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MAJOR ARTICLE

Risk of Invasive Fungal Infections in Patients with Chronic Lymphocytic Leukemia treated with Bruton Tyrosine Kinase Inhibitors – A Case-Control Propensity Score Matched Analysis

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Background: Prior reports have suggested a possible increase in the frequency of invasive fungal infections (IFIs) with use of a Bruton tyrosine kinase inhibitors (BTKi) for treatment of chronic lymphoid malignancies such as chronic lymphocytic leukemia (CLL), but precise estimates are lacking. We aim to characterize the prevalence of IFIs among patients with CLL, for whom BTKi are now the first line recommended therapy.

Methods: We queried TriNetX, a global research network database, to identify adult patients with CLL using the ICD-10 codes (C91.1) and laboratory results. We performed a case-control propensity score-matched analysis to determine IFIs events by BTKi use. We adjusted for age, sex, ethnicity, and clinical risk factors associated with an increased risk of IFIs.

Results: Among 5,358 matched patients with CLL, we found an incidence of 4.6% of IFIs in patients on a BTKi vs. 3.5% among patients with CLL not on a BTKi at five years. Approximately 1% of patients with CLL developed an IFI while on a BTKi within this period. Our adjusted IFI event analysis found an elevated rate of *Pneumocystis jirovecii* pneumonia (PJP) (0.5% vs. 0.3%, p=0.02) and invasive candidiasis (3.5% vs 2.7%, p=0.012) with the use of a BTKi. The number needed to harm for patients taking a BTKi was 120 and 358 for invasive candidiasis and PJP, respectively.

Conclusions: We found an adjusted elevated rate of PJP and invasive candidiasis with BTKi use. The rates are however low with a high number needed to harm. Additional studies stratifying other IFIs with specific BTKi are required to identify at-risk patients and preventive, cost-effective interventions.

Keywords: *Pneumocystis jirovecii* pneumonia, Aspergillosis, Cryptococcosis, Candidiasis, Invasive fungal infections, Bruton Tyrosine Kinase Inhibitors, Chronic Lymphocytic Leukemia

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common type of chronic leukemia in the U.S., affecting approximately 200,000 people.[1] Novel and highly effective therapies targeting B-cell receptor (BCR) signaling pathways have revolutionized treatment and improved outcomes. Among these therapies, Bruton tyrosine kinase inhibitors (BTKi) irreversibly inhibit the Bruton tyrosine kinase, an enzyme involved in the BCR signaling pathway crucial in the pathogenesis of CLL.[2]

The landmark study that led to the approval of ibrutinib, the first BTKi approved by the U.S. Food and Drug Administration (FDA), did not identify an increased risk for invasive fungal infections (IFIs). However, subsequent reports emerged, revealing atypical IFIs, such as central nervous system (CNS) aspergillosis, initially in patients from Israel receiving concomitant glucocorticoids shortly after its approval.[3] Moreover, observational data and post-marketing surveillance have corroborated an increased risk of severe infectious complications, including

IFIs such as pulmonary and extrapulmonary aspergillosis, fusariosis, mucormycosis, cryptococcosis, and pneumocystosis.[4-8]

A retrospective analysis of a case series of patients on ibrutinib found a 5% rate of IFIs, with *Pneumocystis jirovecii* pneumonia (PJP) accounting for 3.8% of cases.[9] Typically, IFIs associated with BTKi's manifest during the first six months of therapy, particularly in patients concurrently receiving glucocorticoids and those with a history of prior chemotherapy exposure.[7] Nevertheless, despite the reported increased risk for IFIs, the availability of high-quality data to determine their frequency and guide preventive strategies in this patient population remains limited.

Additionally, the underlying immunosuppression associated with CLL and the concomitant use of immunosuppressive medications confound the attribution of an increased risk of IFIs solely to treatment with a BTKi. As such, our study utilized a large multinational database to determine the prevalence of IFIs in patients with CLL treated with a BTKi and to identify associated risk factors for IFI development.

