Abstract No. 11188

Real-World Outcomes of SSRI Use in Metastatic Melanoma Patients Treated with Immune Checkpoint Inhibitors

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Background

Immune checkpoint inhibitors (ICIs) have transformed outcomes for **metastatic melanoma**, yet substantial variability in response remains.

Concomitant medications may modulate antitumor immunity and influence ICI effectiveness. **Selective serotonin reuptake inhibitors** (SSRIs) have been shown in preclinical and translational studies to enhance T-cell-mediated antitumor immunity and synergize with PD-1 blockade[1].

Real-world evidence in melanoma is limited. **We assessed whether baseline SSRI use is associated with improved ICI outcomes in a large real-world cohort of metastatic melanoma patients.**

Methods

Study Design: Retrospective cohort study using a nationally representative real-world dataset from the Atropos Evidence™ Network, integrating open claims and EHR data mapped to OMOP CDM v5.3.

Population, Comparators, and Matching: Adults with metastatic melanoma initiating first-line pembrolizumab, nivolumab, or ipilimumab (identified by ICD & RxNorm codes). Index date = ICI initiation. The comparator arms were ≥30 days of SSRI use prior to index vs no prior SSRI exposure. Matching across the cohorts was accomplished using 1:1 high-dimensional propensity score (hdPS) matching using ICD, CPT, and RxNorm features fitted with LASSO-regularized logistic regression. GLP-1 and statin baseline exposures were hdPS features.

Outcomes: 1-year OS, time to ICI discontinuation, duration of ICI therapy, and post-index steroid use.

Characteristic	Unmatched cohort: No SSRI n = 3,290	Unmatched cohort: SSRI n = 307	Unmatched cohort: SMD	PS-matched cohort: No SSRI n = 304	PS-matched cohort: SSRI n = 304	PS-matched cohort: SMD
DEMOGRAPHICS						
Female, n (%)	1,043 (31.7%)	151 (49.2%)	0.37	156 (51.3%)	148 (48.7%)	0.05
Age, mean (SD)	65.6 (13.5)	65.8 (12.0)	0.01	65.7 (12.9)	65.8 (12.0)	0.01
White race, n (%)	1,921 (58.4%)	194 (63.2%)	0.10	193 (63.5%)	192 (63.2%)	0.01
Hispanic ethnicity, n (%)	20 (0.6%)	4 (1.3%)	0.09	1 (0.3%)	4 (1.3%)	0.11
COMORBIDITIES						
Charlson score, mean (SD)	12.1 (2.8)	12.7 (2.9)	0.24	12.8 (2.9)	12.7 (2.9)	0.04
Diabetes, no complications, n (%)	414 (12.6%)	61 (19.9%)	0.22	48 (15.8%)	59 (19.4%)	0.10
Diabetes, with complications, n (%)	361 (11.0%)	55 (17.9%)	0.22	54 (17.8%)	55 (18.1%)	0.01
Congestive heart failure, n (%)	375 (11.4%)	51 (16.6%)	0.16	49 (16.1%)	51 (16.8%)	0.02
Chronic pulmonary disease, n (%)	719 (21.9%)	114 (37.1%)	0.36	119 (39.1%)	111 (36.5%)	0.05
Cerebrovascular disease, n (%)	696 (21.2%)	79 (25.7%)	0.11	82 (27.0%)	78 (25.7%)	0.03
Mild liver disease, n (%)	800 (24.3%)	98 (31.9%)	0.18	75 (24.7%)	97 (31.9%)	0.16
Renal disease, n (%)	478 (14.5%)	49 (16.0%)	0.04	67 (22.0%)	49 (16.1%)	0.15
Rheumatic disease, n (%)	147 (4.5%)	26 (8.5%)	0.19	23 (7.6%)	26 (8.5%)	0.04
BASELINE MEDICATIONS						
Statin, n (%)	1,054 (32.0%)	151 (49.2%)	0.37	155 (51.0%)	149 (49.0%)	0.04
GLP-1 receptor agonist, n (%)	61 (1.9%)	14 (4.6%)	0.19	16 (5.3%)	14 (4.6%)	0.03

Baseline SSRI use was not associated with improved survival or other immunotherapy outcomes

*Despite strong mechanistic rationale, this real-world analysis shows **no clinically meaningful benefit** of baseline SSRI use across overall survival, ICI discontinuation, duration of therapy, or steroid use.*

