

Risk of Second Primary Malignancies in Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma Receiving First-Line Therapy: A Real-World Study

1401

Vanthana Bharathi,¹ Lili Zhou,² Ayad K. Ali,² Qianhong Fu,² Wassim Aldairy,² Alessandra Ferrajoli¹

¹Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; ²BeOne Medicines Ltd, San Carlos, CA, USA

CONCLUSIONS

- This analysis in real-world patients highlights a higher incidence of SPMs in patients treated with CIT compared with patients under observation or treated with covalent BTK inhibitor monotherapy
- No differences in the incidence of cutaneous malignancies, including NMSC and melanoma, were observed between the CIT and observation groups or between the covalent BTK inhibitor and observation groups
- Although the observation time of 24 months is short, these findings emphasize the importance of ongoing cancer surveillance in patients with CLL/SLL and highlight the need for prospective studies to further explore the relationship between treatment modality and SPMs
- Further longer-term follow-up is planned

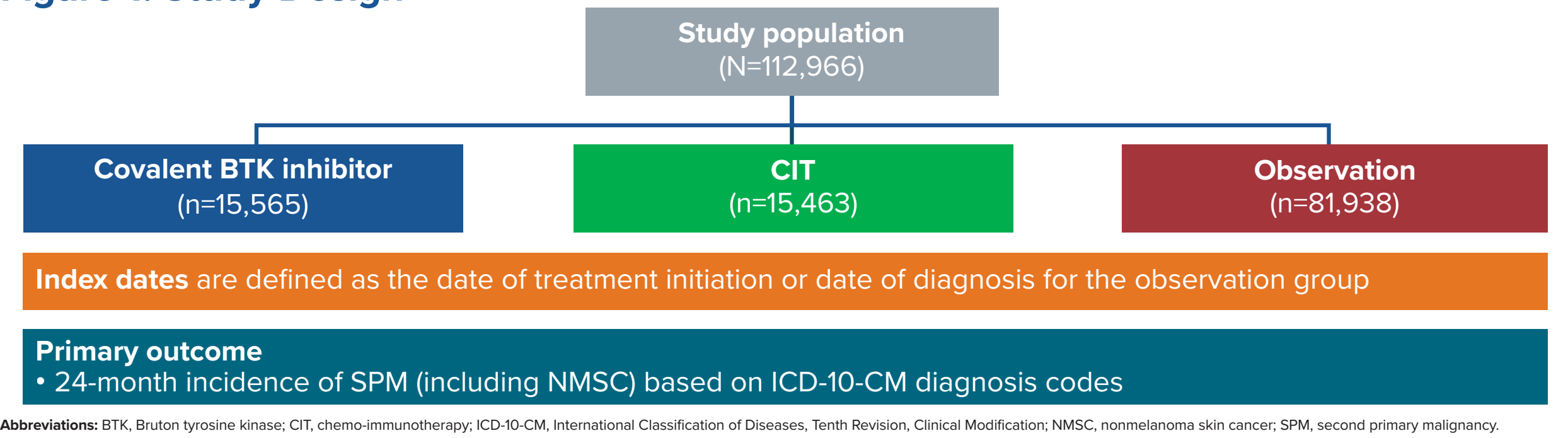
INTRODUCTION

- Compared with the general population, patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) are at an increased risk of developing second primary malignancies (SPMs), particularly nonmelanoma skin cancer (NMSC), melanoma, and other solid tumors¹⁻³
- This increased risk is due to underlying immune dysfunction, individual risk, and the effects of treatment¹⁻³
- Covalent Bruton tyrosine kinase (BTK) inhibitors have become widely used in the first-line setting for the treatment of CLL/SLL⁴; therefore, it is important to understand how first-line treatment strategies may influence the incidence of SPMs
- This real-world study aimed to evaluate the incidence of SPMs in patients treated with BTK inhibitors or chemo-immunotherapy (CIT) and to compare these rates with those in patients managed with observation