METHODS:

Global federated research network:

We queried TriNetX, a global research network database (https://trinetx.com/), in August 2023 to identify adult patients with chronic lymphocytic leukemia based on the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) code (C91.1) and laboratory results over the previous decade. TriNetX datasets include clinical patient data such as demographics, diagnoses, procedures, laboratories, and medications – commonly referred to as real-world data. TriNetX has global data for approximately 100 million patients from more than 80 medical centers across the U.S., Canada, Europe, Australia, Indonesia, and various other countries. Our group has published several reports using the same methodology.[10-13] TriNetX, LLC complies with the Health Insurance Portability and Accountability Act (HIPAA), the U.S. federal law protecting healthcare data's privacy and security, and any additional data privacy regulations applicable to the contributing healthcare organization (HCO). Each HCO delivers electronic medical record (EMR) systems data collected during patient care. Received data is either structured or unstructured data processed by Natural Language Processing Technology. Most participating HCOs are large academic medical institutions with inpatient and outpatient facilities, thereby offering comprehensive data representing the entire patient population under their care. Most HCOs provide an average of seven years of historical data. TriNetX receives data directly from HCOs research repository into the TriNetX environment, or the HCO sends TriNetX data extracts in the form of CSV files coded in the TriNetX Data Dictionary. HCO and other data providers update their data at various times, with over 80 percent refreshing in one-, two-, or four-week frequency intervals. The average lag time for a HCOs source data to refresh is

one month. TriNetX maps the data to a standard, controlled set of clinical terminologies and transforms it into a proprietary data model. This transformation process includes extensive data quality assessment that includes data cleaning that rejects records that do not meet the TriNetX quality standards. TriNetX is certified by the International Organization for Standardization (ISO) 27001:2013 standard and maintains an Information Security Management System (ISMS) to ensure the protection of the healthcare data it has access to and to meet the requirements of the HIPAA Security Rule.

Study design and population:

The analysis comprised of a comparative assessment of the clinical characteristics between patients with CLL (identified through ICD-10 code C91.1 and a lymphocyte count ≥ 5.0 x 10^3/μL) who were either on (n=6,548) or off (n=36,164) Bruton's tyrosine kinase inhibitors (BTKi). We excluded individuals with any history of prior IFI within 3 months before the index event (Supplementary Material). The earliest encounter was identified as the index event in patients with multiple encounters. Demographic characteristics, diagnoses, procedures, medications, complications, and measurements were captured without time constraints before the index event (e.g., laboratory test results; see supplementary materials. Tables S1-S4). Comorbidities were selected based on frequency and clinical importance. Results were reported after propensity score matching (PSM) was performed to control for differences between cases and controls. For the PSM analysis by BTKi use, we controlled for age, sex, ethnicity, HIV infection, chronic lower respiratory diseases, neoplasms, aplastic anemia, chronic kidney disease (CKD), systemic connective tissue disorders, CLL, transplant status, glucocorticoids (prednisone, dexamethasone, methylprednisolone, and prednisolone), immunosuppressants, antineoplastics, and trimethoprim-sulfamethoxazole. To estimate the five-year relative risk of IFIs, we calculated the number needed to harm (NNH) using a previously described formula (NNH=1/[control event rate] − [experimental event rate]).[14]

Global federated research network outcome measures:

The primary outcome was the proportions of IFIs at one year and five years. Calculations of incidence rates were captured after propensity score matching. The secondary outcomes included the need for hospitalization and mortality (Supplementary Material. Table S4).

