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Glucagon-like peptide-1 receptor agonist exposure is associated with lower secondary malignancy risk during watch-and-wait in chronic lymphocytic leukemia: a time-varying analysis

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The authors declare no conflicts of interest.

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AI use declaration

ChatGPT (OpenAI) was used to assist with language editing, and development and quality checking of analytical code. All AI-assisted content was subject to review by the authors, who retain full responsibility for the accuracy, integrity, and interpretation of the study.

Data-sharing statement

The patient-level data underlying this study are held by Clalit Health Services and are not publicly available due to patient privacy and institutional data-access restrictions. Access to the underlying data is subject to approval by Clalit Health Services and applicable ethical and data-governance requirements.

Chronic lymphocytic leukemia (CLL) is the most common leukemia in Western countries and is characterized by profound immune dysregulation [1,2]. Defects in both humoral and cellular immunity, contribute not only to an increased susceptibility to infections but also to a substantially increased risk of second primary malignancies[1,3-5].

Patients with CLL have a higher incidence of second primary malignancies than the general population, including hematologic malignancies, cutaneous cancers and a broad range of solid tumors[3-5]. Although part of this excess risk has traditionally been attributed to the leukemogenic and carcinogenic effects of cytotoxic chemotherapy[6], an increased risk of second primary malignancies has also been observed in the era of targeted therapies, including Bruton tyrosine kinase inhibitors (BTKis) [7,8]. Importantly, excess risk is already evident during the watch-and-wait period, before initiation of CLL-directed therapy, indicating that the underlying disease biology itself plays a central role.[9,10].

Glucagon-like peptide-1 receptor agonists (GLP-1RA), widely used to treat type 2 diabetes and obesity, have pleiotropic effects beyond glycemic control, including anti-inflammatory and potential immunomodulatory properties[11]. Emerging studies suggest that GLP-1RA therapy may influence the risk of selected malignancies[12]. However, whether GLP-1RA exposure is associated with the risk of second primary malignancies in patients with CLL has not been investigated.

We evaluated whether time-varying exposure to GLP-1RA was associated with reduced risk of developing a secondary malignancy during the watch-and-wait period following CLL diagnosis.

We conducted a retrospective population-based cohort study using deidentified longitudinal electronic health records from Clalit Health Services, Israel's largest healthcare organization. The source cohort comprised 5,504 patients diagnosed with CLL from 2002 through 2024. The study was approved by the institutional Helsinki Committee and conducted in accordance with the Declaration of Helsinki.

Patients with the other malignancy before the CLL index date were excluded. Patients were required to have at least 3 months of follow-up after CLL diagnosis. Follow-up began at CLL diagnosis and ended at the first relevant secondary malignancy, initiation of CLL-directed therapy, death, 15 years after CLL diagnosis, or June 17, 2026, whichever occurred first.

The primary endpoint was the first secondary malignancy diagnosed after CLL, including hematologic malignancies, melanoma, and other solid tumors. Separate endpoint-specific

cohorts were used for hematologic malignancies, other solid tumors, and melanoma; each endpoint analysis considered the first event of that type.

GLP-1RA use was modeled as a time-varying exposure. Patients contributed “unexposed“ person-time from CLL diagnosis until 3 months after GLP-1RA initiation and “exposed” person-time thereafter. Initiators who did not complete the 3-month of treatment were considered as “unexposed”. Time-dependent survival was visualized using Simon-Makuch curves (Figure 1A and Supplementary Figure S1A).

Covariates included age, sex, diabetes mellitus, HbA1c, body mass index, hemoglobin, platelet count, and white blood cell count. Endpoint-specific Cox models used backward elimination, sequentially removing covariates with P>0.05. A post hoc descriptive analysis assessed paired BMI before and approximately 6 and 12 months after GLP-1RA initiation.

A complementary analysis was performed by matching patients with similar propensity scores to assess the consistency of the findings. As this approach did not fully account for changes in treatment exposure over time, it was considered a supportive analysis.

