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PERSISTENCE WITH ORAL THERAPY AS REFLECTION OF ACTUAL COMPLIANCE FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) – A NATIONAL PRESCRIBED DRUG AND PATIENT REGISTER STUDY FROM SWEDEN

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| DISCLOSURES

Elisa Nevalainen is an employee of IQVIA Nordics.

INTRODUCTION

- Discrepancies in patient outcomes between clinical trials and clinical practice can exist^{1,2}
 - This may be due to a variety of factors, including greater patient heterogeneity in routine clinical practice vs clinical trials^{3,4}
- Chronic comorbidities are common in patients with CLL since many patients with CLL are older¹
 - Median age at CLL diagnosis is 70 years⁵
 - Multidisciplinary management of care for patients with CLL may be challenging
- Sweden has comprehensive national patient and prescription registers
 - A unique base for real-world data on CLL drug use and persistence and the impact of comorbidities

Aims of this study were to gather real-world insights by describing oral drug persistence and to examine the impact of comorbidities on drug persistence in patients with CLL in Sweden

CLL, chronic lymphocytic leukemia.

1. Rotbain EC, et al. *Clin Epidemiol*. 2021;13:1155-1165. 2. Aarup K, et al. *Eur J Haematol*. 2020;105(5):646-654. 3. Kim H-S, et al. *J Korean Med Sci*. 2018;33(34):e213. 4. Nazha B, et al. *Future Oncol*. 2021;17(8):965-977. 5. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: leukemia — chronic lymphocytic leukemia (CLL). Accessed May 4, 2023. <https://seer.cancer.gov/statfacts/html/clyl.html>

METHODS

Pseudonymized data from the National Prescribed Drugs Register and National Patient Register in Sweden were used

Patients with new prescription of oral CLL drugs for continuous use

Period: Jan 1, 2017-Dec 31, 2021

90-day grace period to avoid excluding patients with short treatment breaks^a

9-month “lookback period” to identify patients who were new to treatment

No data on previous intravenous treatment were available

Patients with CLL or SLL
(CLL: *ICD-10* C91.1
SLL: *ICD-10* C83.0)

Prescriptions:

- Ibrutinib
- Acalabrutinib
- Idelalisib
- Venetoclax

Patients assessed in 3 disease groups to analyze the effect of common comorbidities on persistence^b

Groups:

- Infections
- Autoimmune diseases
- Cardiovascular diseases

Kaplan-Meier analysis methods were used to describe the data

ICD-10, International Classification of Diseases, Tenth Revision; SLL, small lymphocytic lymphoma.

^a All drugs required a long grace period to accommodate treatment adjustments and potential toxicities. ^b Persistence was defined as the period between starting and discontinuing an oral drug (ie, the proportion of patients who continued to pick up and refill their prescription of each drug). Persistence outcome was described using the Kaplan-Meier method, and comparisons were made using the log-rank Z test.

RESULTS: PATIENTS

- Prescription data from 2479 patients were collected
 - 1425 patients had CLL and 115 had SLL
- The majority (87%) of patients with CLL were prescribed ibrutinib
 - Fewer patients were prescribed acalabrutinib and idelalisib

	Ibrutinib, n ^a	Venetoclax, n ^a	Acalabrutinib, n ^a	Idelalisib, n ^a	Total, n
Patients with an observed indication ^b	1308	265	123	87	1511
CLL	1234	258	117	80	1425
SLL	97	12	7	7	115
Patients without an indication	392	538	15	53	968
Total no. of patients on drug	1700	803	138	140	2479

^a Patients who were prescribed multiple drugs or switched drugs may be included in ≥1 category. ^b Patients who had an indication change (CLL to SLL or SLL to CLL) may be included in more than one category.