Statistical analysis

All statistical analyses were conducted on the TriNetX platform. Descriptive statistics were presented as means and standard deviations for continuous variables and as frequency and proportions for categorical variables. Continuous data were compared using independent t-tests, whereas categorical data were compared using $\chi 2$ or Fisher's exact test, as appropriate. Propensity score matching was performed using a 1:1 greedy nearest-neighbor algorithm, utilizing a caliper width of 0.1 pooled standard deviations (SD). Covariate balance comparing cases and controls was assessed using standardized mean difference, and absolute values > 0.1

were considered positive for residual imbalance. The t-test statistic compared the two cohorts after PSM to report differences between cohorts. A *p-value* of <0.05 was used to indicate statistical significance. Graphs were designed using GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA (www.graphpad.com).

Data access

The corresponding author had full access to data in the study and had final responsibility for the decision to submit the manuscript for publication. The aggregated datasets generated and analyzed in the current study are available from the TriNetX platform with a subscription or through the corresponding author per a formal request.

Ethics statement

Any data displayed on the TriNetX platform in aggregate form, or any patient-level data provided in a data set generated by the TriNetX platform, only contains de-identified data as per the de-identification standard defined in Section 164.514(a) of the HIPAA Privacy Rule. Geographic reporting at the regional level prevents potential re-identification through the localization of patients or HCOs. Research utilizing TriNetX does not require ethical approval because patient-identifiable information is not accessible to users. According to the Colorado Multiple Institutional Review Board (COMIRB) at the University of Colorado Denver, the current project is in HIPAA compliance. Analysis of clinical data was performed under an approved protocol (COMIRB Protocol 15-1340).

Patient consent statement

The study does not include factors necesstaing patient consent.

RESULTS:

Clinical characteristics of patients with CLL by btki use

After balancing the cohorts for the selected covariates, TriNetX matched 5358 patients in each group (Table 1). Key demographic variables were well-balanced with more Hispanic patients but fewer African American with CLL not receiving a BTKi. Patients on a BTKi had higher rates of lymphadenopathy, malaise, dyspnea, and cough, while solid and other hematologic malignancies besides CLL were evenly distributed between both groups. However, overlapping non-follicular lymphoma was more common in patients with CLL on a BTKi. In contrast, acute lymphoblastic leukemia and myeloid leukemia —although infrequent—were slightly more common in patients with CLL not on a BTKi. Anti-CD20 monoclonal antibodies were administered to less than 10% of patients with slightly more frequent use observed among patients with CLL on a BTKi. Additionally, patients with CLL on a BTKi had higher total lymphocyte counts. Patients with CLL on BTKi received ibrutinib (84%) or other BTKi (16%).

The proportion of invasive fungal infections in patients with CLL by btki use

There were 244 (4.6%) episodes of IFIs among patients with CLL on a BTKi compared to 188 (3.5%) in patients with CLL not on a BTKi. Figure 1 provides the incidence of IFIs for patients with CLL by BTKi exposure after PSM. Invasive candidiasis was more common in the BTKi group (3.5% vs. 2.7%), with an excess of 45 cases, translating to an OR of 1.3 and risk difference of 0.008 (p=0.012). Invasive aspergillosis was less common in the BTKi group (0.2% vs. 0.4%), with an OR of 0.5 and risk difference of -0.002 (p=0.068). There was a non-significant excess of cryptococcosis in the BTKi group, with an OR of 1.6 and risk difference of 0.001 (p=0.24). PJP was more prevalent in the BTKi group (0.5% vs. 0.3%), with an excess of 15 cases and an OR of 2.1 (p=0.02). The incidence of candidiasis, aspergillosis, cryptococcosis and PJP was 705, 37, 60, and 108 episodes per 100,000 patients per year on BTKi treatment, respectively.

Other secondary outcomes in patients with CLL by btki use

A total of 1,142 patients with CLL in the BTKi group and 1,177 patients with CLL not on a BTKi, died within one year. However, the five-year mortality risk did not differ significantly between the two groups (OR: 0.96, CI: 0.87-1.04, p=0.289) (risk difference of -0.009). The log-rank test for survival was also non-significant (p=0.504). More patients with CLL on a BTKi had been hospitalized at five years compared to those without BTKi (OR: 1.4, CI: 1.3-1.6, p<0.0001).

