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Received: March 2, 2026.

Accepted: October 2, 2026.

Citation: Matthew S. Davids, Jacob Ambrose, Enrico de Nigris, Jennifer Prescott, Siyang Leng, Jing Yang, Christina M. Zettler, Laura L. Fernandes, Ching-Kun Wang and Paul M. Barr. Real-world treatment patterns and outcomes in patients with chronic lymphocytic leukemia previously exposed to both covalent Bruton's tyrosine kinase inhibitor and B-cell lymphoma 2 inhibitor therapy.

Haematologica. 2026 Oct 8. doi: 10.3324/haematol.2026.300690 [Epub ahead of print]

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Real-world treatment patterns and outcomes in patients with chronic lymphocytic leukemia previously exposed to both covalent Bruton's tyrosine kinase inhibitor and B-cell lymphoma 2 inhibitor therapy

Running head: Outcomes of patients with CLL after cBTKi/BCL-2i

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Keywords: CLL, refractory, BTKi, BCL2i, targeted therapy

Financial support: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

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Data-sharing statement: The data underlying this article were provided by COTA, Inc. and cannot be shared due to privacy reasons. Summary-level data are provided throughout the manuscript and in the accompanying tables and figures.

Conflict of Interest: M.S.D. reports royalties or licenses from UpToDate; consulting fees from AbbVie, BeOne Medicines, Bristol Myers Squibb, Janssen, Ascentage Pharma, Eli Lilly, MSD, Genentech, AstraZeneca, Galapagos, Genmab, Nuvalent, and Schroedinger; participation on a data safety monitoring board or advisory board for German CLL Study Group; and institutional grants or contracts (to Dana-Farber Cancer Institute) from AstraZeneca, Novartis, MEI Pharma, and Ascentage Pharma. J.A., C.M.Z., L.L.F., and C.K.W. report current employment and equity ownership in COTA, Inc.. E.d.N. reports current employment in Merck Sharp & Dohme (UK) Limited, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and equity ownership in Merck & Co., Inc., Rahway, NJ, USA. J.P., S.L., and J.Y. report current employment by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and equity ownership in Merck & Co., Inc., Rahway, NJ, USA. PMB; consulting for COTA, AbbVie, Bristol Myers Squibb, Janssen, Eli Lilly, Merck, Adaptive Biotechnologies, Genentech, MEI Pharma, TG Therapeutics, AstraZeneca, and BeiGene

Acknowledgements: N/A

Targeted therapies such as covalent Bruton's tyrosine kinase inhibitors (cBTKis; e.g., first generation: ibrutinib and second generation: acalabrutinib and zanubrutinib) and venetoclax, a B-cell lymphoma 2 inhibitor (BCL2i) have revolutionized the treatment paradigm for chronic lymphocytic leukemia (CLL), displacing chemoimmunotherapy (CIT) as the preferred treatment for newly diagnosed and relapsed or refractory (R/R) disease.¹ These agents have improved patient outcomes, meaningfully extending progression-free and overall survival (PFS, OS) for the CLL patient population.^{2,3} Patients with R/R CLL who have been exposed to and discontinued both therapeutic classes for any reason, however, have few effective therapeutic options. The unmet need is even greater for patients with double-refractory disease – CLL that does not respond to BTKi and BCL2i therapy or progresses during or shortly after discontinuing each agent.^{1,4} Our analysis sought to characterize the real-world population of double-exposed patients with CLL and to describe real-world treatment patterns and outcomes of this patient population with emphasis on the double-refractory population.

Patients in the COTA real-world, electronic health record (EHR)-based dataset qualified by meeting the following criteria: adults with CLL exposed to both a BTKi and BCL2i (i.e., double-exposed (DE)); in any order, in any line of therapy (LOT), concurrently or sequentially) and who subsequently initiated another LOT on or before May 31, 2024. The initiation of this LOT after double-exposure was the study index date. Patients were ineligible if they had a concurrent primary malignancy or histologic transformation prior to index, history of other hematologic malignancy, or insufficiently precise key study dates.

BTKi refractoriness was defined as: discontinuation of BTKi due to inadequate response or progression ≥ 14 days after BTKi initiation OR progression documented from 14 days after BTKi

initiation to the earlier of: 60 days after BTKi end or initiation of next LOT. BCL2i refractoriness was defined using the same parameters as BTKi refractoriness. For patients who received their first BCL2i in combination with another agent, an additional criterion required a progression event anytime between the end of the combination regimen (after at least 11 months of receipt in 1L or 23 months in 2L+) and the initiation of the next LOT. Progression data were based on physician-documentation of progression of disease. Patients were designated double-refractory (DR) based on refractoriness to both classes per these definitions. Those who did not meet the definition for refractory to both classes were categorized as non-DR. Analyses were conducted in the overall population and by DR status. COTA's de-identified real-world database is approved by WCG IRB for use in research (Study #1174746).