RESULTS: ORAL TREATMENT TYPES IN CLL

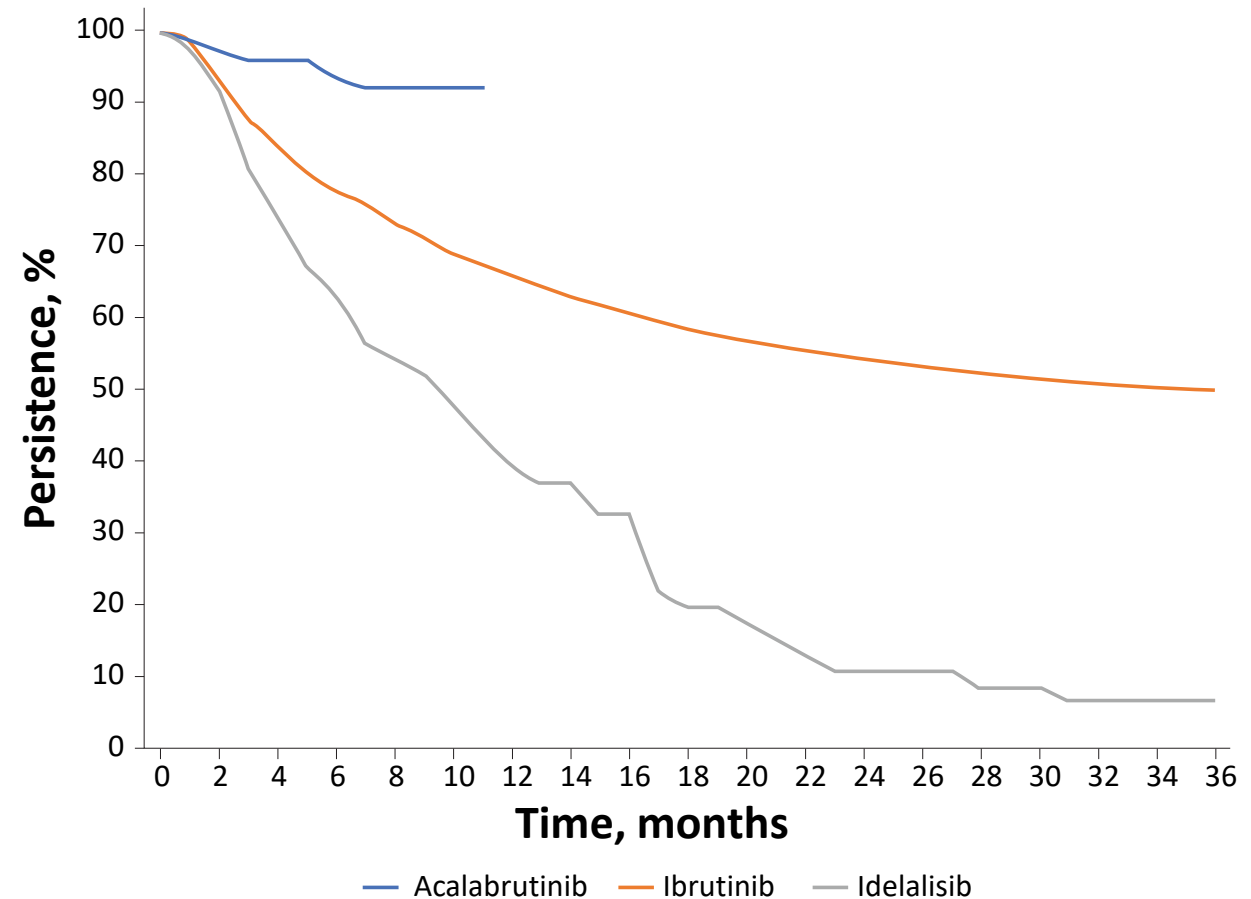
- The most common CLL treatment was ibrutinib
 - Median treatment time was 1.4 years (505 days)
- The most common change in treatment was from ibrutinib to venetoclax
- The second most common change was from ibrutinib to acalabrutinib

	Patients, n (% of study population, N=2098)	Median days on first treatment	Median days on second treatment
Ibrutinib	844 (40)	505	
Ibrutinib → venetoclax	105 (5)	437	238
Venetoclax	71 (3.4)	273	
Acalabrutinib ^a	46 (2.2)	153	
Ibrutinib → acalabrutinib ^a	31 (1.5)	226	129
Idelalisib → ibrutinib ^b	11 (0.5)	296	704
Ibrutinib → idelalisib ^b	10 (0.5)	113	119
Idelalisib	9 (0.4)	176	

^a Acalabrutinib has only been reimbursed for treatment-naive CLL/SLL patients with del(17p)/TP53 mutation, as well as previously treated patients, since March 2021. ^b Low patient numbers mean that individual patients have a significant impact on the treatment duration.