Assessment of relative risk and number needed to harm for invasive fungal infections

For IFIs, the NNH with a BTKi was 98. Invasive candidiasis had an NNH of 120, invasive aspergillosis had a number need to treat (NNT) of 536, and cryptococcosis had an NNH of 894. PJP had a NNH of 358 (Table 2).

DISCUSSION

In our analysis of 5,358 matched patients with CLL, we observed a 4.6% incidence of IFIs in patients on a BTKi, compared to 3.5% in patients not on a BTKi over five years, resulting in annual rates of 0.9% and 0.7%, respectively. Approximately 1% of patients with CLL developed an IFI while on a BTKi during this period. Our adjusted analysis revealed higher rates of PJP and invasive candidiasis with use of a BTKi, with 3.5% of BTKi patients experiencing invasive candidiasis, compared to 2.7% in those not using a BTKi. Additionally, 0.5% of BTKi patients developed PJP versus 0.3% of non-BTKi patients over five years, indicating an annual PJP risk of 0.1% per year.

The reported percentage of IFIs in patients with CLL on a BTKi varies from 0.7% to 1.6%[7,15,16] with invasive aspergillosis and cryptococcosis being the most common systemic fungal infections. In cases of IFIs among BTKi users, 40% of patients were also using glucocorticoids,

and the median onset of infection was 45 days.[17] *Aspergillus* spp. (22%), *Cryptococcus* spp. (26%), Mucorales (6%) and *Pneumocystis jirovecii* (1%) were the most frequent IFI described in the study. Another study that examined the frequency of PJP in 96 patients with CLL treated with ibrutinib found a 5% incidence, with an estimated risk of 2 cases per 100 patient years, which significantly overestimates our annual PJP risk of 0.1%.[18] That estimation was limited by the small number of patients, the lack of a control group, and absence of adjustment for additional PJP risk factors. A recent systematic review found 14 cases of aspergillosis (3%), 1 of cryptococcosis (0.2%), and 6 of PJP (1.2%) among 490 patients on BTKi combination therapy.[19] The increased risk of invasive candidiasis observed in our study had not been reported previously and needs confirmation through prospective studies. Ibrutinib is associated with dermatologic toxicities, including mucositis and mucocutaneous infection, which can be both predisposing conditions for invasive candidiasis.[20]

BTKis predominantly affect the survival and function of B-cells, but the increased risk of IFIs can not be solely attributed to its effect on B-cells. BTKi can alter the function of alveolar macrophages, neutrophils, T-cell, natural killer cells and the cytokine milleu needed to control infection.[21,22] Additionally, other immune deficiencies may result from off-target effects on pathways that regulate innate fungal inmmunity. For example, ibrutinib impairs neutrophil chemotaxis, macrophage activation through inhibition of both NFAT and nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), and impairs production of tumor necrosis factor α[23]. Attribution of an increased risk of IFIs to BTKi alone is further confounded by the additional risk factors (e.g. increasing age, previous lymphocyte depleting therapy such as fludarabine and rituximab, corticosteroid use, etc.) frequently found in patients with CLL.

Our study adjusted for known risk factors for IFIs between the two groups, allowing for more precise estimates. Notably, the NNH only reached double digits for the total IFI episodes, highlighting the safety-benefit of this medication class. In a cohort of patients with CLL treated with a BTKi, the estimated NNT with trimethoprim-sulfamethoxazole to prevent 1 case of PJP was 42.[24] Our adjusted IFI event analysis found an elevated rate of PJP albeit at a low annual risk of 0.1% per year with use of a BTKi. The rates are however low with a high number needed to harm. Our findings do not support routine PJP prophylaxis in this patient population, considering the historical PJP risk of greated than 6.2% per person-year as the recommended threshold for primary prophylaxis in non-HIV immunocompromised patients.[25]