Of N=6,674 records in this dataset, 371 were previously treated with cBTKi and venetoclax (**Supplemental Figure 1**). The final cohort included N=81 patients who initiated subsequent therapy and otherwise met eligibility criteria. The patient population is demographically similar to the typical CLL population with about two-thirds treated in the community (**Table 1**). Seventeen patients (21.0%) were DR, and sixty-four (79.0%) were non-DR. Patients who were DR had a median age of 68 years at index, and patients who were non-DR had a median age of 71.5 years at index.

The overall DE population received a median of 4 LOTs prior to index (**Table 1**). More than 85% of patients were exposed to chemotherapy and/or anti-CD20 therapy and/or CIT in any LOT prior to index (**Supplemental Table 1**). **Supplemental Figure 2** shows the therapies received at index among the overall cohort. About one-third of patients received venetoclax and an anti-CD20 antibody at index, 25.9% received BTKi monotherapy, 14.8% received anti-CD20+/-chemotherapy, and the remainder of patients received other regimens (24.7%). Among

patients in the DR group, the majority (70.1%) received a cBTKi and/or venetoclax at index, despite refractoriness to both classes. Median time to treatment discontinuation (rwTTD) of index LOT was 7.9 months (95% CI: 5.1, 16.3) overall, 5.1 months (95% CI: 2.7, not reached (NR)) among the DR subgroup, and 13.8 months (95% CI: 5.8, 21.0) among the non-DR group (**Table 2**). The most common reason for treatment discontinuation of first cBTKi and BCL2i among the overall population was toxicity (48.7% and 44.9% of patients with documented reasons, respectively).

Patients who were DR generally experienced shorter times to event compared to patients who were non-DR. Median follow-up time from index (reverse KM) was 26.9 months (95% CI: 15.8, 36.2) overall and was longer for the non-DR group (28.3 months) compared to the DR group (15.4 months) (**Table 1**). Median rwPFS from index LOT initiation was 19.9 months (95% CI: 10.1, 35.7) and was significantly worse for the DR group (3.2 months) compared to the non-DR group (24.0 months) (HR: 0.32 (95% CI: 0.15, 0.69)) (**Table 2 & Figure 1**). Median OS from index LOT initiation was not reached (**Table 2 & Figure 1**). Outcomes are poor for patients with CLL who are DE and are demonstrably worse for patients who are DR compared to those who are non-DR. While 78% of patients in the non-DR group were alive two years after index, that proportion drops to only 31% for the DR group.

Our study highlights the unmet need for patients with DE and especially DR CLL among a population that received additional therapy following double-exposure. Median age at diagnosis was younger than a typical CLL population, likely due to the requirement for receipt of multiple LOTs (for exposure to both targeted therapies and subsequent LOT initiation). There was no clear standard of care following double-exposure, with only about one-third of patients receiving any single regimen after exposure to both agents. Nearly 46% of patients were re-treated with

venetoclax (+/- other therapies) at index, and about 34% were re-treated with a BTKi at index. Among the DR group, more than 70% of patients were re-treated with a BTKi and/or BCL2i at index. This pattern of “re-cycling” therapies, especially among patients with known refractoriness, highlights a lack of available treatment options for patients who have been previously exposed to existing therapeutic classes.

Of note, two novel therapies, namely pirtobrutinib (non-covalent BTKi) and lisocabtagene maraleucel (liso-cel, autologous CD19-targeted CAR-T), received FDA (accelerated) approvals for the DE indication between 2023 and 2025.⁵⁻⁷ Due to relatively recent approvals, only two patients in this study received pirtobrutinib at index, and one additional patient received an investigational CAR-T therapy at index. Future research is needed to understand the real-world uptake of these agents and their resulting outcomes among DE and DR patients. Additionally, further investigation is needed to assess the impact of novel agents currently under study (e.g., other non-covalent BTKis such as nemtabrutinib, as well as BTK degraders and bispecific antibodies) in this patient population considering unknown disease susceptibility to novel therapies following acquired resistance mutations with cBTKi treatment.⁸

By requiring subsequent LOT initiation in our study, we excluded patients with significant unmet need – those with progressive disease following DE, but who could not initiate subsequent therapy due to age, fitness, and/or the aggressive nature of their disease. There were an additional 53 records in the database that met all qualification criteria (i.e., DE and discontinued both BTKi and BCL2i therapy) except index LOT initiation and subsequently had a date of death. Eleven of those patients experienced progressive disease following their second targeted therapy exposure and prior to the date of death. Additional therapeutic options may have benefitted these patients, further highlighting the unmet need in this population.