RESULTS: PERSISTENCE IN CLL

- Drug persistence for ibrutinib was 50% at 36 months
- Persistence for idelalisib was $\leq 10\%$ at 36 months
 - 50% persistence was reached at ≈ 10 months
- Data for acalabrutinib had a very short follow-up^a
 - 9-month persistence was 92%



^a Acalabrutinib has only been on the market since 2021.

RESULTS: COMORBIDITIES

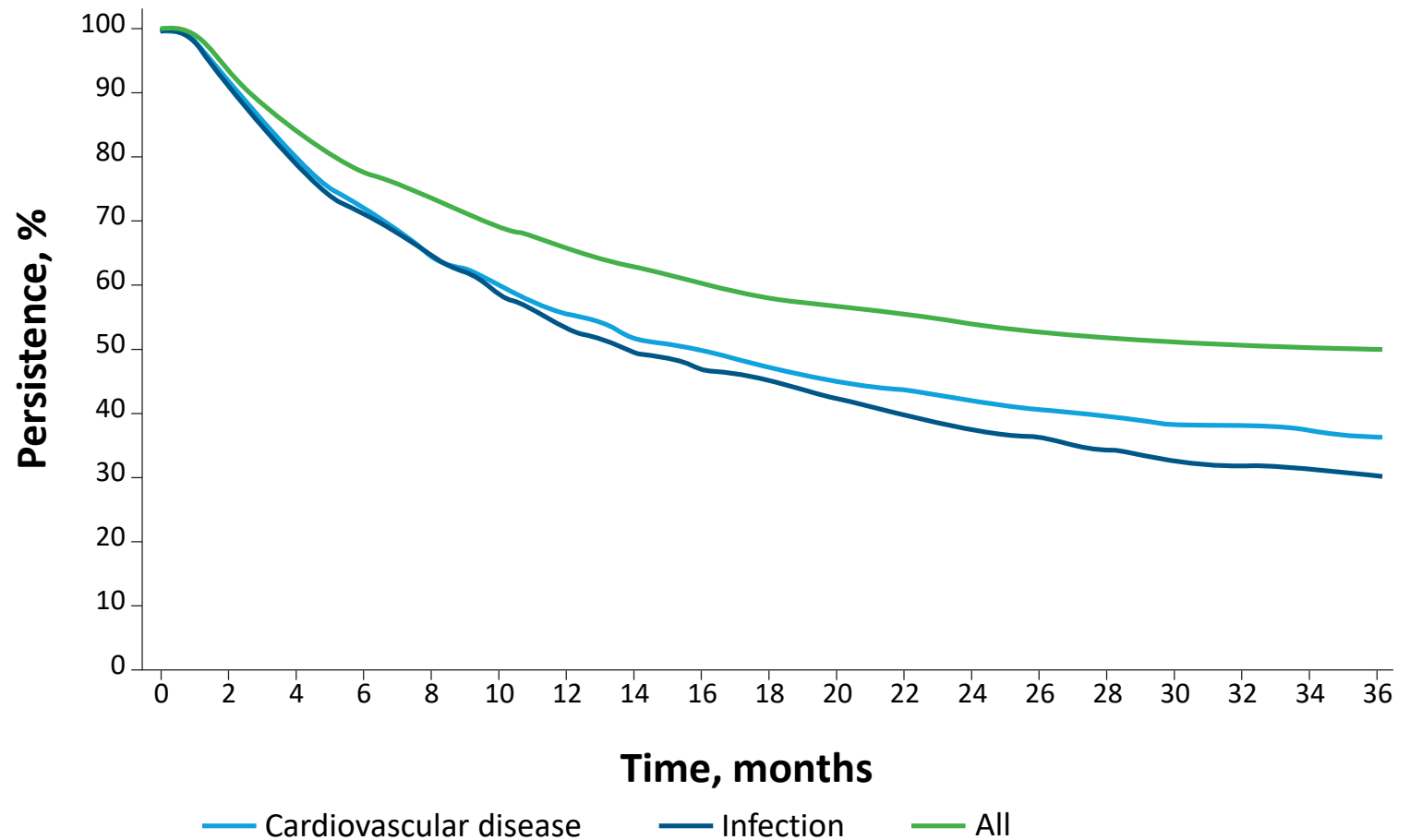
- Of 2479 patients with a prescription, 1528 (62%) had a comorbidity diagnosis at the time of or after their first prescription^a
- The most common comorbidities were infection and cardiovascular disease