Our study is limited by its retrospective design and the use of ICD-10 codes for diagnosis, which may introduce selection bias and the potential for misclassification. We did not have access to microbiology or histology data to identify the organism's species and to use the consensus definitions of the Infectious Diseases Group of the European Organization for Research and Treatment of Cancer and the Mycoses Study Group[26], which could have underestimated the rates of events. We could not estimate precise BTKi doses and exposure duration, limiting the extrapolation of the findings. In addition, missing data may impair the strength of the association. Furthermore, the risk of IFIs associated with newer and more selective BTKi, such

as acalabrutinib[27] and zanubrutinib[28] could not be discerned from that of ibrutinib. The platform also limited a subgroup analysis by participating centers. Patients not on a BTKi may have undisclosed comorbidities or not have indications for treatment that could influence the results. Finally, the risk if invasive fungal infections in patients taking a BTKi for other indications (i.e., non-Hodgkin lymphoma, Waldeström macroglobulinemia, and graft versus host disease) was not examined due to limitations of data extraction to one disease entity. Studies to better understand the risk factors associated with development of IFIs according to the BTKi indication are needed. This is however one of the largest studies of patients with CLL ever analyzed, with more than 10,000 subjects with a specific and robust adjustment of comorbidities and other risk factors.

CONCLUSION

BTKi offers an incredible therapeutic advantage in patients with CLL. We found a 4.6% incidence of IFIs in patients on a BTKi, with an estimated additional 1% risk of IFI in patients with CLL while on a BTKi over five years compared to those not on BTKi. While we observed higher rates of PJP and invasive candidiasis with BTKi use, the absolute rates are low, and the number needed to harm is high. Consequently, our findings do not support routine PJP prophylaxis in this patient population, considering the historical PJP risk threshold for primary prophylaxis in non-HIV immunocompromised patients. Further studies are needed to identify at-risk patients and cost-effective preventive interventions for different IFIs associated with BTKi.

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Potential Conflict of Interest: None

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Table 1. Post propensity score matching clinical characteristics of patients with CLL using or not Bruton tyrosine kinase inhibitors.

Characteristic Name	CLL on BTKi (n=5,358)	CLL off BTKi (n=5,358)	P-value
Demographics			
Age at Index	69.54±11.05	69.28±13.08	0.268
White	4428 (83%)	4393 (82%)	0.376
Black or African American	417 (8%)	302 (6%)	<0.001
Hispanic or Latino	96 (2%)	147 (3%)	0.001
Asian	81 (2%)	78 (1%)	0.811
American Indian or Alaska Native	10 (<1%)	15 (<1%)	0.317
Male	3311 (62%)	3310 (62%)	0.984
Symptoms			
Enlarged lymph nodes	1834 (34%)	934 (17%)	<0.001

Malaise and fatigue	1579 (29%)	1265 (24%)	<0.001
Dyspnea	1320 (25%)	1180 (22%)	0.001
Cough	1265 (24%)	1074 (20%)	<0.001
Pain in throat and chest	1125 (21%)	1078 (20%)	0.261
Nausea and vomiting	686 (13%)	679 (13%)	0.839
Diarrhea, unspecified	659 (12%)	629 (12%)	0.373
Fever, unspecified	636 (12%)	514 (10%)	<0.001
Headache	562 (10%)	509 (10%)	0.088
Cachexia	46 (1%)	45 (1%)	0.916
Comorbidities			
Neoplasms	5033 (94%)	5111 (95%)	0.001
Malignant neoplasms of lymphoid tissue	4986 (93%)	5004 (93%)	0.489
Lymphoid leukemia	4844 (90%)	4901 (91%)	0.055
CLL of B-cell type	4779 (89%)	4827 (90%)	0.128
Connective tissue diseases	2974 (56%)	3035 (57%)	0.235
Hypertensive diseases	2580 (48%)	2760 (52%)	0.001
Chronic lower respiratory diseases	1065 (20%)	1118 (21%)	0.204
Diabetes mellitus	1051 (20%)	1149 (21%)	0.019
Non-follicular lymphoma	987 (18%)	549 (10%)	<0.001
PV and myelodysplastic syndrome	941 (18%)	859 (16%)	0.034
Chronic kidney disease	741 (14%)	765 (14%)	0.505
Fever of unknown origin	715 (13%)	593 (11%)	<0.001
Melanoma	646 (12%)	630 (12%)	0.633
Neutropenia	494 (9%)	470 (9%)	0.418
Heart failure	487 (9%)	576 (11%)	0.004