Of 5,504 patients in the CLL cohort, 456 initiated GLP-1RA therapy during follow-up. After excluding patients who did not meet the eligibility criteria, 3,461 patients were included in the primary analysis, including 276 who achieved effective GLP-1RA exposure.
Baseline characteristics are summarized in Table 1.
Over a median follow-up of 4.5 years (interquartile range, 2.2–7.9), 619 patients developed secondary malignancy. In an analysis accounting for changes in GLP-1RA use over time (time varying) GLP-1RA use was associated with a 39% lower adjusted hazard of developing a secondary malignancy using (aHR, 0.61; 95% CI, 0.38–0.97; P=0.04) (Supplementary Figure S1B).
After accounting for BMI at baseline, the association between GLP-1RA use and the outcome remained similar (HR, 0.58; 95% CI, 0.33–1.01; P=0.05). Baseline BMI itself was not significantly associated with the outcome (HR, 1.01; 95% CI, 0.97–1.05; P=0.50).

Among patients who started GLP-1RA treatment, mean BMI decreased by 1.13 kg/m² at approximately 6 months (n=138) and by 1.04 kg/m² at approximately 12 months (n=131). A reduction in BMI of at least 5% was observed in 33.3% and 35.1% of patients at these time points, respectively (Supplementary Table S2).

In a separate analysis focusing on hematologic malignancies, GLP-1RA use was similarly associated with a lower hazard of developing a hematologic malignancy (4,196 patients; 405

events; aHR, 0.55; 95% CI, 0.30–0.99; P=0.05). The distribution of first hematologic malignancies in this endpoint-specific cohort is shown in Table 2, Panel B.

Associations were not statistically significant for other solid malignancies (4,200 patients; 387 events; aHR, 0.76; 95% CI, 0.44–1.33; P=0.34) or melanoma (4,932 patients; 42 events; aHR, 1.12; 95% CI, 0.27–4.69; P=0.87) (Supplementary Figure S1B).

In the primary analytic cohort, 276 patients achieved effective GLP-1RA exposure after the prespecified minimum 3-month of treatment, whereas 3,185 contributed to the unexposed cohort. Of the 619 first secondary malignancies overall, 304 (49.1%) were other solid malignancies, 286 (46.2%) were hematologic malignancies, and 29 (4.7%) were melanoma (Table 2, Panel A).

Propensity score matching identified 253 matched pairs (506 patients) with well-balanced baseline characteristics (all absolute standardized mean differences [SMDs] <0.10; Supplementary Table S1; Supplementary Figure S1C). During follow-up, sixty-eight secondary malignancy events occurred in the matched cohort, 14 among GLP-1RA users and 54 among controls. In this matched analysis, GLP-1RA use was associated with a lower hazard of developing a secondary malignancy (aHR, 0.22; 95% CI, 0.12–0.39; P<0.005). These findings were consistent with the primary analysis, which accounted for changes in GLP-1RA administration over time (Table 2, Panel C).

Next, separate propensity score-matched analyses were performed to evaluate the occurrence of hematologic and solid malignancies.

The matched hematologic cohort included 654 patients (327 matched pairs) and 54 events; fixed duration (static) GLP-1RA exposure was associated with a lower hazard of hematologic malignancy (aHR, 0.23; 95% CI, 0.12–0.45; P<0.005). The matched cohort for other solid malignancies included 568 patients (284 matched pairs) and 45 events. GLP-1RA use was associated with a lower hazard of these malignancies (aHR, 0.32; 95% CI, 0.17–0.63; P<0.005). However, this association was not statistically significant in the primary analysis, which accounted for changes in GLP-1RA use over time. Since the matched analyses used a fixed definition of GLP-1RA exposure and showed stronger associations than the primary analyses, their findings should be considered supportive and exploratory rather than confirmatory (Table 2, Panel C).

Crude Kaplan-Meier curves for the propensity score-matched primary and hematologic-malignancy cohorts are shown in Figure 1B-C. These unadjusted curves use fixed duration (static) “effective-exposure” and do not account for time-dependent GLP-1RA initiation. Finally, we performed a separate analysis of melanoma incidence. The matched cohort included 690 patients (345 matched pairs), with only 3 events. The results did not show a statistically significant association between GLP-1RA use and melanoma incidence (aHR, 2.16; 95% CI, 0.30–15.67; P=0.45).

In the analysis of secondary malignancy burden, all 619 patients with a primary secondary-malignancy event were included. Among these patients, 113 (18.3%) developed at least two different types of secondary malignancies during follow-up while not receiving CLL-directed treatment, and 15 developed three or more types. Overall, 754 distinct patient-malignancy pairs were identified (Table 2, Panel D).

