies are needed to improve outcomes. Preclinical studies suggest that cyclooxygenase-dependent pathways modulate antitumor immunity. In our study, we found that patients who received immune checkpoint inhibitors (ICI) for advanced non-small cell lung cancer while taking nonsteroidal anti-inflammatory drugs (NSAIDs) had better overall survival than patients who were not taking NSAIDs. This may indicate that concurrent administration of NSAIDs may enhance ICI efficacy, although this requires further study.

Disclosure

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CRediT authorship contribution statement

Nikhil T. Sebastian: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing. **William A. Stokes:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Madhusmita Behera:** Concep-

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tualization, Methodology, Writing – review & editing. **Renjian Jiang:** Data curation, Methodology, Formal analysis, Visualization. **David A. Gutman:** Data curation, Software, Formal analysis, Supervision. **Zhonglu Huang:** Methodology, Formal analysis, Data curation, Visualization. **Abigail Burns:** Project administration, Resources. **Vidula Sukhatme:** Conceptualization, Funding acquisition. **Michael C. Lowe:** Conceptualization, Methodology, Investigation. **Suresh S. Ramalingam:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Vikas P. Sukhatme:** Conceptualization, Funding acquisition, Methodology, Writing – review & editing. **Drew Moghanaki:** Conceptualization, Funding acquisition, Methodology, Investigation, Writing – original draft, Writing – review & editing.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cllc.2022.12.013.

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