THERAPEUTIC ADVANCES in
*Vaccines and Immunotherapy*

*Original Research*

# Association between cannabis use and clinical outcomes in patients with solid malignancies receiving immune checkpoint inhibitors

*Ther Adv Vaccines Immunother*

2024, Vol. 12: 1–15

DOI: 10.1177/25151355241309095



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***Abstract***

**Background:** Cannabis (CAN) use has risen significantly over the last few decades. CAN has potent immunosuppressive properties, which could antagonize the effect of immunotherapy (IO). The impact of CAN use on clinical cancer outcomes remains unclear.

**Objectives:** In this study, we evaluated the clinical effect of CAN use on clinical outcomes among patients with solid malignancies receiving IO.

**Design:** This is a retrospective cohort study of all patients with solid malignancies receiving IO between August 2014 and August 2018.

**Methods:** Patients were stratified based on CAN use to CAN users and CAN non-users. The primary outcome was overall survival (OS), and the secondary outcomes were progression-free survival (PFS) and disease control rate (DCR). Univariable and multivariable logistic and Cox regression analyses were performed to compare the outcomes between the two groups, adjusting for covariates.

**Results:** The records of 106 patients were reviewed, 28 (26%) of whom were CAN users and 78 (74%) were CAN non-users. One patient was excluded. Most CAN users consumed dronabinol (82%). The median follow-up for OS and PFS was 29.2 months. Median OS in the CAN users was 6.7 months compared to 17.3 months in the CAN non-users (HR, 1.78; 95% CI, 1.06–2.97; $p = 0.029$). The median PFS was 4.8 months in the CAN users compared to 9.7 months in the CAN non-users (HR, 1.74; 95% CI, 1.09–2.79; $p = 0.021$). DCR was 11% among CAN users and 38% among CAN non-users (OR, 0.23; 95% CI; 0.06–0.68; $p = 0.007$). An exploratory racial disparity analysis showed that this negative impact of CAN was primarily seen in White patients.

**Conclusion:** In this single institutional experience, CAN use was associated with worse OS, PFS, and DCR among cancer patients receiving IO. Prospective trials are needed to further study this potential antagonistic interaction between CAN and IO and explore the racial disparities related to CAN exposure.

## Plain language summary

### Impact of cannabis use on clinical outcomes in patients with cancer receiving immunotherapy

Cannabis (CAN) use has risen significantly over the last few decades. The clinical effect of CAN consumption on cancer patients receiving immunotherapy (IO) remains unknown. In this study, we identified 106 cancer patients receiving IO. Patients who did not consume

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CAN lived longer than those who consumed CAN. Additionally, patients who consumed CAN were more likely for their cancer to recur and had more rapid cancer recurrence than those who did not. This unfavorable effect of CAN is predominantly seen in white patients.

***Keywords:*** African American, Cannabis, immune checkpoint inhibitors, IO, race

Received: 6 February 2024; revised manuscript accepted: 3 December 2024.

## Introduction

For centuries, cannabis (CAN) has been used as an herbal remedy for various symptoms with the earliest evidence of CAN smoke discovered in ancient tombs.[1] There are more than 90 different types of CAN, containing more than 60 compounds including $^{\Delta}$9-tetrahydrocannabinol (THC) and cannabidiol (CBD).[2,3] In the United States (US), more than half of the adult population have tried CAN at some point in their lives.[3] Moreover, public support for legalizing the consumption of CAN has risen from 12% in 1969 to 66% in 2018.[3] Consequently, the recreational use of CAN was first legalized in 2012 in Washington with 23 other states and territories followed suit to date.[4,5] In addition, 38 states have legalized the use of CAN for medical purposes.[6]

The endocannabinoid system participates in numerous physiological and pathological processes in various organs of the human body. Exogenous CAN interacts with the endocannabinoid system, which leads to a range of clinical symptoms and various changes in organ functions.[3] In patients with cancer, CAN use has been shown to improve pain, nausea, vomiting, anorexia, and weight loss.[7–9] To date, three CAN preparations are approved for medical use by the US Food and Drug Administration (FDA), dronabinol, nabilone, and CBD.[10] Dronabinol is the most commonly prescribed CAN agent and it is approved for the treatment of chemotherapy-associated nausea when unresponsive to conventional therapy and for treatment of anorexia and weight loss in patients with acquired immunodeficiency syndrome.[11] The efficacy of dronabinol in the treatment of chemotherapy-induced nausea is augmented when combined with conventional antiemetic agents.[12,13]

Despite the growing public interest in the use of CAN to treat cancer and the widespread publicity that CAN could halt cancer progression, the available data to support this argument are limited and predominantly preclinical.[3,14–16] Nonetheless, CAN is widely used by cancer patients. A study from the Netherlands reported that 25% of cancer patients are using CAN, with 46% of the CAN users motivated by the belief that CAN treats cancer. Approximately 54% of these users were undergoing immunotherapy.[17] Another study from the United States reported that 41% of patients used CAN after their cancer diagnosis, most commonly edibles (60%) followed by smoking (44%) with more than 54% using CAN for sleep, 44% for mood, 42% for pain, and 42% for recreation.[18]

Conversely, several recent studies have implicated CAN in the acceleration of cancer progression. The tumorigenesis effect of CAN may be influenced by the cancer type and CAN dose and concentration.[3,19,20] In addition, CAN processes potent anti-inflammatory, immunosuppressive, and immunomodulatory properties, which may reduce the natural ability of the immune system to perform cancer surveillance.[21] These properties appear to vary based on CAN formulation and dose.[22,23]

