

Effect of Sodium-Glucose Cotransport-2 Inhibitors on Outcomes in Patients with Lung Cancer Receiving Immune Checkpoint Inhibitors: A Large Real-World Cohort Study

Maria Santiago Estevez¹, Hakeem Asad¹, Yoshito Nishimura¹, Antonious Hazim², Richard C. Godby¹

¹Division of Hematology, Mayo Clinic, Rochester, Minnesota, USA. ²Mayo Clinic, Phoenix, Arizona, USA

Correspondence: santiagoestevez.maria@mayo.edu

Introduction

Background:

- Immune checkpoint inhibitors (ICIs) improve outcomes across malignancies but are associated with immune-related adverse events (irAEs).
- Although low-grade irAEs can be treated with temporary ICI discontinuation, some grade 2 or severe events often necessitate permanent ICI discontinuation and high-dose corticosteroids.
- Emerging evidence suggests that higher peak corticosteroid doses are associated with worse outcomes including reduced progression-free survival (PFS), overall survival (OS), and tumor-specific survival.
- Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have been known to possess anti-inflammatory effects, but its association with outcomes in ICI recipients is unknown.

Aim:

- To analyze the effect of SGLT2i on outcomes in patients with lung cancer receiving ICIs.

Methods

Retrospective cohort study using Mayo Clinic Discovery to identify lung cancer patients treated with ICIs including programmed cell death protein 1 (PD-1), PD ligand 1 (PD-L1), and/or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors through December 2025. Patients were stratified by exposure to SGLT2i.

The primary endpoint was 1-year OS.

Secondary endpoint included systemic prednisone use (surrogate for irAEs).

Propensity score matching with age, sex, race, and heart failure was performed at the ratio of 1:1 and caliper of 0.0044.

Cohort A represents patients exposed to SGLT2i.

Cohort B represents patients without exposure to SGLT2i.

OS was analyzed using the Kaplan-Meier method and compared using log-rank testing. Hazard ratios (HR) were estimated using Cox proportional hazards models. Categorical outcomes were compared using chi-squared testing.

Results

- A total of **6,368** lung cancer patients treated with ICIs were included; 265 (4.2%) exposed to SGLT2i and 6,105 (95.8%) not exposed to SGLT2i.
- Baseline demographics were comparable between groups with the **median age of 71.2 years** (interquartile range (IQR) 64.6–77.1) in those with SGLT2i and **69.3 years** (IQR 62.0–76.2) in those without SGLT2i, but not race (89.7% vs. 93.5% White; $p = 0.015$) and sex where those with SGLT2i were **predominantly male** (73.0%) compared to those without SGLT2i (52.9%, $p < 0.001$).
- Propensity match analysis identified a total of **197** exposed to SGLT2i (Cohort A) and 197 without exposure to SGLT2i (cohort B) (**Table 1**). One-year OS was **significantly higher** in the SGLT2i group compared to the non-SGLT2i group (61.2% vs. 50.5%; $p=0.021$). Prednisone **use was higher** in patients not exposed to SGLT2i (14.2% vs. 9.1%), although not statistically significant.

Table 1. Propensity Score Matching: SGLT2 Inhibitor Use in Patients with Lung Cancer Treated with Immune Checkpoint Inhibitors

Characteristic	SGLT2i	No SGLT2i	Chi-square	p-value
Total patients	197	197	-	-
Median age, Years (IQR)	71.6 (64.5-78)	71.0 (65.0-77.0)	-	-
Race (White)	97 %	96.4%	0.08	-
Sex (male)	72.6%	72.1%	0.01	-
52 -week Survival	61.2%	50.5%		0.021
Prednisone use	9.1%	14.2%	2.5	0.4