Comorbidity ^a	Ibrutinib, n ^b	Venetoclax, n ^b	Acalabrutinib, n ^b	Idelalisib, n ^b	Total, n
Infection	691	425	26	99	1044
Cardiovascular disease	766	330	39	81	1042
Autoimmune disease	189	187	4	21	352
No comorbidity	636	258	91	26	951

^a Comorbidities registered on or after the first drug dispensation date were included. It was not possible to differentiate between newly diagnosed and existing comorbidities. ^b Counts of patients may include duplicates from patients who were prescribed multiple drugs or changed drugs.

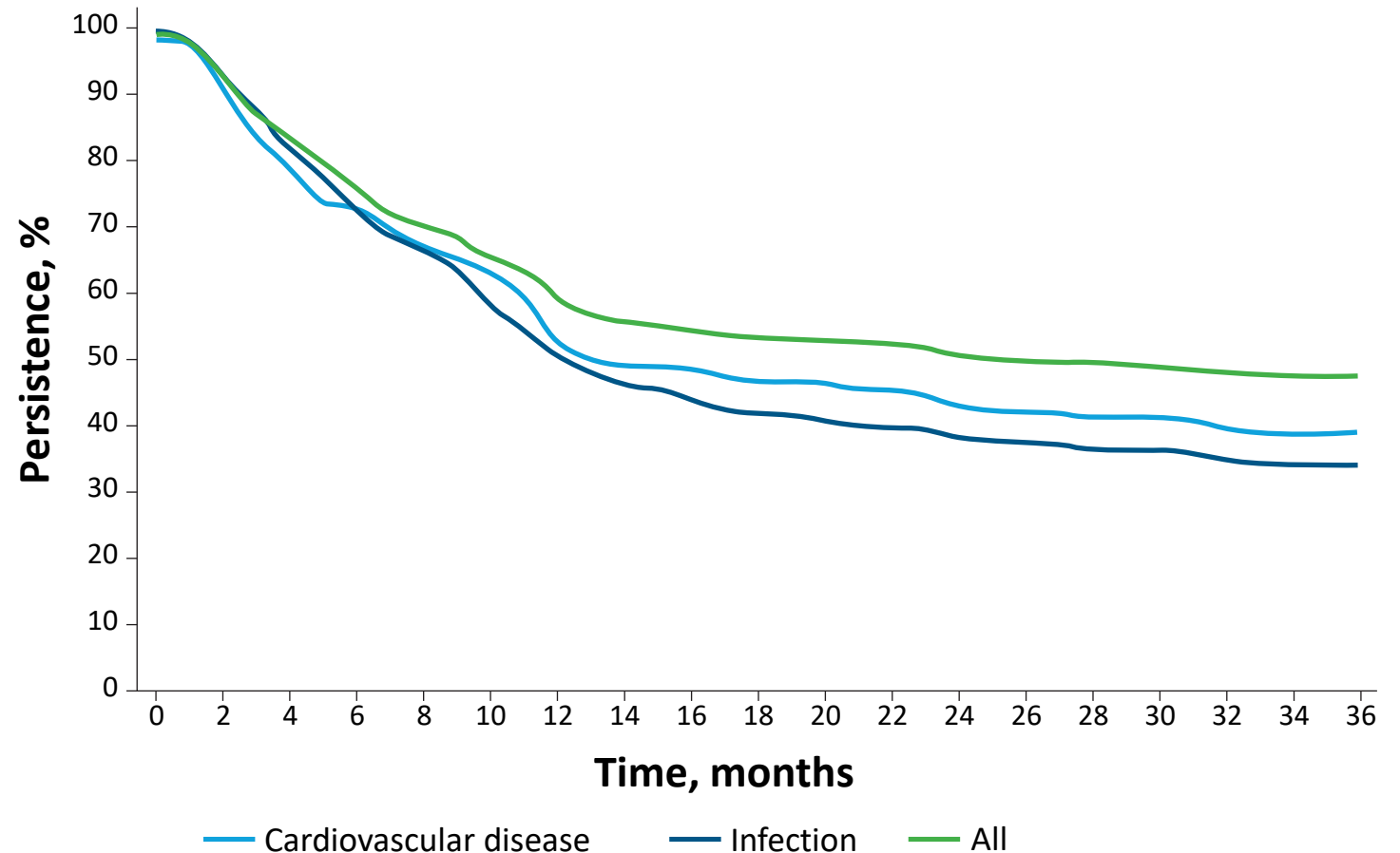
RESULTS: PERSISTENCE OF IBRUTINIB AND COMORBIDITIES

- In patients treated with ibrutinib, the presence of infection or cardiovascular disease increased the likelihood of ibrutinib discontinuation
 - Infection (n=111; $P<.05$)
 - Cardiovascular disease (n=168; $P<.05$)