The use of immune checkpoint inhibitors (IO) has risen significantly over the last decade. IO exerts its antineoplastic activity by augmenting the antitumoral immunity, which results in tumor cell death. Therefore, it is plausible to expect a negative interaction between IO and immunosuppressive agents such as steroids and CAN. Published literature about the interaction between IO and CAN is limited. A recent retrospective

study on patients with multiple advanced malignancies receiving IO showed the detrimental effect of CAN use on progression-free survival (PFS) or overall survival (OS).[24] Another similar study showed that CAN use resulted in a lower response rate to IO but no effect on PFS or OS.[25] Another more homogeneous study of non-small-cell lung cancer (NSCLC) patients receiving pembrolizumab monotherapy showed a trend toward worse OS among CAN users with no effect on PFS.[26] Interestingly, are-analysis of the former two studies noted some unreported significant differences between the CAN users and non-users, which could have confounded the concluded results.[27] In addition, all of these studies have used very high doses of plant-based CAN, such high doses are not typically used in the United States. Moreover, concomitant tobacco use appears to be another potential confounding factor in some of the published studies.[27] Given the conflicting results of these published studies, it remains unclear how CAN use impacts clinical outcomes among cancer patients receiving IO, and further studies on the safety of their concomitant use are warranted. The objective of this study is to assess the association between CAN use and clinical outcomes among patients with solid malignancies receiving IO. Unlike the previously reported studies, we focus on the use of prescribed pharmacological CAN in modest doses. We also explore the potential effects of a few other variables such as patients' race of this association.

## Materials and methods

### *Patients*

From August 2014 to August 2018, medical records of all consecutive cancer patients who received at least 2 months of IO were reviewed, regardless of their clinical course. The patients who met these eligibility criteria within the study period were considered the sample size. These patients were then stratified based on their CAN use (CAN users and CAN non-users). Demographic data, tobacco use, tumor type, tumor stage, metastatic site, prior lines of therapy, type of IO agent used, and PD-L1 expression were collected and documented. Follow-up was determined based on the information obtained from the medical records.

### *Immunotherapy agents*

All patients with solid malignancies receiving immune checkpoint inhibitors were included. Receiving at least 2 months of IO was required to be included in this study as this duration was judged to be adequate IO exposure to drive a clinical benefit. All IO agents were administered by oncology-certified registered nurses in accordance with the manufacturer's published administration guidelines. PD-L1 expression was measured by the appropriate assay for the respective IO agent used.

### *CAN usage*

Patients who consumed CAN anytime between initiation and discontinuation of IO were classified as CAN users. We included patients who received any type of CAN and at any frequency. These included medical prescriptions such as dronabinol and/or recreational use such as CBD. Both oral and inhaled CAN formations were included. Records of CAN use were obtained from prescription logs and provider documentation.

### *Study design*

This retrospective cohort study sequentially assessed the impact of CAN use on cancer outcomes in patients receiving IO. Study outcomes were specified prior to the initiation of this study. The primary outcome was OS, which was defined as the duration from the date of administration of the first dose of IO until death from any cause. OS is considered the gold standard endpoint in measuring the effect of certain exposures on cancer patients. In addition, OS would also capture any non-cancer-related deaths among the groups that could be related to CAN exposure. Secondary outcomes included PFS and the disease control rate (DCR). The PFS was defined as the duration from the date of administration of the first dose of IO until progression (defined as the date of the last administration of IO that immediately preceded radiologic documentation of disease progression) or death from any cause, whichever occurred first. The DCR was defined as the proportion of patients achieving complete response (CR), partial response (PR), and stable disease (SD). Clinical response was assessed using response evaluation criteria in solid tumors (RECIST) version 1.1, being the standard response assessment criteria at the study institution.[28] The reporting of this study conforms

with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Supplemental 1).[29]

### *Statistical analysis*

Categorical variables were summarized by count and frequency and median and range were used to summarize continuous variables. Comparisons between groups were performed by Fisher's exact test and Wilcoxon rank-sum test for categorical and continuous variables, respectively. One Asian patient was excluded to decrease the heterogeneity of the data and to avoid additional confounding since the Asian race has been associated with better survival in patients receiving IO.[30] The distributions of OS and PFS were graphically described using Kaplan–Meier (KM) curve and their median and 95% confidence interval (CI) were estimated by KM estimates. A log-rank test was used to compare KM curves between groups. Univariable and multivariable Cox regression models were used to assess the association between prechosen eight covariates (age, race, sex, smoking status, tumor site, immunotherapy agent, site of metastasis, and PD-L1 expression) and survival outcomes (OS and PFS), along with CAN group. The proportional hazard assumption was verified based on Schoenfeld residuals, and no violation was found. Univariable and multivariable logistic regression models were used to assess the association between the prechosen eight covariates and DCR, along with the CAN group. Particularly, Firth's logistic regression models were used to reduce bias in maximum likelihood estimation caused by rare events. For categorical variables with three or more levels, we also calculated global *p*-values using likelihood ratio tests. To select covariates among eight prechosen covariates for multivariable Cox and logistic models, LASSO-based penalized Cox and logistic models were used with leave-one-out cross-validation for each outcome. The multivariable Cox and logistic regression analyses were then performed with the selected covariates on each outcome.