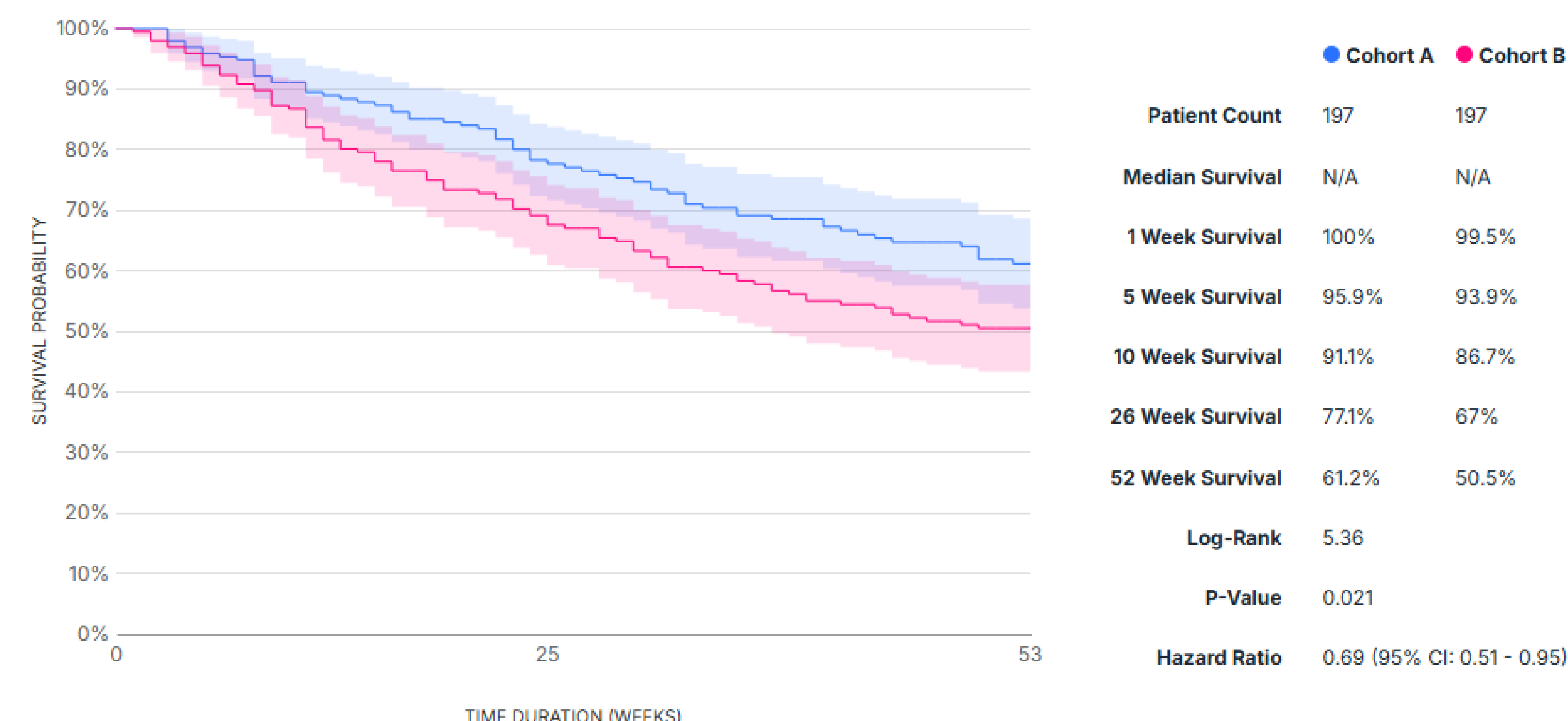


Figure 1. Survival in Patients with Lung Cancer Treated with Immune Checkpoint Inhibitors. Cohort A (Blue) represents patients exposed to SGLT2i, whereas Cohort B (pink) represents patients not exposed to SGLT2i.

Discussion

- SGLT2i exposure was associated with improved 52 week survival in patients with lung cancer receiving ICI therapy after propensity matching.
- The known anti-inflammatory properties of SGLT2i may attenuate irAE-driving inflammatory pathways and reduce the need for high dose corticosteroids and ICI discontinuation.
- Prednisone use was used as a surrogate for irAEs.
- SGLT2i use was associated with a lower rate of prednisone use (9.1% vs. 14.2%); however, this difference did not represent a statistical significance.
- Prospective studies are needed to confirm this association and examine the incidence of irAEs and time to ICI discontinuation.
- Despite propensity matching, baseline sex and race imbalance and unmeasured confounders limit the causal interpretation of the study.

Take away points and Future Directions

- In patients with lung cancer treated with ICIs, SGLT2i exposure was associated with significantly improved one-year OS.
- There was a lower use of systemic prednisone in those with SGLT2i exposure which may suggest potentially lower incidence of severe irAEs in the cohort.
- SGLT2i supports further study as an adjunct in ICI recipients, especially those with diabetes, heart failure, or CKD, where metabolic and immunomodulatory benefits may overlap.

Future Directions

- Confirm the survival benefit through prospective studies, including biomarker studies of inflammation to clarify whether an anti-inflammatory mechanism drives the observed effect.
- Examine if timing of SGLT2 initiation relative to ICI start affects survival.
- Assess minimum duration of exposure needed to observe a survival benefit in patients receiving SGLT2i therapy.

AI use:

- Figure 1 created through Mayo CPS website. No other AI service was used.