In this population-based study of patients with CLL who were managed without CLL-directed therapy, GLP-1RA exposure was associated with a lower risk of developing a first secondary malignancy. The association was also observed for secondary hematologic malignancies, whereas no statistically significant association was identified for other solid tumors or melanoma. These findings suggest that GLP-1RA exposure may be associated with reduced secondary-malignancy risk in CLL, although the results should be interpreted as observational and hypothesis-generating.

The primary analysis treated GLP-1RA use as a time-varying exposure, reflecting the fact that patients could initiate treatment at different times after their CLL diagnosis. In a complementary propensity score-matched analysis, the association was in the same direction but was stronger than in the primary analysis. Similar findings were observed for hematologic malignancies. For other solid tumors the matched analysis suggested an association between GLP-1RA use and a lower hazard of developing a secondary malignancy, whereas the primary analysis, which accounted for changes in GLP-1RA use over time, did not show a statistically significant association. We therefore consider the matched analyses supportive rather than confirmatory, with the time-varying models providing the main estimates of association.

These findings may be clinically relevant because patients with CLL are at increased risk of second primary malignancies even before receiving CLL-directed therapy. The observed association with hematologic malignancies is of particular interest given emerging reports

suggesting a possible relationship between GLP-1RA use and hematologic cancer incidence in patients with diabetes. [13-15].

The descriptive analysis also highlighted the broader burden of secondary malignancy in CLL. Among patients who developed a secondary malignancy, nearly one in five subsequently developed more than one distinct malignancy type during eligible follow-up. This again illustrates that secondary cancers represent an important ongoing clinical problem in this population.

Several biological mechanisms could potentially contribute to the observed association: GLP-1RA therapy improves glycemic control and body weight and has anti-inflammatory and potential immunomodulatory effects. [11] Such effects could be relevant in CLL, which is characterized by chronically impaired immune surveillance. However, available data regarding GLP-1RA therapy and cancer risk remain heterogeneous across different tumor types. [12-15] The absence of a clear association with other solid tumors or melanoma in our study also argues against a uniform anticancer effect. The observed BMI reductions are consistent with weight loss following GLP-1RA initiation, but do not establish whether weight loss contributes to the observed association or distinguish its role from other potential mechanisms.

The study suffers from several limitations: As an observational study, the analysis remains susceptible to residual and unmeasured confounding, including differences between patients who did and did not receive GLP-1RA therapy. The propensity score–matched analysis used a static exposure definition and therefore was considered complementary to the time-varying analysis. In addition, nonmelanoma skin cancer was excluded because it could not be identified reliably across the available data sources. Finally, the number of events was limited for some individual cancer categories, particularly melanoma, resulting in imprecise estimates.

Overall, our findings suggest that GLP-1RA use was associated with a lower hazard of developing a secondary malignancy in patients with untreated CLL, with the strongest association observed for hematologic malignancies.

Further clinical and mechanistic studies are needed to determine whether GLP-1RA exposure may influence cancer risk in patients with CLL.

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Table 1. Baseline characteristics of the primary analytic cohort according to subsequent achievement of effective GLP-1RA exposure during follow-up.

Groups are descriptive; GLP-1RA exposure was modeled as time varying in the primary analysis.

Characteristic	No effective GLP-1RA exposure (N=3,185)	Achieved effective GLP-1RA exposure (N=276)
Age, years, mean (SD)	70.54 (11.74)	65.15 (9.52)
Male sex, n (%)	1,769 (55.5%)	161 (58.3%)
HbA1c, mean (SD)	6.18 (0.88)	7.12 (1.41)
BMI, kg/m², mean (SD)	27.28 (4.83)	32.11 (5.37)
Platelet count, mean (SD)	206.68 (75.48)	226.07 (70.22)
WBC count, mean (SD)	30.01 (36.52)	22.01 (13.99)
Hemoglobin, mean (SD)	13.20 (1.72)	13.73 (1.60)
Diabetes mellitus, n (%)	896 (28.1%)	210 (76.1%)

Table 2. Secondary-malignancy outcomes, sensitivity analyses, and burden.