## Results

### *Patient characteristics*

A total of 105 patients received IO during the study period with a median duration of follow-up of 29.2 months for OS and PFS (see Figure S1 and Supplemental 2). As expected, the CAN users were more likely to be younger (median age: 59.2 vs 68.4 years; $p = 0.013$) and tobacco users (96.4% vs 74.0%; $p = 0.012$). There was no difference between the groups in race, sex, primary tumor site, IO agent used, stage, site of metastasis, PD-L1 expression, and line of therapy. Most patients had lung cancer (61.9%), all of whom, but one, were NSCLC. Most patients in both groups received nivolumab (60.0%) followed by pembrolizumab (25.7%). Most of the patients in the CAN group received 5–10 mg daily dosing of dronabinol (82%) and the rest used recreational CAN (14%) and CBD oil (4%). The median duration of IO use was similar between the two groups at 4.2 months (range, 1.84–29.21) in the CAN users and 6.0 months (range, 1.38–52.67) in the CAN non-users ($p = 0.25$). Table 1 summarizes the baseline characteristics of the study patients.

### *Overall survival*

The median OS was compared between the two groups. With a median follow-up of 29.2 months, the OS in the CAN users was 6.7 months (95% CI, 5.42–25.92) compared to 17.3 months (95% CI, 11.10–40.38) in the CAN non-users (HR, 1.78; 95% CI, 1.06–2.97; $p = 0.029$; Figure 1(a)). After adjustment for age, race, sex, tumor primary site, and PD-L1 expression, CAN use remained significantly associated with worse OS (HR, 2.25; 95% CI, 1.25–4.05; $p = 0.007$; Table 2).

### *Progression-free survival*

The median PFS was compared between the two groups. With a median follow-up of 29.2 months, the median PFS was 4.8 months (95% CI, 3.45–16.13) in the CAN users compared to 9.7 months (95% CI, 5.95–18.63) in the CAN non-users (HR,1.74; 95% CI, 1.09–2.79; $p = 0.021$; Figure 1(b)). After adjustment for race, tumor primary site, IO agent used, and site of metastasis, CAN use remained significantly associated with worse PFS (HR, 2.21; 95% CI, 1.33–3.68; $p = 0.002$; Table 3). In the multivariable analysis, race was an independent predictor of PFS. Patients of the White race had worse PFS compared to those of the Black race (HR, 2.04; 95% CI, 1.06–3.93; $p = 0.034$; Table 3).

**Table 1.** Patients' characteristics.

| Variable | All (*n* = 105) | CAN user (*n* = 28) | CAN non-user (*n* = 77) | *p* Value* |
|---|---|---|---|---|
| Age, year—median (range) | 65.74 (34.64, 89.45) | 59.18 (44.93, 82.56) | 68.38 (34.64, 89.45) | 0.013 |
| Race—no. (%) | | | | 0.080 |
| White | 87 (82.9) | 20 (71.4) | 67 (87.0) | |
| Black | 18 (17.1) | 8 (28.6) | 10 (13.0) | |
| Sex—no. (%) | | | | 0.125 |
| Male | 50 (47.6) | 17 (60.7) | 33 (42.9) | |
| Female | 55 (52.4) | 11 (39.3) | 44 (57.1) | |
| Smoking status—no. (%) | | | | 0.012 |
| Non-smoker | 21 (20.0) | 1 (3.6) | 20 (26.0) | |
| Smoker | 84 (80.0) | 27 (96.4) | 57 (74.0) | |
| Tumor site—no. (%) | | | | 0.199 |
| Lung | 65 (61.9) | 20 (71.4) | 45 (58.4) | |
| Head & neck | 12 (11.4) | 4 (14.3) | 8 (10.4) | |
| Other | 28 (26.7) | 4 (14.3) | 24 (31.2) | |
| Immunotherapy agent—no. (%) | | | | 0.927 |
| Nivolumab | 63 (60.0) | 17 (60.7) | 46 (59.7) | |
| Pembrolizumab | 27 (25.7) | 9 (32.1) | 18 (23.4) | |
| Nivolumab/ipilimumab | 6 (5.7) | 1 (3.6) | 5 (6.5) | |
| Atezolizumab | 6 (5.7) | 1 (3.6) | 5 (6.5) | |
| Durvalumab | 2 (1.9) | 0 (0) | 2 (2.6) | |
| Avelumab | 1 (1.0) | 0 (0) | 1 (1.3) | |
| Duration of the immunotherapy use, month—median (range) | 5.45 (1.38, 52.67) | 4.21 (1.84, 29.21) | 5.98 (1.38, 52.67) | 0.254 |
| Stage at IO therapy—no. (%) | | | | >0.99 |
| III | 1 (1.0) | 0 (0) | 1 (1.3) | |
| IV | 104 (99.0) | 28 (100.0) | 76 (98.7) | |
| Site of metastasis—no. (%) | | | | 0.403 |
| Visceral | 61 (58.1) | 14 (50.0) | 47 (61.0) | |
| Bones | 23 (21.9) | 6 (21.4) | 17 (22.1) | |
| CNS | 21 (20.0) | 8 (28.6) | 13 (16.9) | |

*(Continued)*

**Table 1.** (Continued)

| Variable | All ($n=105$) | CAN user ($n=28$) | CAN non-user ($n=77$) | $p$ Value* |
|---|---|---|---|---|
| PDL1 expression—no. (%) | | | | 0.464 |
| 0% | 24 (22.9) | 8 (28.6) | 16 (20.8) | |
| 1%–49% | 10 (9.5) | 4 (14.3) | 6 (7.8) | |
| >49% | 11 (10.5) | 3 (10.7) | 8 (10.4) | |
| Unknown | 60 (57.1) | 13 (46.4) | 47 (61.0) | |
| Line of treatment—no. (%) | | | | 0.355 |
| 1 | 16 (15.2) | 3 (10.7) | 13 (16.9) | |
| 2 | 31 (29.5) | 12 (42.9) | 19 (24.7) | |
| 3 | 38 (36.2) | 9 (32.1) | 29 (37.7) | |
| >3 | 20 (19.0) | 4 (14.3) | 16 (20.8) | |

*$p$ value calculated by Wilcoxon rank-sum test for continuous variables and Fisher's exact test for categorical variables.
CAN, Cannabis.