METHODS

- Between January 2019 and December 2024, patients with newly diagnosed CLL/SLL were identified using the Symphony Health Solutions database
 - The Symphony Health Solutions database contains deidentified and tokenized information that allows linkage of patient-level data from various sources, such as hospital claims, physician offices, and prescription data, with record dates as recent as 1 month prior
- Patients were categorized into three cohorts based on clinical management of CLL/SLL (Figure 1):
 1. **First-line covalent BTK inhibitor monotherapy:** ibrutinib, acalabrutinib, or zanubrutinib
 2. **First-line CIT:** chemotherapies (eg, bendamustine, chlorambucil) or immunotherapies (eg, anti-CD20 or anti-CD52 antibodies)
 3. **Observation:** “Watch and Wait” (no CLL/SLL-directed therapies after cancer diagnosis)
- The primary outcome included the 24-month incidence of SPMs (excluding second hematologic malignancies), including NMSC, melanoma, and other solid tumors, based on International Classification of Diseases, Tenth Revision, Clinical Modification diagnosis codes
- Baseline demographics, including age, sex, race and ethnicity, were compared across groups
- Incidence rates in the groups were compared using χ^2 tests, with statistical significance set at $P<.05$; odds ratios (ORs) were also calculated
- Incidence rates by age, sex, and race and ethnicity were estimated

Figure 1. Study Design



RESULTS

Baseline Demographics

- A total of 112,966 patients were included in this analysis: 15,565 patients received covalent BTK inhibitor monotherapy as initial therapy, 15,463 received CIT as initial therapy, and 81,938 remained on observation
- Baseline demographics are shown in Table 1
- Mean age was similar across groups (68-69 years), and male sex was predominant (55%-59%)
- Approximately 20% of patients had missing data for race and ethnicity; among those with available data, the majority were non-Hispanic White (82%-84%)

Table 1. Baseline Demographics

	Covalent BTK inhibitor monotherapy (n=15,565)	CIT (n=15,463)	Observation (n=81,938)
Age at index date, years			
Mean (SD)	69 (8.2)	68 (9.2)	68 (9.0)
Median	72	71	72
Sex, n (%)			
Female	6317 (40.6)	6745 (43.6)	37,273 (45.5)
Male	9248 (59.4)	8718 (56.4)	44,665 (54.5)
Race and ethnicity, n (%)			
White, non-Hispanic	10,308 (83.0)	10,165 (83.6)	54,561 (81.8)
Black, non-Hispanic	1250 (10.1)	1030 (8.5)	5154 (8.0)
Asian, non-Hispanic	193 (1.6)	179 (1.5)	900 (2.4)
Hispanic	627 (5.1)	749 (6.2)	3535 (5.5)

Fewer than 1% of the values for age and sex are missing.
Abbreviations: BTK, Bruton tyrosine kinase; CIT, chemo-immunotherapy.

Incidence of SPMs

- The 24-month SPM incidence is shown in Table 2
- The incidence of SPMs was higher in the CIT group (14.9%) than in both the covalent BTK inhibitor group (12.0%; OR, 1.29; 95% CI, 1.21-1.38; $P<.0001$) and observation group (13.7%; OR, 1.10; 95% CI, 1.05-1.16; $P<.0001$)
- The cumulative incidence curve also showed that SPM rates were consistently highest in the CIT group, followed by the observation and covalent BTK inhibitor groups (Figure 2)
- The incidence of solid tumors excluding NMSC was also greater with CIT (10.5%) vs covalent BTK inhibitor (7.7%; OR, 1.42; 95% CI, 1.31-1.54; $P<.0001$) and observation (9.8%; OR, 1.09; 95% CI, 1.03-1.15; $P=0.004$), consistent with the cumulative incidence curve (Figure 3)
- The incidence of SPMs was higher in older, male, and non-Hispanic White patients (Figure 4); in each subgroup, the incidence of SPMs was higher in the CIT group than in both the covalent BTK inhibitor and observation groups (eg, among non-Hispanic White patients, the incidence was 16.1% in the CIT group, 14.3% in the observation group, and 12.8% in the covalent BTK inhibitor group)
- The incidences of NMSC (5.0% in the covalent BTK inhibitor group, 5.3% in the CIT group, and 4.8% with observation) and melanoma (0.6% in the covalent BTK inhibitor group, 0.7% in the CIT group, and 0.7% with observation) were similar across groups

Table 2. Development of SPM at the 24-Month Follow-Up

	Covalent BTK inhibitor monotherapy (n=15,565)	CIT (n=15,463)	Observation (n=81,938)	CIT vs covalent BTK inhibitor OR (95% CI); P-value	CIT vs observation OR (95% CI); P-value
Overall SPM, n (%)	1860 (11.9)	2308 (14.9)	11250 (13.7)	1.29 (1.21-1.38); <.0001	1.10 (1.05-1.16); <.0001
SPM excluding NMSC	1191 (7.7)	1629 (10.5)	8012 (9.8)	1.42 (1.31-1.54); <.0001	1.09 (1.03-1.15); .004
NMSC	774 (5.0)	822 (5.3)	3909 (4.8)	1.07 (0.97-1.19); .17	1.12 (1.04-1.21); .004
Melanoma	98 (0.6)	100 (0.6)	566 (0.7)	1.02 (0.78-1.36); .85	0.93 (0.76-1.16); .54
Other solid tumors	1109 (7.1)	1553 (10.0)	7572 (9.2)	1.45 (1.34-1.58); <.0001	1.10 (1.04-1.16); .002