Results/Graphs/Data

Figure 1

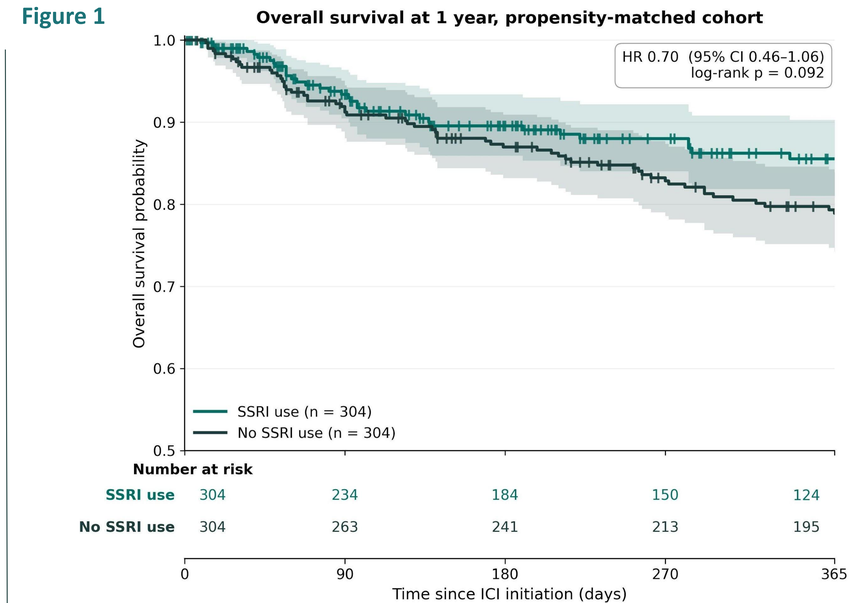

Figure 2

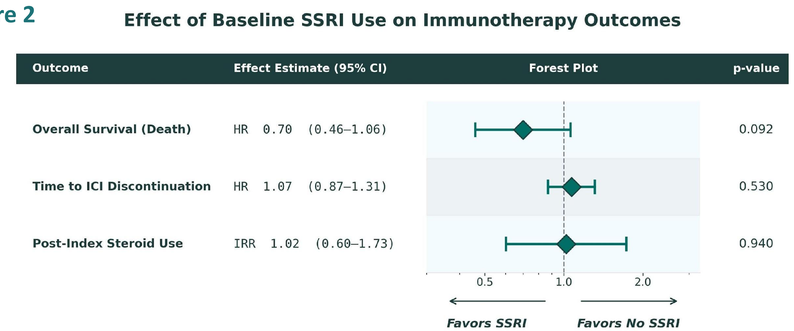

Figure 3

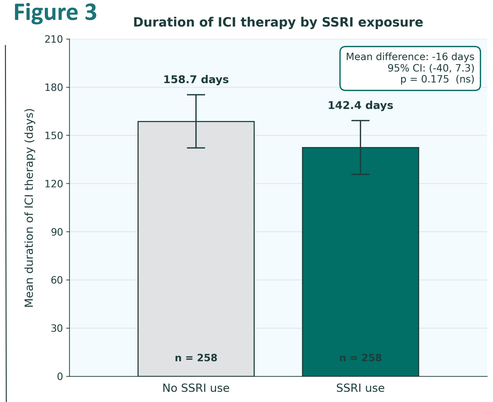

Figure 1. Kaplan-Meier curves for 1-year overall survival in metastatic melanoma patients initiating immune checkpoint inhibitors, comparing those with baseline SSRI exposure (n = 304) to propensity-matched patients without prior SSRI use (n = 304). Baseline SSRI use was associated with a numerically lower but not statistically significant risk of death (HR 0.70; 95% CI 0.46–1.06; p = 0.092).

Figure 2. Forest plot of effect estimates comparing baseline SSRI users (n = 304) versus non-users (n = 304) on overall survival, time to ICI discontinuation, and post-index steroid use after 1:1 high-dimensional propensity score matching. None of the three outcomes reached statistical significance, with all 95% confidence intervals crossing the null.

Figure 3. Mean duration of immune checkpoint inhibitor (ICI) therapy among propensity-score matched patients with metastatic melanoma, stratified by baseline SSRI exposure (n = 258 per arm). No statistically significant difference was observed between groups (mean difference −16 days, 95% CI −40 to 7.3; p = 0.175).

Future Directions for Research

A prospective randomized trial of SSRI exposure concurrent with first-line ICI in metastatic melanoma is needed to test the mechanistic hypothesis suggested by preclinical work. Other primary cancer types commonly treated with ICIs should be studied as well (eg, lung, breast, kidney, etc.).

Other exposures that may have in influence on ICI efficacy are actively being researched (eg, GLP-1, statins) and should be studied in the real-world setting.

Data, Reference, and Contact

Analyses were generated using the Atropos Evidence™ Network (Apollo dataset, v2.0.0): a de-identified national EHR + linked claims dataset of 142M+ U.S. patients with linked death records.

Reference:
Nicholas DeVito et al. Addressing Common Medications That Influence Immunotherapy Response in Solid Tumors. J Clin Oncol 44, 529-533(2026). DOI:10.1200/JCO-25-01811

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