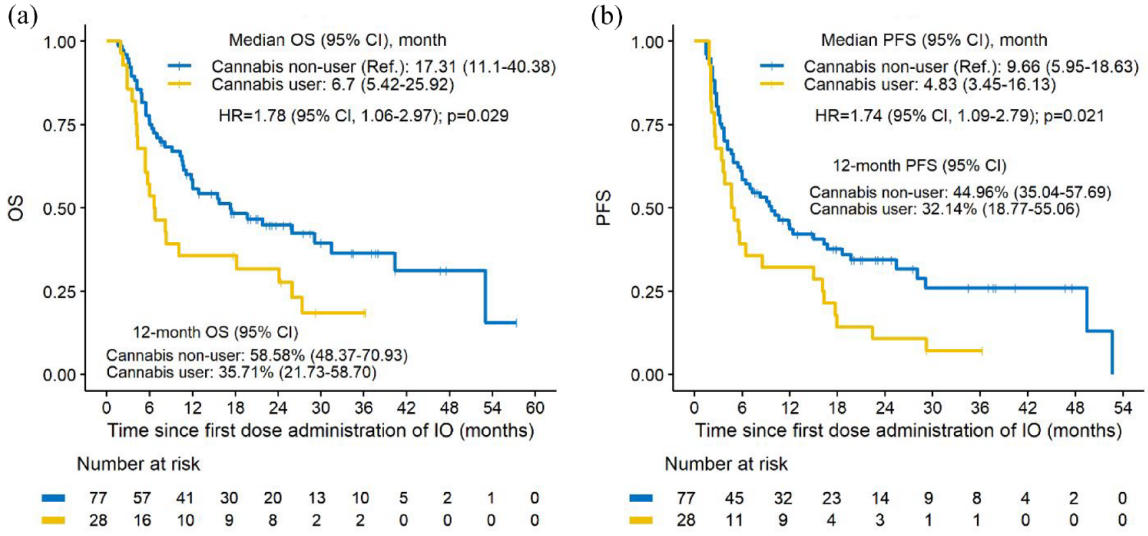


**Figure 1.** Kaplan–Meier curves for (a) OS and (b) PFS by group (cannabis user vs non-user, non-user as reference).
CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

### *Disease control rate*

The DCR was 10.7% among CAN users and 37.7% among CAN non-users (OR, 0.23; 95% CI, 0.06–0.68; $p=0.007$; Figure 2 and Supplemental 3). After adjustment for race, IO agent used, and PD-L1 expression, CAN use remained significantly associated with worse DCR (OR, 0.14; 95% CI, 0.03–0.49; $p=0.001$; Supplemental 3). In the multivariable analysis, race was an independent predictor of DCR. Patients of the White race had worse DCR compared to those of the Black race (OR, 0.26; 95% CI, 0.07–0.87; $p=0.03$; Supplemental 3).

## Racial disparity analysis

Race was found to be an independent predictor of PFS (HR, 2.04; $p=0.034$) and DCR (OR, 0.26;

**Table 2.** Univariable and multivariable Cox proportional hazard regression analyses of risk factors associated with and overall survival.

| | | Univariable | | Multivariable# | |
|---|---|---|---|---|---|
| | **Event/*n*** | **HR (95% CI)** | ***p* Value** | **HR (95% CI)** | ***p* Value** |
| Age | 67/105 | 1.01 (0.99–1.04) | 0.271 | 1.02 (0.998–1.05) | 0.071 |
| Race | | | | | |
| Black | 8/18 | Ref. | | Ref. | |
| White | 59/87 | 2.00 (0.95–4.20) | 0.068 | 1.79 (0.78–4.08) | 0.168 |
| Sex | | | | | |
| Male | 34/50 | Ref. | | Ref. | |
| Female | 33/55 | 0.71 (0.44–1.16) | 0.175 | 0.68 (0.41–1.15) | 0.154 |
| Smoking status | | | | | |
| Non-smoker | 13/21 | Ref. | | | |
| Smoker | 54/84 | 1.18 (0.64–2.17) | 0.594 | | |
| Tumor site | | | 0.282$ | | 0.091$ |
| Lung | 43/65 | Ref. | | Ref. | |
| Head & neck | 5/12 | 0.51 (0.20–1.30) | 0.161 | 0.37 (0.13–1.06) | 0.064 |
| Other | 19/28 | 1.03 (0.60–1.77) | 0.911 | 1.04 (0.54–2.01) | 0.896 |
| Immunotherapy agent | | | 0.732$ | | |
| PD1[a] | 57/90 | Ref. | | | |
| PDL1[b] | 6/9 | 1.27 (0.55–2.96) | 0.580 | | |
| PD1 + CTLA4[c] | 4/6 | 1.40 (0.50–3.87) | 0.520 | | |
| Site of metastasis | | | 0.859$ | | |
| Visceral | 40/61 | Ref. | | | |
| Bones | 14/23 | 1.19 (0.64–2.19) | 0.579 | | |
| CNS | 13/21 | 1.07 (0.57–2.01) | 0.838 | | |
| PDL1 expression | | | 0.543$ | | 0.776$ |
| 0% | 19/24 | Ref. | | Ref. | |
| 1%–49% | 4/10 | 0.55 (0.19–1.62) | 0.279 | 0.62 (0.20–1.87) | 0.392 |
| >49% | 5/11 | 0.59 (0.22–1.58) | 0.294 | 0.79 (0.28–2.24) | 0.663 |
| Unknown | 39/60 | 0.88 (0.50–1.52) | 0.642 | 1.02 (0.55–1.91) | 0.945 |
| Group | | | | | |
| Cannabis non-user | 45/77 | Ref. | | Ref. | |
| Cannabis user | 22/28 | 1.78 (1.06–2.97) | 0.029 | 2.25 (1.25–4.05) | 0.007 |