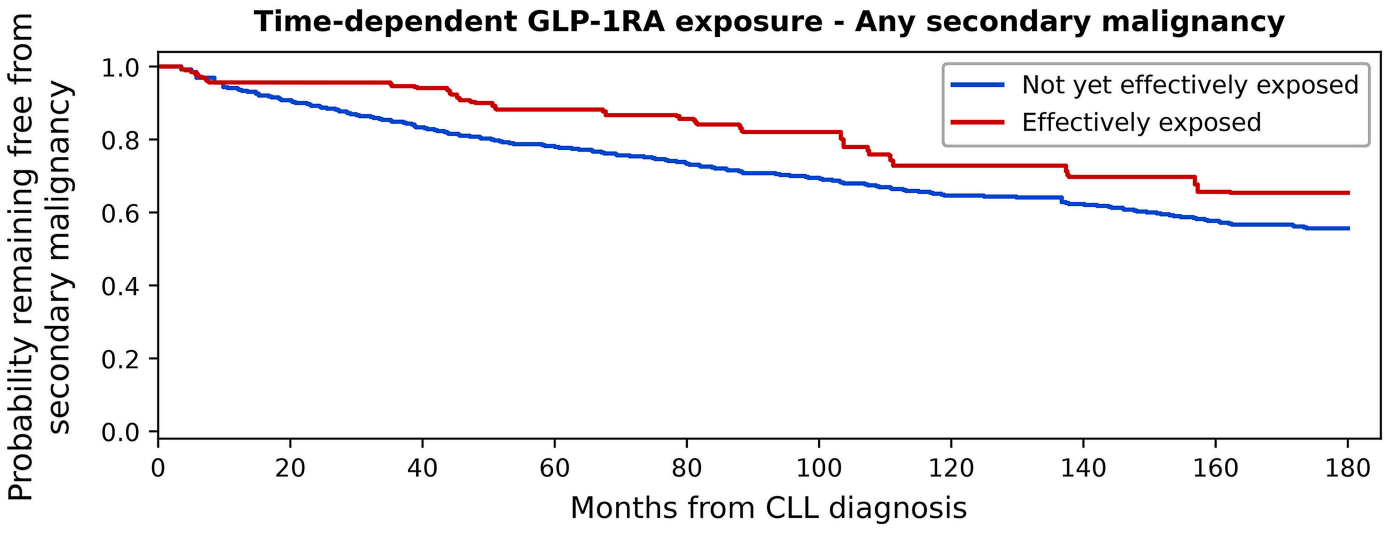
Panel A. Composition of first secondary malignancies in the primary analytic cohort (first event of any type)					
First-event category within primary analytic cohort			**Patients, N**		**Percent of 619 events**
Solid tumor			304		49.1%
Hematologic malignancy			286		46.2%
Melanoma			29		4.7%
Total			619		100.0%
Panel B. Distribution of first secondary hematologic malignancies in the hematologic endpoint-specific cohort					
Diagnosis group			**Events, N**		**Percent of 405 hematologic-malignancy events**
Non-Hodgkin lymphoma / Mycosis fungoides			227		56.0%
Acute leukemia			118		29.1%
Hodgkin lymphoma			17		4.2%
Myelodysplastic syndrome			13		3.2%
Myelo-/lymphoproliferative syndrome			11		2.7%
Multiple myeloma			10		2.5%
Polycythemia vera			9		2.2%
Total			405		100.0%
Panel C. Complementary propensity score-matched static Cox analyses by endpoint (separate matched cohorts)					
Endpoint	**Matched cohort, N**	**Matched pairs, N**	**Events, N**	**Adjusted HR (95% CI)**	**P**
Any secondary malignancy	506	253	68	0.22 (0.12–0.39)	<0.005
Hematologic malignancy	654	327	54	0.23 (0.12–0.45)	<0.005
Other solid malignancy	568	284	45	0.32 (0.17–0.63)	<0.005
Melanoma	690	345	3	2.16 (0.30–15.67)	0.45
Panel D. Descriptive burden of distinct secondary malignancy types during eligible treatment-free follow-up					
Distinct malignancy types per patient			**Patients, N**		**Percent of analytic cohort**
0			2,842		82.1%
1			506		14.6%
2			98		2.8%
3+			15		0.4%

Panel A first-event categories sum to 619. In Panel C, static effective-exposure classification was used, and robust variance was clustered by matched set. For Panel D, the analytic cohort comprised 3,461 patients; among the 619 patients with at least one secondary malignancy, 113 (18.3%) developed at least two distinct malignancy types and 15 developed three or more. Overall, 754 distinct patient-malignancy pairs were observed during eligible follow-up.