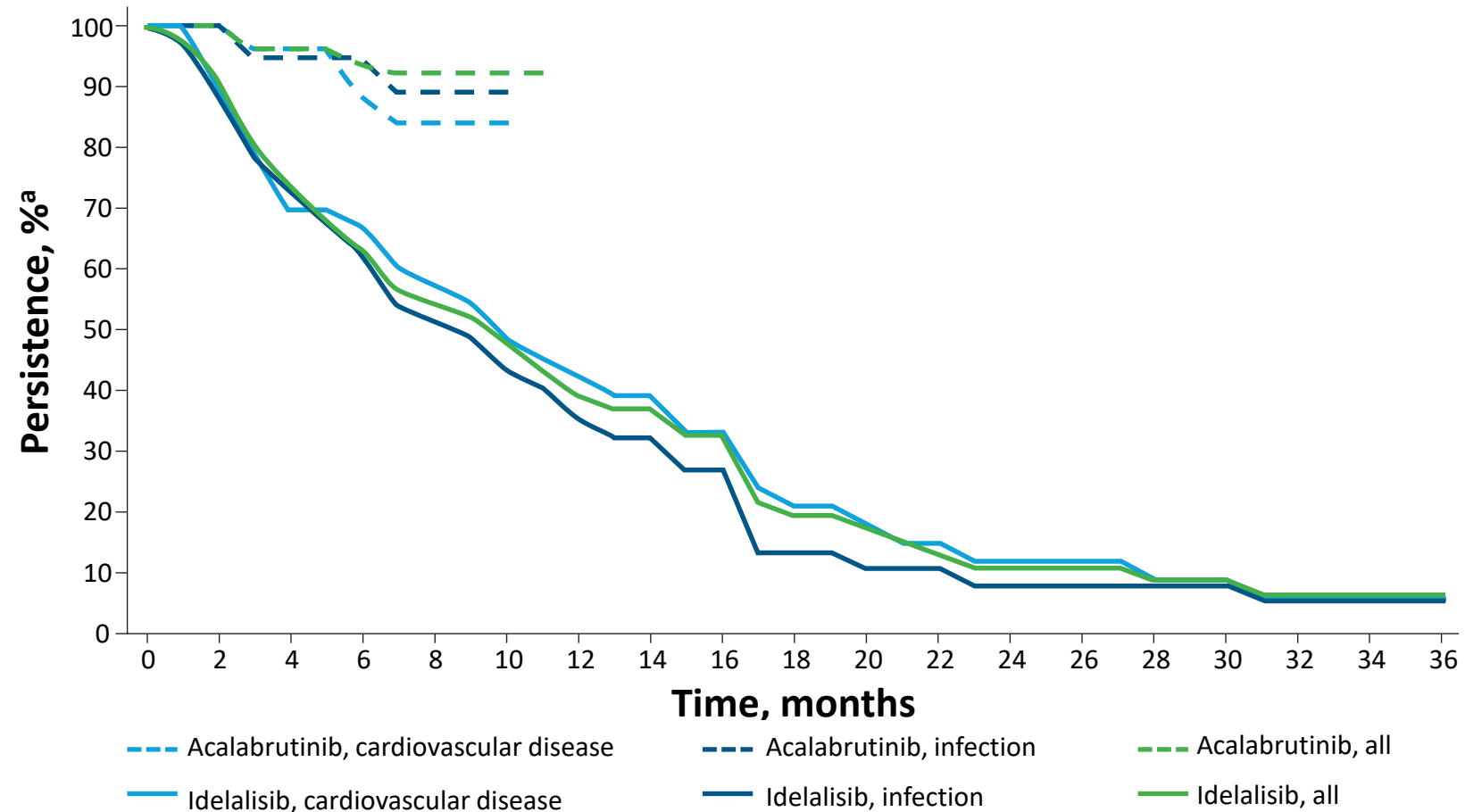
RESULTS: PERSISTENCE OF VENETOCLAX AND COMORBIDITIES

- Similarly, in patients treated with venetoclax, the presence of infection increased the likelihood of venetoclax discontinuation
 - Infection (n=42; $P < .05$)
- The presence of a cardiovascular comorbidity did not significantly impact venetoclax treatment persistence



RESULTS: PERSISTENCE OF IDELALISIB AND ACALABRUTINIB AND COMORBIDITIES

- For idelalisib and acalabrutinib, no statistically significant difference was seen among any of the comorbidity groups



^a Acalabrutinib has only been on the market since 2021.

LIMITATIONS

- The persistence analysis only described adherence to dispensation of drugs
- Information on the dispensed volume was not available from the National Board of Health and Welfare, and reasons for discontinuation could not be provided
 - Dispensation date could only be tracked to the latest dispensation in a specific month
 - A proxy calculation for the number of packs dispensed per patient was developed using prescription sales data
- Only retail-dispensed products were included; in Sweden, the only drugs for CLL that were dispensed from a retail pharmacy were oral medicines
 - Treatments given in a hospital setting (eg, chemotherapy or oral drugs given during hospitalization) were missing from the register, and a patient's usage history by therapy line could not be confirmed
 - The impact of hospital-given drugs was expected to be covered by the grace period
- Acalabrutinib first became available in Sweden in 2021^{1,2}; thus, follow-up durations are limited