Event/*n*, numbers of events (death) and patients.
#Covariates for multivariable analysis were selected using LASSO-based penalized Cox regression.
$Global *p* value obtained by the likelihood ratio test.
[a]Nivolumab, pembrolizumab.
[b]Atezolizumab, durvalumab, and avelumab.
[c]Nivolumab/ipilimumab.
CI, confidence interval; HR, hazard ratio; PD-L1, Programmed death-ligand 1.

**Table 3.** Univariable and multivariable Cox proportional hazard regression analyses of risk factors associated with progression-free survival.

| | | Univariable | | Multivariable# | |
|---|---|---|---|---|---|
| | **Event/*n*** | **HR (95% CI)** | ***p* Value** | **HR (95% CI)** | ***p* Value** |
| Age | 80/105 | 0.997 (0.98–1.02) | 0.783 | | |
| Race | | | | | |
| Black | 12/18 | Ref. | | Ref. | |
| White | 68/87 | 1.72 (0.92–3.20) | 0.087 | 2.04 (1.06–3.93) | 0.034 |
| Sex | | | | | |
| Male | 39/50 | Ref. | | | |
| Female | 41/55 | 0.85 (0.54–1.33) | 0.477 | | |
| Smoking status | | | | | |
| Non-smoker | 15/21 | Ref. | | | |
| Smoker | 65/84 | 1.22 (0.69–2.14) | 0.493 | | |
| Tumor site | | | 0.450$ | | 0.622$ |
| Lung | 52/65 | Ref. | | Ref. | |
| Head & neck | 7/12 | 0.62 (0.28–1.37) | 0.234 | 0.70 (0.31–1.60) | 0.399 |
| Other | 21/28 | 0.95 (0.57–1.58) | 0.833 | 0.82 (0.42–1.62) | 0.573 |
| Immunotherapy agent | | | 0.418$ | | 0.461$ |
| PD1[a] | 68/90 | Ref. | | Ref. | |
| PDL1[b] | 8/9 | 1.69 (0.80–3.54) | 0.166 | 1.80 (0.71–4.57) | 0.219 |
| PD1 + CTLA4[c] | 4/6 | 1.20 (0.44–3.29) | 0.728 | 1.46 (0.46–4.62) | 0.524 |
| Site of metastasis | | | 0.425$ | | 0.620$ |
| Visceral | 46/61 | Ref. | | Ref. | |
| Bones | 18/23 | 1.45 (0.84–2.50) | 0.185 | 1.33 (0.75–2.38) | 0.331 |
| CNS | 16/21 | 1.17 (0.65–2.11) | 0.598 | 1.14 (0.62–2.09) | 0.680 |
| PDL1 expression | | | 0.560$ | | |
| 0% | 22/24 | Ref. | | | |
| 1%–49% | 8/10 | 0.95 (0.42–2.16) | 0.910 | | |
| >49% | 6/11 | 0.54 (0.22–1.35) | 0.187 | | |
| Unknown | 44/60 | 0.83 (0.49–1.40) | 0.475 | | |
| Group | | | | | |
| Cannabis non-user | 54/77 | Ref. | | Ref. | |
| Cannabis user | 26/28 | 1.74 (1.09–2.79) | 0.021 | 2.21 (1.33–3.68) | 0.002 |

Event/*n*, numbers of events (progression and death) and patients.
#Covariates for multivariable analysis were selected using LASSO-based penalized Cox regression.
$Global *p* value obtained by the likelihood ratio test.
[a]Nivolumab, pembrolizumab.
[b]Atezolizumab, durvalumab, avelumab.
[c]Nivolumab/ipilimumab.
CI, confidence interval; HR, hazard ratio.

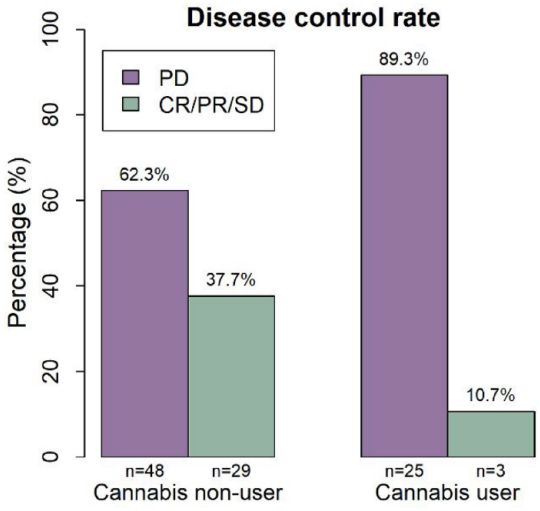


**Figure 2.** Bar plot showing the proportion of patients by group (cannabis user vs non-user) and disease control rate.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