SPM did not include second hematologic malignancies. The NMSC, melanoma, and other solid tumor groups were not mutually exclusive as a patient could develop two or more solid tumors during the 24-month follow-up period.
Abbreviations: BTK, Bruton tyrosine kinase; CIT, chemo-immunotherapy; NMSC, nonmelanoma skin cancer; OR, odds ratio; SPM, second primary malignancy.

Figure 2. Cumulative Incidence Curve of SPM at 24 Months

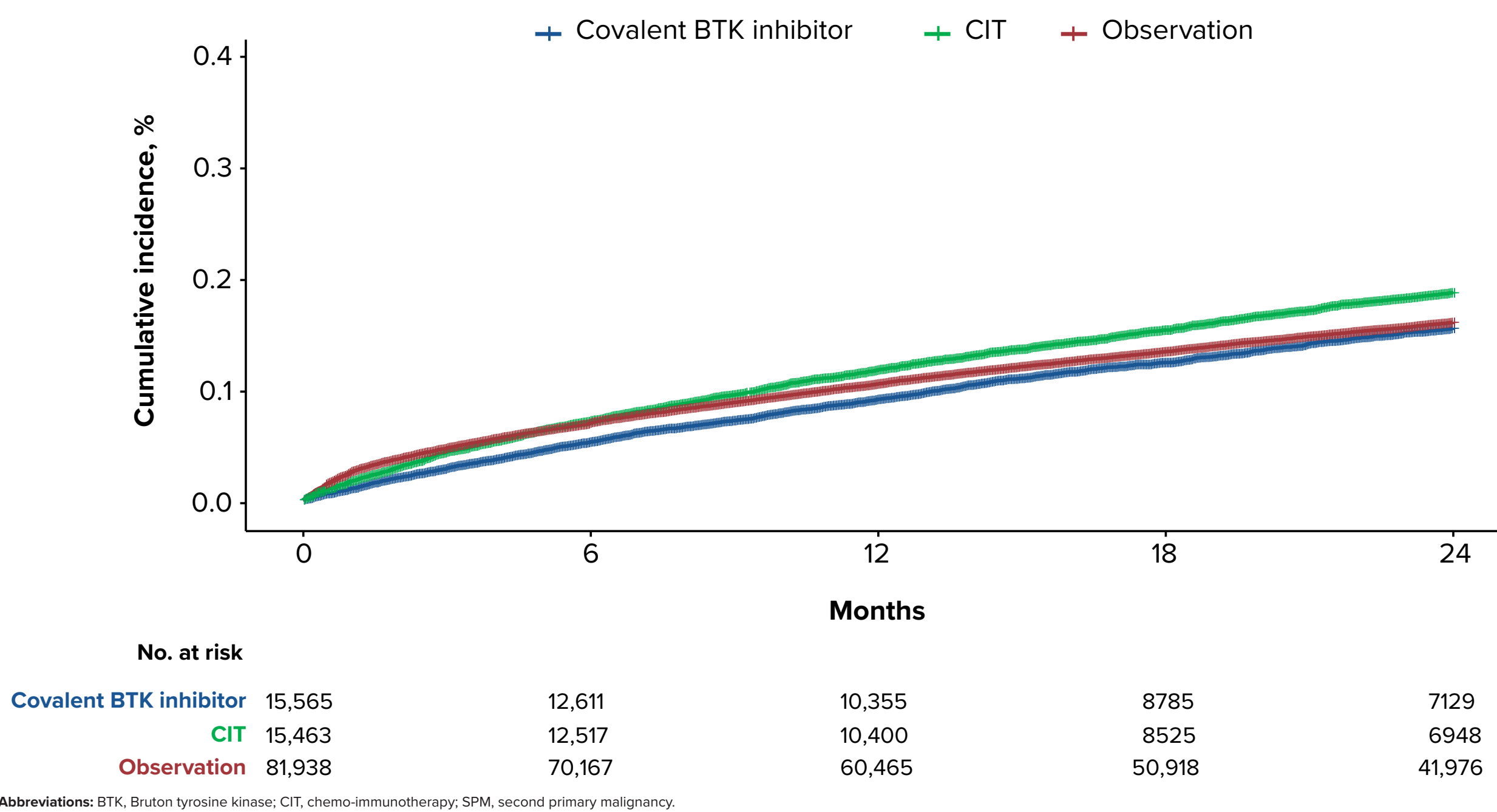


Figure 3. Cumulative Incidence Curve of SPM (Excluding NMSC) at 24 Months

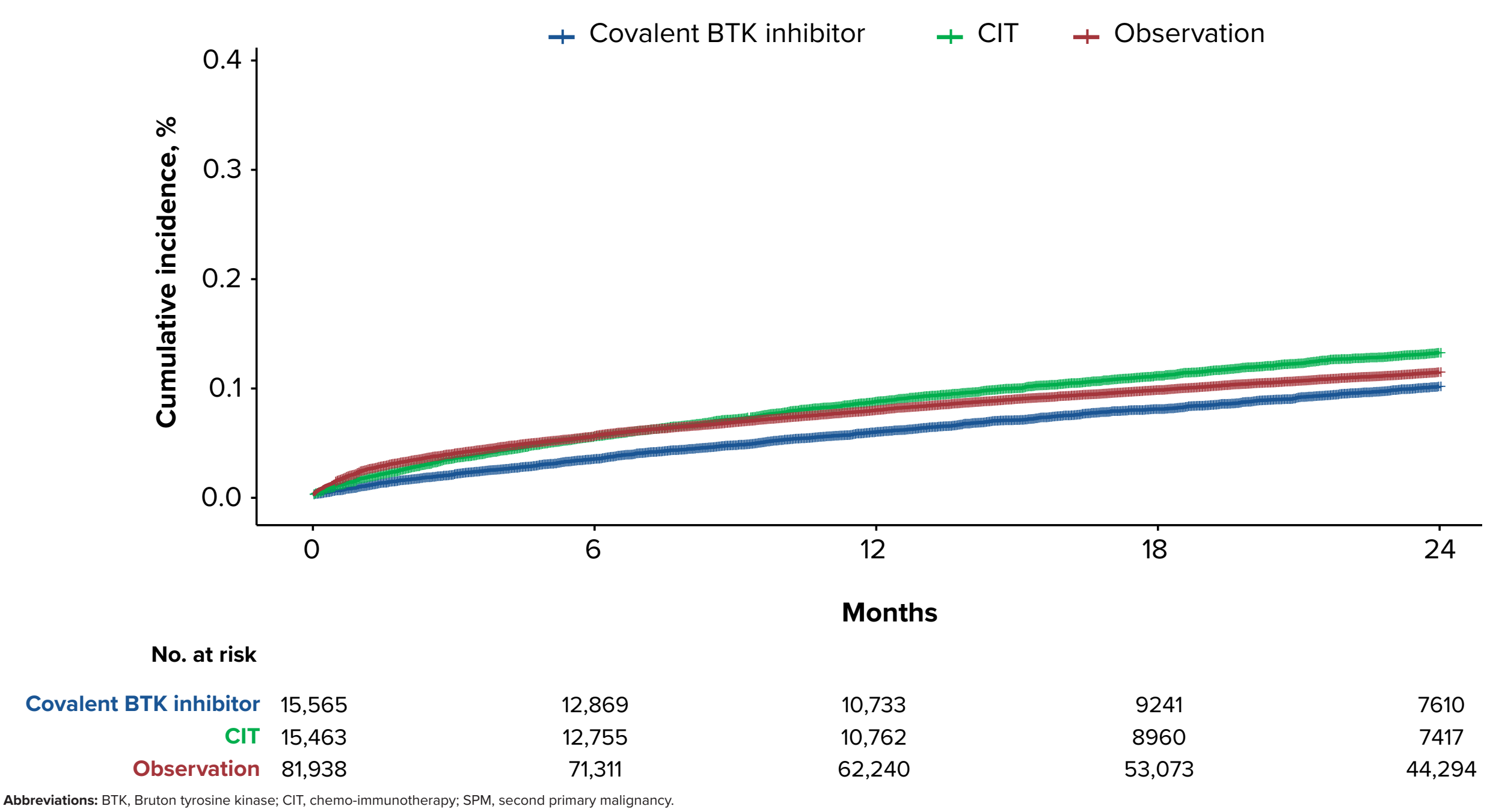
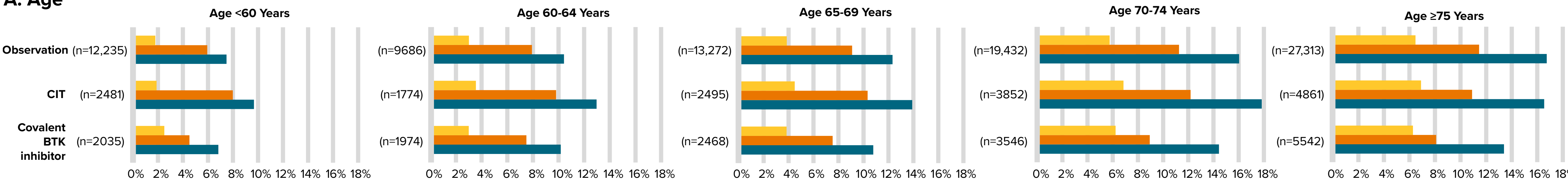
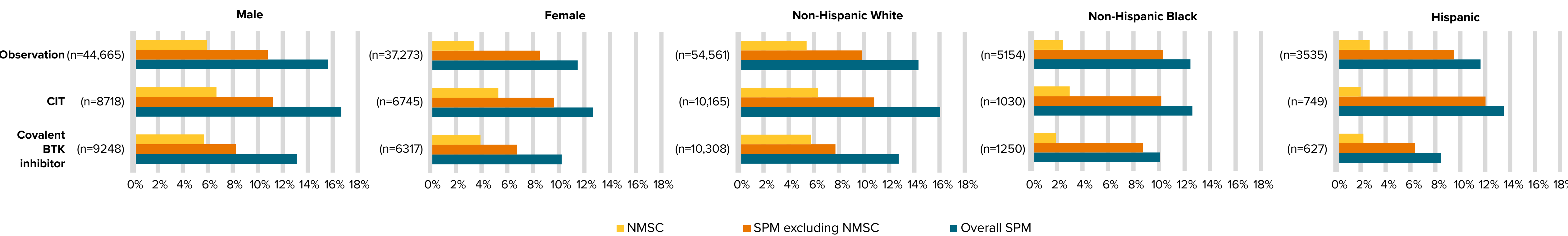