A strength of this study is that it leveraged a contemporary, real-world, curated database, which includes granular information for patients with CLL. The COTA database includes patients treated in diverse treatment settings (both academic centers and community practices) and locations (Northeast, Mid-Atlantic, Southern, and Western regions of the US). Study limitations are related to the nature of real-world data. Although all eligible patients were included in this observational study, we acknowledge that factors such as socioeconomic status could have influenced treatment choice. This information was not captured in the dataset and is therefore, not reportable. Despite robust abstractor training and quality measures, data collected from EHR sources may not be complete as treatment provided outside of the provider network may not be captured or due to lack of explicit documentation in the record. Additionally, algorithmically assigned LOT may not capture all nuances in real-world clinical practice, leading to potential misclassification. Similarly, while definitions of refractoriness vary slightly in the literature, our systematic definition aimed to be most consistent with progression during or shortly after discontinuation of the given therapy.

While targeted agents such as BTKi and BCL2i therapy have improved outcomes for patients with CLL, our study highlights persistent unmet need for patients whose disease has progressed following exposure to both treatment classes. Patients who are refractory to both classes experience worse outcomes and have the greatest need for novel agents. Due to the recency of BCL2i approval (for R/R disease in 2016 and for 1L treatment in 2019) and the effectiveness of these therapies in the real-world setting, the subpopulation of DE and/or DR patients is relatively small and new, but growing.⁹ Additional research is needed to better understand uptake of newly approved therapies and optimal therapy sequencing, as well as to identify additional, novel treatment options to administer following double-exposure.

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Table 1: Characteristics by DR status

Table 1. Characteristics by DR status	DE (N= 81)	Subgroup: DR Status	
		DR (N= 17)	Non-DR (N= 64)
Age at Initial Dx, median [IQR]	59.0 [53.0, 68.0]	61.0 [53.0, 64.0]	59.0 [53.0, 68.0]
Age at Index, median [IQR]	71.0 [63.0, 77.0]	68.0 [64.0, 74.0]	71.5 [62.0, 77.0]
Sex, n (%)			
Female	27 (33.3)	4 (23.5)	23 (35.9)
Male	54 (66.7)	13 (76.5)	41 (64.1)
Race, n (%)			
Asian	1 (1.2)	0 (0.0)	1 (1.6)
Black or African American	7 (8.6)	1 (5.9)	6 (9.4)
White	63 (77.8)	14 (82.4)	49 (76.6)
Other Race	9 (11.1)	2 (11.8)	7 (10.9)
Unknown	1 (1.2)	0 (0.0)	1 (1.6)
Practice Type, n (%)			
Academic	27 (33.3)	4 (23.5)	23 (35.9)
Community	54 (66.7)	13 (76.5)	41 (64.1)
Index LOT, n (%)			
2L	1 (1.2)	0 (0.0)	1 (1.6)
3L	14 (17.3)	1 (5.9)	13 (20.3)
4L	23 (28.4)	4 (23.5)	19 (29.7)
5L	17 (21.0)	6 (35.3)	11 (17.2)
6L+	26 (32.1)	6 (35.3)	20 (31.2)
Follow up time from index (months; Reverse KM), median (95% CI)	26.9 (15.8, 36.2)	15.4 (11.9, NR)	28.3 (17, 39.9)
Total LOTs Received Prior to Index, median [IQR]	4.0 [3.0, 5.0]	4.0 [3.0, 5.0]	3.0 [3.0, 5.0]
First cBTKi Received (Prior to Index), n (%)			
Acalabrutinib	7 (8.6)	2 (11.8)	5 (7.8)
Ibrutinib	71 (87.7)	15 (88.2)	56 (87.5)
Zanubrutinib	3 (3.7)	0 (0.0)	3 (4.7)
Index LOT Classes Received, n (%)			
Anti-CD20 + BCL2i	28 (34.6)	6 (35.3)	22 (34.4)
BTKi monotherapy	21 (25.9)	5 (29.4)	16 (25.0)

Anti-CD20 +/- Chemotherapy	12 (14.8)	3 (17.6)	9 (14.1)
Other therapies	20 (24.7)	3 (17.6)	17 (26.6)
Abbreviations: BCL2i = BCL2 inhibitor; BTKi = Bruton's tyrosine kinase inhibitor; CI = confidence interval; DE = Double exposed; DR = Double refractory; dx = diagnosis; IQR = interquartile range; KM = Kaplan-Meier; LOT = line of therapy			