$p = 0.030$). Therefore, an exploratory subgroup analysis was performed to assess the relationship between CAN use and clinical outcomes among various races. Among patients receiving IO, CAN use was associated with lower OS, PFS, and DCR in White patients but not in Black patients (Supplemental 4 and Figure S2). The median OS was 5.7 months among White CAN users and 15.7 months among White CAN non-users. Alternatively, the median OS was not reached among Black CAN users and was 29.1 months among Black CAN non-users. The median PFS was 3.7 months among White CAN users and 9.1 months among White CAN non-users. On the other hand, the median PFS was 17.0 months among Black CAN users and 29.1 months among CAN non-users (Figure 3).

## Discussion

Despite the established benefit of CAN in palliating symptoms, there remains a substantial concern about the potential negative effect on clinical outcomes and the possible antagonistic interaction with antineoplastic agents, particularly IO. Preclinically, Xiong et al.[31] showed using a mouse model that THC reduces the therapeutic effect of PD-1 blockade by suppressing T cell-mediated antitumor immunity. On the other hand, preclinical investigations conducted by Waissengrin et al. detected no detrimental effect of concomitant use of CAN and IO.[26] In our study, we sought to examine the relationship between CAN use and clinical outcomes in patients receiving IO. We extended upon the previously reported studies to evaluate the effect of modest doses of prescribed CAN on cancer outcomes, which is more clinically relevant in the United States. We found a significant inverse relationship between CAN use and OS, PFS, and DCR among patients receiving IO. This impact persisted despite adjusting for multiple variables such as age, gender, race, IO agent used, tumor type, site of metastasis, and PD-L1 expression. These findings are consistent with some but not all of the reported studies exploring this matter. Bala-Sela et al. conducted a prospective observatory study on 102 patients with advanced cancers receiving IO, 34 of whom received monthly CAN doses of 20–40 g. They reported lower OS, PFS, and DCR in CAN users.[32] Another retrospective study by Taha et al. evaluated 140 patients with advanced cancers receiving nivolumab, 51 of whom had a monthly CAN dose of $\geqslant$20 g, and observed a lower response rate (RR) in the CAN users without effect on OS or PFS.[25] Another study by Waissengrin et al. examined 201 patients with metastatic NSCLC treated with pembrolizumab and consumed a median monthly CAN dose of 30 g. Authors of this study reported no significant effect of CAN on time-to-progression or OS. The median time-to-progression was 5.6 months in the CAN users and 6.1 months in the CAN non-users ($p = 0.386$). The median OS was numerically higher in the CAN nonusers (54.9 vs 23.6 months) but did not reach statistical significance ($p = 0.08$). The trend toward worse OS in the CAN users was attributed to a higher disease and symptom burden.[33] However, the difference in outcome between the groups is larger in OS compared to time-to-progression, which may indicate a potential impact of CAN use on survival that may have been veiled in this patient population. Of note, all the above studies used exceedingly high CAN doses ($\geqslant$20 g monthly, i.e., >666 mg per day). Such high doses are rarely used therapeutically in the United States. In our study, most patients received lower CAN doses of 5–10 mg daily ($\leqslant$0.31 g monthly) and we still noticed a similar adverse impact on clinical outcomes, indicating that even lower doses of CAN induce significant immunosuppression sufficient to counteract the antineoplastic effect of IO. In