Figure legend:

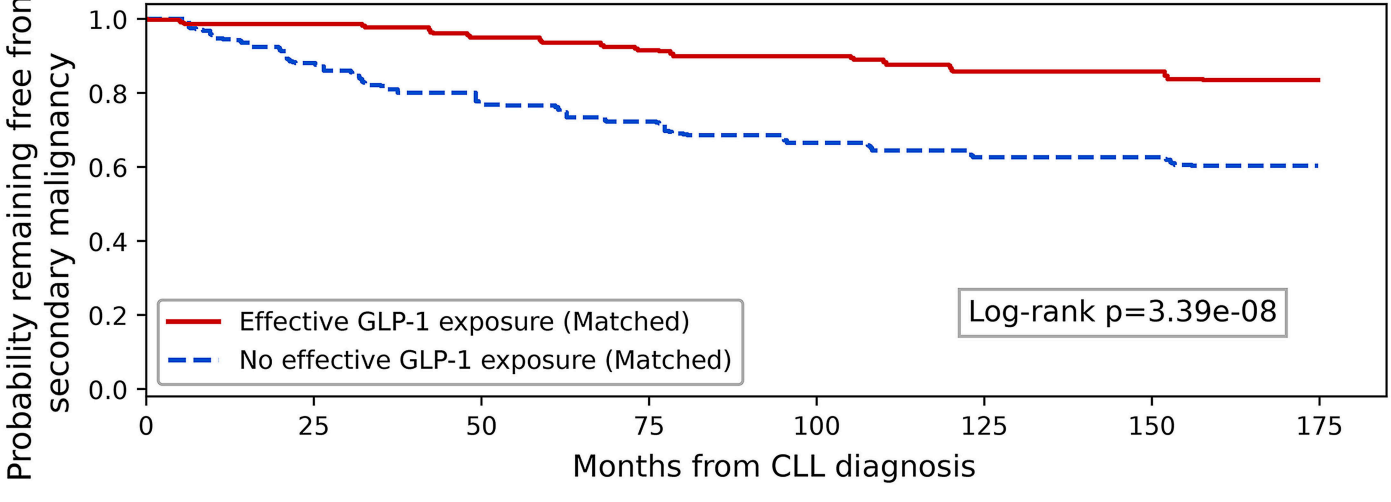
Figure 1: GLP-1RA exposure and secondary malignancy risk during watch-and-wait in CLL. (A) Simon-Makuch curve showing the probability of remaining free from any secondary malignancy in the primary cohort. Patients were classified as "Not yet effectively exposed" until 3 months after GLP-1RA initiation and as "Effectively exposed" thereafter. (B) Unadjusted Kaplan-Meier curves for any secondary malignancy in the propensity score-matched primary cohort. (C) Unadjusted Kaplan-Meier curves for hematologic malignancy in a separate propensity score-matched cohort. Panels B and C use a fixed exposure classification and, unlike Panel A, do not account for changes in GLP-1RA exposure over time. The tables below all three plots show the number of patients still at risk at the indicated months. In Panel A, the counts are grouped by exposure status at each time point; in Panels B and C, they are grouped according to the matched exposure groups. Abbreviations: CLL, chronic lymphocytic leukemia; GLP-1RA, glucagon-like peptide-1 receptor agonist.