Noninfective enteritis and colitis	470 (9%)	513 (10%)	0.15
Solitary pulmonary nodule	435 (8%)	306 (6%)	<0.001
Aplastic anemia	396 (7%)	389 (7%)	0.795
Acute lymphoblastic leukemia	242 (5%)	318 (6%)	0.001
Myeloid leukemia	171 (3%)	414 (8%)	<0.001
Transplanted organ and tissue status	134 (3%)	134 (3%)	1
Severe sepsis	122 (2%)	168 (3%)	0.006
Pulmonary fibrosis	100 (2%)	112 (2%)	0.405
Bone marrow transplant status	78 (1%)	94 (2%)	0.219
Fibrosis and cirrhosis of the liver	64 (1%)	73 (1%)	0.439
Sarcoidosis	33 (1%)	22 (<1%)	0.137
Systemic lupus erythematosus (SLE)	24 (<1%)	31 (1%)	0.344
HIV	15 (<1%)	15 (<1%)	1
Medications			
GLUCOCORTICOIDS	3056 (57%)	3127 (58%)	0.165
Dexamethasone	1513 (28%)	1481 (28%)	0.491
Prednisone	1323 (25%)	1364 (25%)	0.361
Methylprednisolone	1110 (21%)	1136 (21%)	0.537
Prednisolone	293 (5%)	328 (6%)	0.148
ANTINEOPLASTICS	1988 (37%)	1918 (36%)	0.16
Anti-CD20 monoclonal antibodies	527 (10%)	444 (8%)	0.005
Rituximab	478 (9%)	391 (7%)	0.002
Trimethoprim-sulfamethoxazole	970 (18%)	983 (18%)	0.745
Fluconazole	454 (8%)	535 (10%)	0.007
IMMUNE SUPPRESSANTS*	202 (4%)	209 (4%)	0.725

Laboratories

Leukocytes (10^3/µL)	62.65 ± 90.27	40.33 ± 257.9	<0.001
Hemoglobin (mg/dL)	11.73 ± 2.3	12.31 ± 2.39	<0.001
Hematocrit (%)	36.38±6.54	37.39 ± 6.93	<0.001
Platelets (10^3/µL)	158.12 ± 80.02	190.65 ± 125.09	<0.001
Lymphocytes (10^3/µL)	67.8 ± 27.7	41.6 ± 23.9`	<0.001
Neutrophils (10^3/µL)	26.1 ± 130.5	5.6 ± 5.0	<0.001
Creatinine (mg/dL)	1.1 ± 0.57	1.08 ± 0.63	0.067
Lactate dehydrogenase (IU/mL)	290.89±413.38	316.1±535.84	0.043
Hemoglobin A1c (%)	6.34 ± 1.6	6.41 ± 1.57	0.233
Ferritin (mcg/L)	315.03 ± 625.74	679.03 ± 2894.65	<0.001
C-reactive protein (mg/dL)	28.97 ± 52.32	32.94 ± 55.92	0.157
CD4 T-cells (cells/µL)	1077.5 ± 3705.62	2100.5 ± 10483.5	0.263
Galactomannan	0.16 ± 0.48	0.13 ± 0.2	0.676
1,3 beta Glucan in serum (pcg/mL)	33.82 ± 48.36	21.32 ± 55.98	0.472