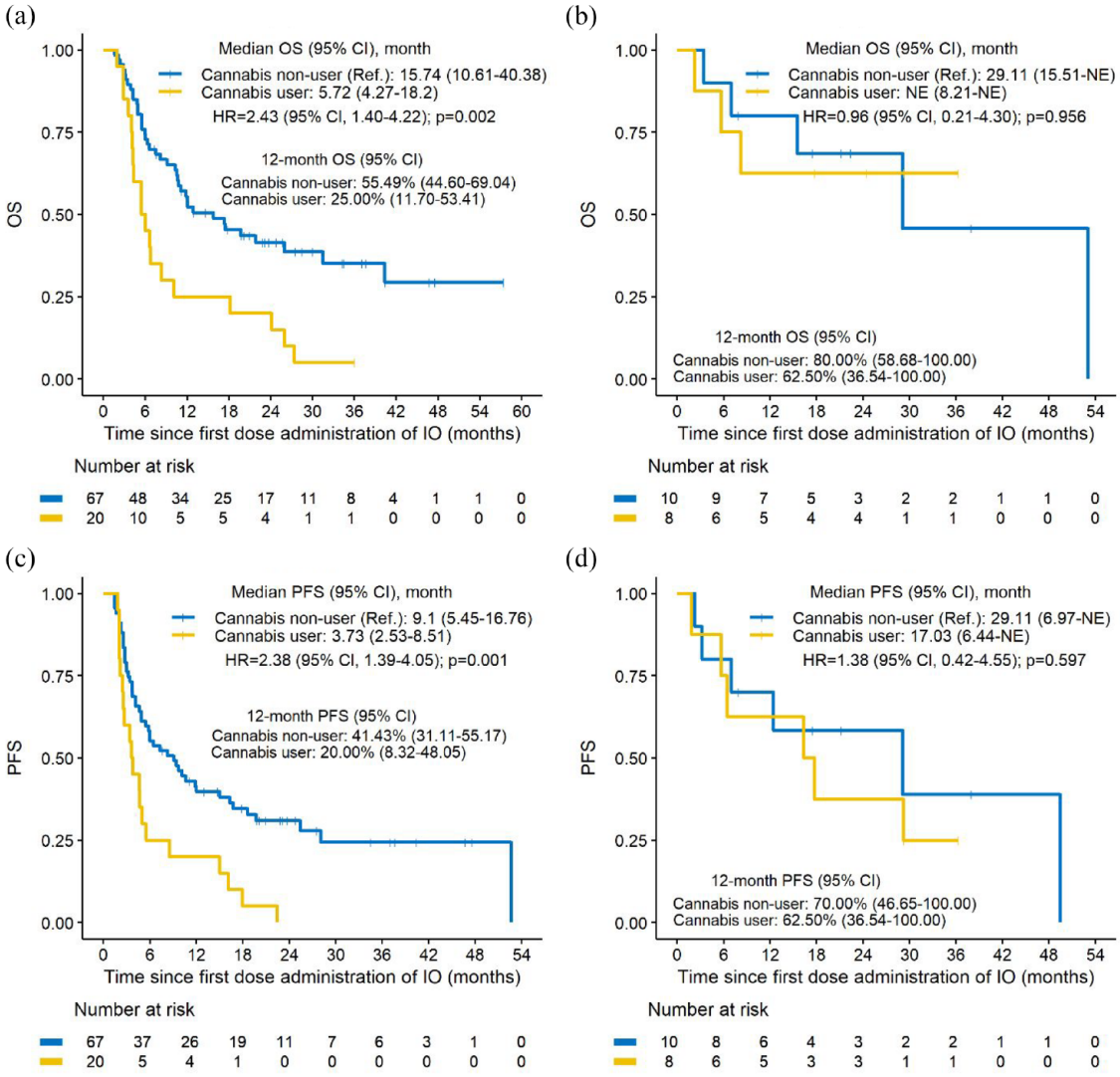


**Figure 3.** Kaplan–Meier curves for OS in White (a) and Black (b) and PFS in White (c) and Black (d) by group (cannabis user vs non-user, non-user as reference). Interaction *p* values between race and group for OS and PFS are 0.181 and 0.297, respectively.
CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival.

addition, most of the patients in our study received a prescribed oral formulation, which mainly contains THC. In the other studies, most of the patients received CAN via inhalation but some received CAN as an oil extract, which is likely CBD based.

There are several mechanisms through which THC suppresses immune signaling. These have been broadly classified into immune cell apoptosis, inhibition of proliferation, suppression of cytokine and chemokine production, and induction of T regulatory cells.[23] THC is known to suppress CD8+ and cytotoxic T lymphocytes and inhibits lymphocyte proliferation, maturation, and response to exogenous stimulation.[34] This subsequently leads to a remarkable immunosuppression, which could interfere with the function of IO. Such immune suppression has been linked to inhibition of cannabinoid receptor 2 and involvement of the JAK/STAT pathway, which mediates inhibition of T-cell activation.[31] On the other hand, while CBD also suppresses T-lymphocytes and modulates the cannabinoid

receptors, resulting in immunosuppression, there have been suggestions that CBD may have an immunostimulatory effect.[35,36] This biphasic response to CBD is believed to be dependent on the dose and concentration of CBD and cell culture conditions, including immune stimulant and response to the immune stimulant. CBD's ability to increase intracellular calcium is likely responsible for the immunostimulatory effect of CBD, which includes neutrophil degranulation, mast cell activation, and chemotaxis.[35,37–39] Therefore, it is possible that the action exerted by THC is responsible for this antagonistic effect to IO seen in our patients. In the study conducted by Waissengrin et al.[33] that showed no significant adverse effect of CAN on clinical outcomes, 49% of the patients in this study used oil extracts, possibly CBD based. On the other hand, lower percentages of patients in the studies reported by Bela-Sela et al. and Taha et al. consumed CAN in an oil form only (25% and 35%, respectively).[25,32] Similar to our study, the predominance of THC in these studies could possibly explain the noticeable adverse effect of CAN on clinical outcomes. Moreover, Taha et al. performed an identification analysis of CAN characteristics using a high-performance liquid chromatography-diode array detector to precisely categorize phytocannabinoids. Although there was no significant difference in RR to IO between THC and CBD and between high and low doses of each, there was a notable numeric trend toward better RR when THC is used in high compared to low doses (29.6% vs 10%) and when CBD is used in low compared to high doses (41.7% vs 16%). Overall, the best RR was seen in patients who received low doses of CBD.[25] While these findings did not reach statistical significance, the study is likely underpowered to assess the difference between these groups due to the small sample size. Nonetheless, this numeric difference in RR to THC and CBD may partly explain the discrepancy between the reported studies.

IO agents are thought to modulate cancer-induced immunosuppression, which occurs by interrupting cell evasion of immune surveillance. The interaction between the antigen-presenting cells and T-lymphocytes results in T-cell activation, a mechanism that is co-stimulated with the expression of multiple molecules on the T-cell surface, ultimately inducing tumor rejection.[25,31,40] On the other hand, CAN induces immunosuppression by impairing the function of the tumor-specific T cell, NK cells, dendritic cells, and macrophages, enhancing T-cell apoptosis and reducing cytokine production in a dose-dependent pattern.[31,41–44] These contradictory effects on the immune system could explain the negative clinical outcomes seen when these agents are used concurrently.