1. Calquence (acalabrutinib). Summary of product characteristics. AstraZeneca; 2023. Accessed May 4, 2023. https://www.ema.europa.eu/en/documents/product-information/calquence-epar-product-information_en.pdf.

2. Sweden Backs High-Cost Protection, Limited Subsidy for Calquence in CLL. Navlin Daily. Published March 30, 2021. Accessed June 7, 2023. <https://www.navlindaily.com/article/7040/sweden-backs-high-cost-protection-limited-subsidy-for-calquence-in-ctl>.

CONCLUSION

- Persistence with oral therapy is a well-recognized factor for an effective treatment¹⁻³
 - Adherence estimates can vary widely but are generally 50% to 90%^{2,3}
 - In comparison, published real-world studies in patients with refractory/relapsed CLL report a median PFS varying from 35 to 47 months with ibrutinib and 11 months with idelalisib⁴⁻⁸
- In this analysis, ≈50% of patients with CLL treated with ibrutinib still picked up their prescriptions after 36 months
 - This study also found that comorbidity was an important factor for lower drug persistence
- For patients with CLL treated with an oral drug for continuous use, persistence with therapy may reflect adherence and possibly function as a proxy for PFS

PFS, progression-free survival.

1. Hohneker J, et al. *J Oncol Pract*. 2011;7(1):65-67. 2. Puts MTE, et al. *Ann Oncol*. 25(3);2014:564-577. 3. Paoletta G, et al. *Pharmacy (Basel)*. 2018;6(1):23. 4. Mato AR, et al. *Ann Oncol*. 2017;28:1050-1056. 5. Mulligan SP, et al. *Leuk Lymphoma*. 2023;64(2):312-318. 6. Mato AR, et al. *Haematologica*. 2018;103(5):874-879. 7. Winqvist M, et al. *Haematologica*. 2019;104:e208-e210. 8. Janssens A, et al. *Clin Hematol Int*. 2022;4(4):133-143.

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