Figure 4. Development of SPM at the 24-Month Follow-Up by Stratification

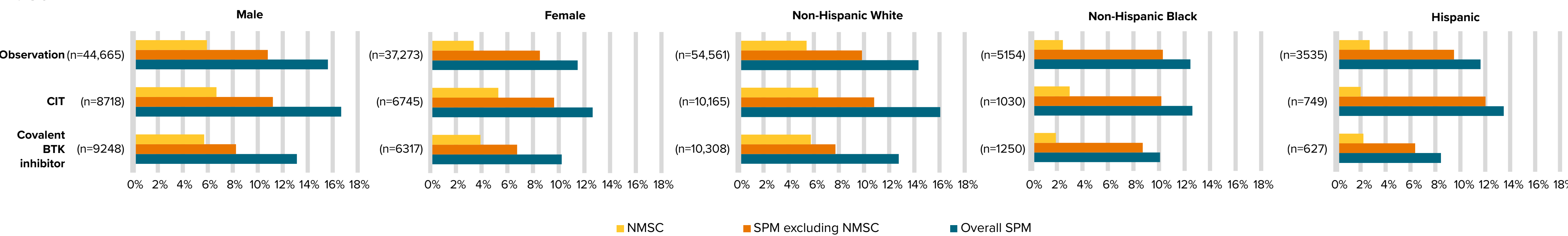
A. Age



B. Sex



C. Race and Ethnicity



Abbreviations: BTK, Bruton tyrosine kinase; CIT, chemo-immunotherapy; NMSC, nonmelanoma skin cancer; SPM, second primary malignancy.

REFERENCES

1. Shen Y, et al. *eJHaem*. 2021;3(1):129-138.
2. Bond DA, et al. *Leukemia*. 2020;34(12):3197-3205.
3. van der Straten L, et al. *Blood Cancer J*. 2023;13(1):15.
4. St-Pierre F, et al. *Blood Lymphat Cancer*. 2022;12:81-98.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeOne Medicines Ltd. Medical writing support was provided by Nancy Tang, PharmD, of Nucleus Global, an Inizio company, and supported by BeOne Medicines.

DISCLOSURES

VB: No disclosures. LZ, WA: Employment and may own stock: BeOne Medicines Ltd. AK: Employment and owns stock: BeOne Medicines Ltd. QF: Employment and may own stock: BeOne Medicines Ltd. Angen. AB:Viv. AP: Consulting or advisory role: Janssen, AstraZeneca, BeOne Medicines Ltd, Genentech; Research funding: Genmab, Genentech, Lilly.