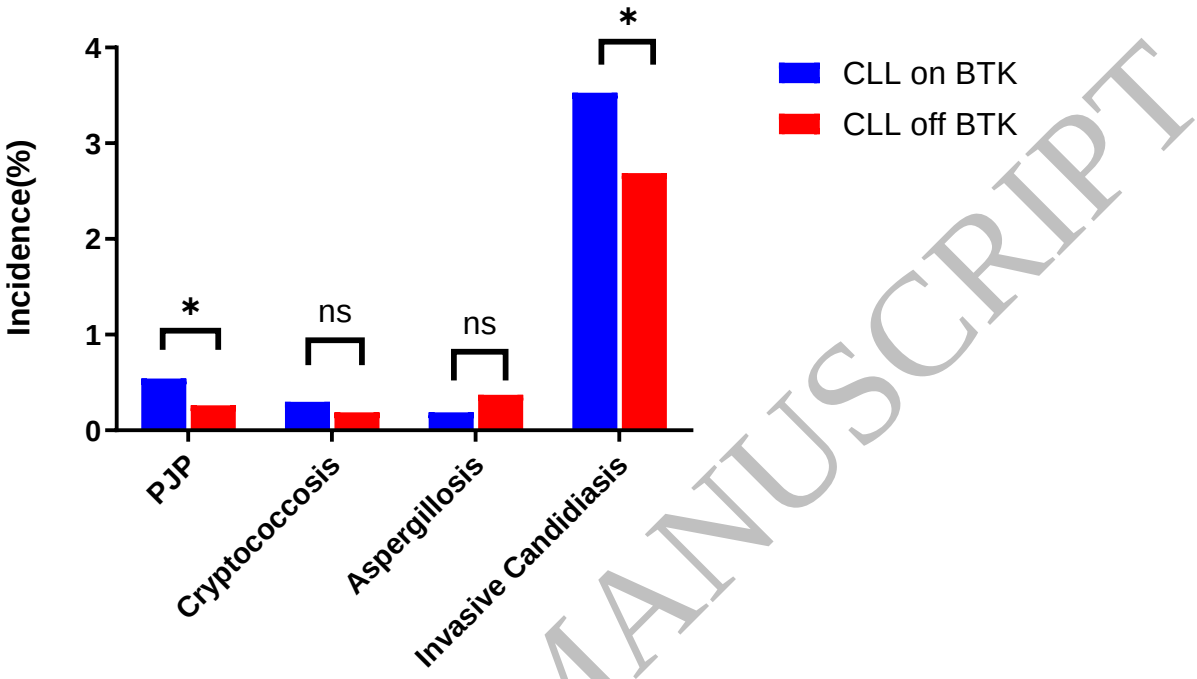
BTKi: bruton tyrosine kinase inhibitors; CLL: chronic lymphocytic leukemia; CD20: cluster differentiation 20. PV: polycythemia vera. * Includes Tacrolimus, Mycophenolate mofetil, Mycophenolic acid, Cyclosporine, Azathioprine, Sirolimus, Infliximab, Basiliximab, Belatacept, Omalizumab, Siltuximab, Belumosudil, Ustekinumab.

Table 2. Relative risk and number needed to harm with invasive fungal infections in patients with CLL on a BTKi at five years

Invasive Fungal Infection	Episodes* (N, %)	Relative Risk	NNH
Pneumocystis jirovecii pneumonia	29 (0.5%)	2.1	358
Cryptococcosis	16 (0.3%)	1.6	894
Aspergillosis	10 (0.2%)	0.5	536**
Invasive Candidiasis	189 (3.5%)	1.3	120

*Among 5,358 matched patients with CLL on a BTKi**Number needed to treat (NNT)

Figure 1. Proportions of invasive fungal infections among patients with CLL captured after propensity score matching at five years by use of BTKi



CLL: chronic lymphocytic leukemia; BTK: bruton tyrosine kinase inhibitors; NS: Non-significant, *p-value<0.05