A



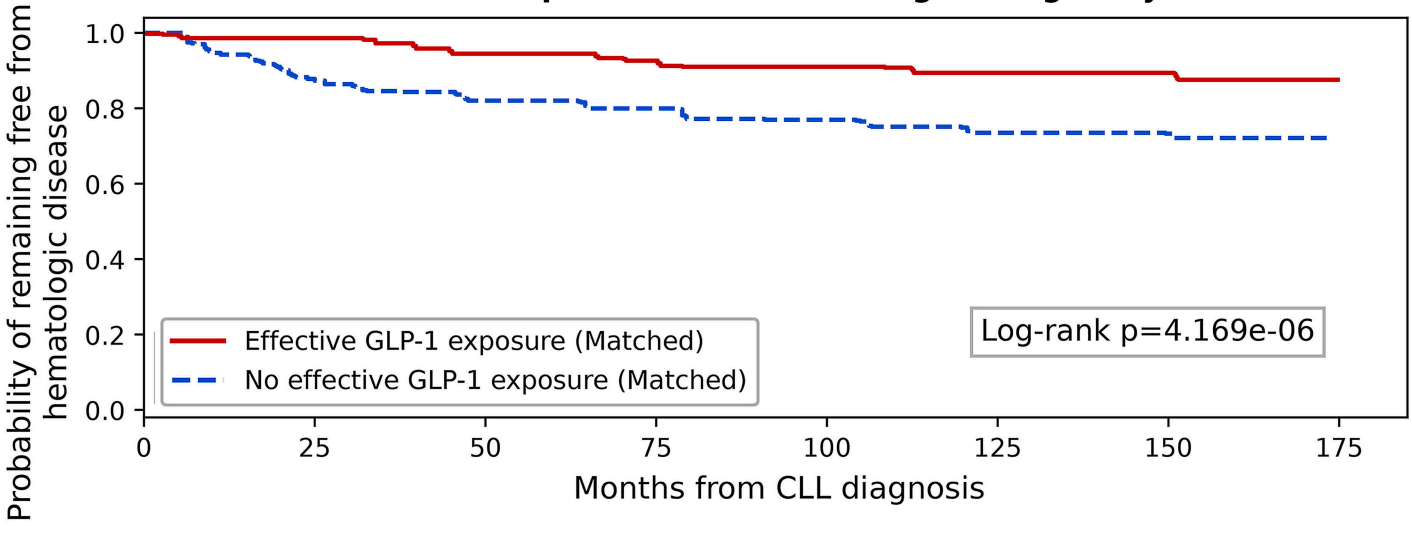
Current exposure state	0	25	50	75	100	125	150	175
Effectively exposed	0	132	99	69	44	30	24	14
Not yet effectively exposed	3461	2529	1720	1175	744	476	287	175

B



Number at risk	0	25	50	75	100	125	150	175
Effective GLP-1 exposure (Matched)	253	225	157	101	65	39	27	15
No effective GLP-1 exposure (Matched)	253	189	125	90	54	30	20	11

C



Number at risk	0	25	50	75	100	125	150	175
Effective GLP-1 exposure (Matched)	327	289	211	138	88	58	37	19
No effective GLP-1 exposure (Matched)	327	262	190	130	79	50	33	16

Supplementary data

Glucagon-like peptide-1 receptor agonist exposure is associated with lower secondary malignancy risk during watch-and-wait in chronic lymphocytic leukemia: a time-varying analysis

Supplementary Table S1. Baseline characteristics and covariate balance before and after 1:1 propensity score matching for the primary composite endpoint.

Characteristic	Full cohort: no effective GLP-1RA (N=3,185)	Full cohort: effective GLP-1RA (N=276)	|SMD| pre-match	Matched control (N=253)	Matched GLP-1RA (N=253)	|SMD| post-match
Age, years	70.54 (11.74)	65.15 (9.52)	0.504	65.86 (10.92)	65.44 (9.57)	0.041
Male sex	1,769 (55.5%)	161 (58.3%)	0.056	158 (62.5%)	146 (57.7%)	0.097
HbA1c	6.18 (0.88)	7.12 (1.41)	0.795	6.94 (1.51)	7.01 (1.32)	0.047
BMI, kg/m²	27.28 (4.83)	32.11 (5.37)	0.946	31.80 (6.30)	31.76 (5.34)	0.006
Platelet count	206.68 (75.48)	226.07 (70.22)	0.266	228.42 (82.85)	223.99 (71.59)	0.057
WBC count	30.01 (36.52)	22.01 (13.99)	0.289	22.82 (12.38)	22.44 (14.43)	0.028
Hemoglobin	13.20 (1.72)	13.73 (1.60)	0.319	13.73 (1.58)	13.70 (1.62)	0.019
Diabetes mellitus	896 (28.1%)	210 (76.1%)	1.094	191 (75.5%)	188 (74.3%)	0.027