Racial disparity in oncology care has been present for decades and has been primarily attributed to access to care. In our study, we performed an exploratory analysis and noted a significant differential effect on CAN among different races. Black patients had no significant detriment in PFS and OS when used CAN. On the other hand, White patients had significantly worse PFS and OS when using CAN compared to White patients who did not use CAN. White patients using CAN had the worst PFS and OS among all racial subgroups (Figure S1). Although this could be attributed to the small number of Black patients in this study, genetic variability in the metabolism of CAN could be responsible for this difference. A study reported by Thethi et al. noted that African American patients have a higher prevalence of endocannabinoid receptor type 1 gene 3813A/G and fatty acid amide hydrolase 385 polymorphisms, and a lower prevalence of endocannabinoid receptor type 1 gene 4895A/G polymorphisms. The difference in genetic compositions of patients of various races could affect the metabolism of CAN, and therefore, affects how CAN interacts with IO among various racial groups.[45]

Tobacco use is strongly associated with worse lung cancer outcomes and survival.[46] The interaction between tobacco and CAN is complex. In our study, CAN users were more likely to be tobacco users as well. This finding concurs with some of the previously published studies on this topic.[25,27] In fact, one of the previously published studies on this topic was criticized for not accounting for this important potentially confounding factor.[24] In our study, tobacco use did not significantly influence the effect of CAN use on PFS and OS.

This study has several limitations. This study is a retrospective with a small sample size, which limits the power of the study. The patients included in this study, the IO agent used, and the CAN agent used are heterogeneous, which could limit

the generalizability of the results and may give opposing results at times. The exact dose used and the compliance with the use of CAN could not be assured and was mainly based on prescription logs and providers' documentation. In addition, some patients may not report or underreport recreational use of CAN (smoked, edible, and CBD formulations), which could influence the results of the study. Underreporting of CAN use could have occurred due to concerns about legal litigation and public stigma as most of the patients were treated before the legalization of CAN in Michigan in November 2018. Public stigma appears to be particularly heightened in cancer patients, resulting in altered behavior and underreporting of CAN use.[47] While the Prescription Drug Reporting Program tracks the use of several controlled drugs, to date prescription CAN is not tracked through this system; thus, this tool is not helpful in monitoring prescribed CAN use. It is also possible that CAN users have higher symptoms and disease burden that could have confounded the outcomes. We attempted to account for several but not all disease and host-related confounding factors, such as age, diagnosis, metastatic site, and stage. However, the impact of unmeasured factors could potentially confound the results of this study. Finally, the study used RECIST criteria to assess response, which was the institutional method used at that time. iRECIST could result in a better evaluation of response in patients undergoing treatment with IO.

In summary, our study showed a negative impact of CAN use on OS, PFS, and DCR in cancer patients undergoing treatment with IO, which could be explained by the antagonistic interaction between CAN and IO. Our exploratory data suggest that the negative effect of CAN is primarily restricted to White patients, and sparing Black patients, which could possibly be explained by the genetic composition of different racial groups and its effect on the metabolism of CAN. A randomized clinical trial is needed to rigorously assess the interaction between CAN and IO and further explore the potential racial disparity in response to CAN and its interaction with IO.

## Declarations

### *Ethics approval and consent to participate*

The study was deemed exempt by the institutional review board at Ascension St John Hospital, Detroit, Michigan, USA. Therefore, informed consent was waived.

### *Consent for publication*

Patient-informed consents were waived by the institutional review board. All authors consented to the publication of this manuscript.

### *Author contributions*

**Tarik Hadid:** Conceptualization; Investigation; Writing – original draft; Writing – review & editing.

**Adam Biedny:** Conceptualization; Writing – review & editing.

**Hirva Mamdani:** Methodology; Validation; Writing – review & editing.

**Asfar Azmi:** Methodology; Validation; Writing – review & editing.

**Seongho Kim:** Data curation; Formal analysis; Methodology; Software; Writing – review & editing.

**Hyejeong Jang:** Data curation; Formal analysis; Methodology; Software; Writing – review & editing.

**Dipesh Uprety:** Methodology; Validation; Writing – review & editing.

**Mohammed Najeeb Al Hallak:** Methodology; Writing – review & editing.

**Ammar Sukari:** Methodology; Supervision; Validation; Writing – review & editing.

### *Acknowledgements*

The authors thank Ayad Al-Katib, MD from the Department of Oncology at Wayne State University for his assistance in reviewing and editing this manuscript.

### *Funding*

The authors received no financial support for the research, authorship, and/or publication of this article.

### *Competing interests*

The authors declare that there is no conflict of interest.

### *Availability of data and materials*

Data are available if needed.

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**Supplemental material**
Supplemental material for this article is available online.

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## Abbreviations

| | |
|---|---|
| CAN | Cannabis |
| IO | Immunotherapy |
| OS | Overall survival |
| PFS | Progression-free survival |
| DCR | Disease control rate |
| HR | Hazard ratio |
| CI | Confidence interval |
| OR | Odds ratio |
| THC | $^{\Delta}$9-tetrahydrocannabinol |
| CBD | cannabidiol |
| US | United States |
| FDA | Food and Drug Administration |
| CTLA-4 | Cytotoxic T-lymphocyte-associated protein 4 |
| PD-L1 | Programmed death-ligand 1 |
| CR | Complete response |
| PR | Partial response |
| SD | Stable disease |
| RECIST | Response evaluation criteria in solid tumors |
| RR | Response rate |
| iRECIST | Modified Response Evaluation Criteria in Solid Tumors in cancer immunotherapy trials |