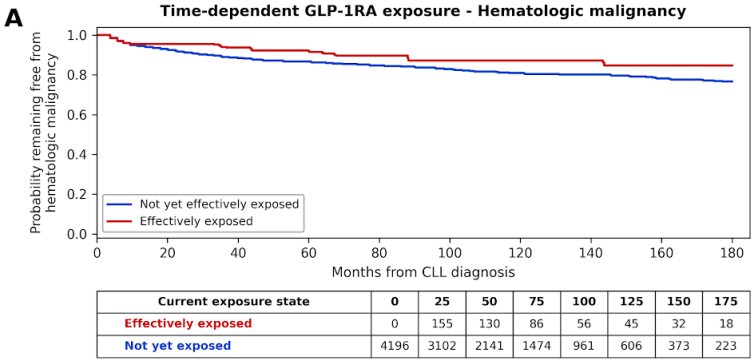
Data are mean (SD) or n (%). Absolute SMD <0.10 was prespecified as acceptable post-matching balance. Abbreviations: BMI, body mass index; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; SMD, standardized mean difference; WBC, white blood cell count. The propensity score-matched cohort represents a complementary static analysis of the primary composite endpoint and is distinct from the separate hematologic endpoint-specific cohort.

Supplementary Table S2. Descriptive longitudinal BMI change after GLP-1RA initiation in the time-varying model cohort.

Characteristic	Approximately 6 months	Approximately 12 months
Patients with paired BMI measurements, N	138	131
Pre-initiation BMI, mean (SD), kg/m²	32.80 (5.93)	32.87 (6.22)
Follow-up BMI, mean (SD), kg/m²	31.67 (5.90)	31.83 (6.03)
Mean absolute BMI change, kg/m²	−1.13	−1.04
Median absolute BMI change, kg/m²	−0.89	−0.58
Mean relative BMI change, %	−3.33	−2.93
≥5% BMI reduction, n (%)	46 (33.3%)	46 (35.1%)

Among 255 GLP-1RA initiators in the time-varying model cohort, 246 (96.5%) had an available BMI measurement within the year preceding treatment initiation. Pre-initiation BMI was the measurement closest to GLP-1RA initiation within days −365 to 0; approximately 6-month BMI was the measurement closest to day 180 within days 90–270; and approximately 12-month BMI was the measurement closest to day 365 within days 270–450. Measurements after the end of eligible follow-up were excluded. BMI values outside 10–100 kg/m² were excluded. The analysis was descriptive and was not intended as a formal mediation analysis. Abbreviations: BMI, body mass index; GLP-1RA, glucagon-like peptide-1 receptor agonist. In a time-varying sensitivity model retaining baseline BMI, the GLP-1RA estimate remained directionally similar (HR, 0.58; 95% CI, 0.33–1.01), while baseline BMI was not independently associated with risk (HR, 1.01; 95% CI, 0.97–1.05).

Supplementary Figure S1. Additional time-varying analyses and propensity score-matching diagnostics. *(A) Time-varying Simon-Makuch curve for hematologic malignancy in the separate hematologic endpoint-specific cohort. Effective GLP-1RA exposure begins 3 months after treatment initiation; the table shows patients still at risk, grouped by current exposure status. (B) Adjusted hazard ratios (dots) and 95% confidence intervals (horizontal lines) from separate time-varying Cox models fitted in separate endpoint-specific cohorts for the primary composite endpoint and endpoint-specific hematologic malignancy, other solid malignancy, and melanoma analyses. Points indicate adjusted hazard ratios and horizontal lines indicate 95% confidence intervals. (C) Balance in baseline characteristics before and after 1:1 propensity score matching for the primary outcome. Smaller standardized mean differences indicate more similar groups; the dashed line at 0.10 marks the predefined threshold for acceptable balance, which all characteristics met after matching. Abbreviations: CLL, chronic lymphocytic leukemia; GLP-1RA, glucagon-like peptide-1 receptor agonist.*



Current exposure state	0	25	50	75	100	125	150	175
Effectively exposed	0	155	130	86	56	45	32	18
Not yet exposed	4196	3102	2141	1474	961	606	373	223