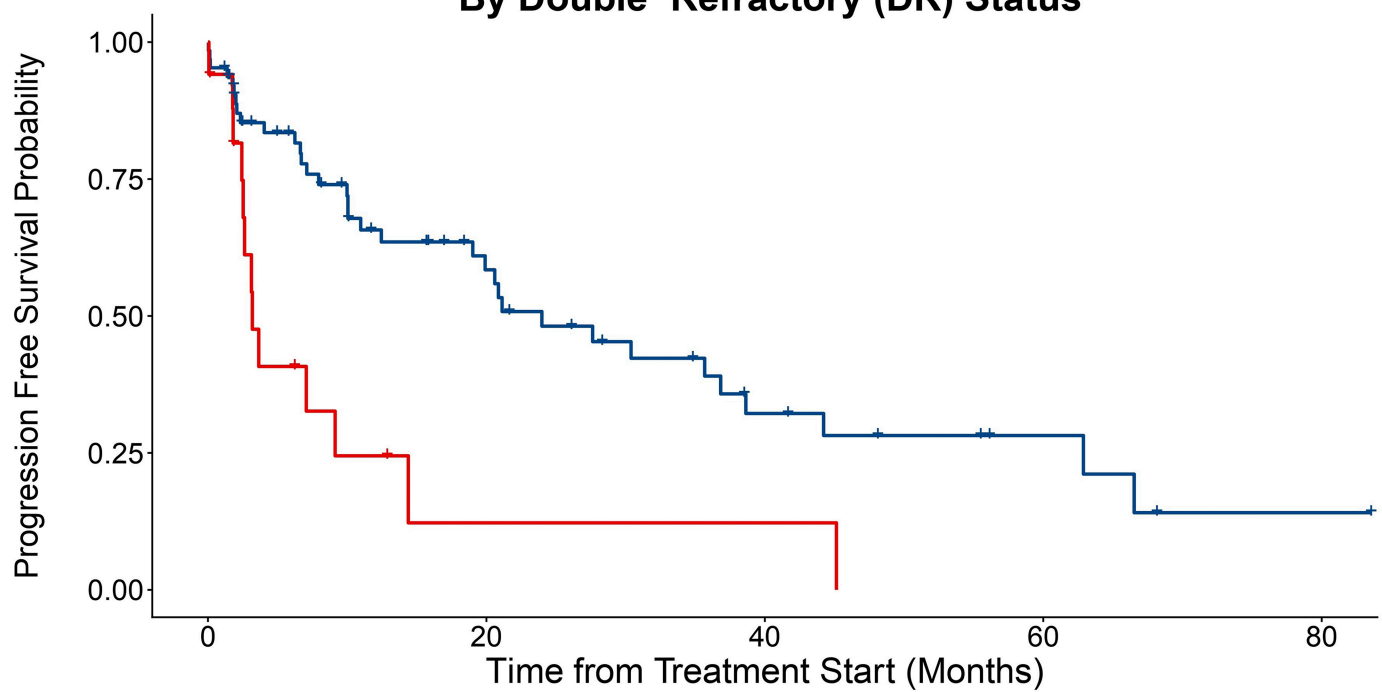
Table 2: Real-world Outcomes

Table 2: Real-world Outcomes	DE (N=81)	Subgroup: DR Status	
		DR (N=17)	Non-DR (N=64)
rwTTD			
Events	58	13	45
Median (95% CI)	7.9 (5.1, 16.3)	5.1 (2.7, NR)	13.8 (5.8, 21.0)
HR (95% CI)	-	Ref	0.52 (0.26, 1.05)
rwTTNT			
Events	42	10	32
Median (95% CI)	21.1 (15.1, 47.6)	5.2 (2.9, NR)	26.0 (20.7, 63.2)
HR (95% CI)	-	Ref	0.36 (0.15, 0.83)
rwPFS			
Events	47	13	34
Median (95% CI)	19.9 (10.1, 35.7)	3.2 (2.5, NR)	24 (19.0, 44.2)
HR (95% CI)	-	Ref	0.32 (0.15, 0.69)
24-month Events	38	12	26
24-month Rate (95% CI)	41% (30%, 56%)	12% (2%, 65%)	48% (36%, 65%)
rwOS			
Events	22	7	15
Median (95% CI)	NR (32.7, NR)	19.6 (16.8, NR)	NR (47.0, NR)
HR (95% CI)	-	Ref	0.36 (0.13, 0.99)
24-month Events	17	6	11
24-month Rate (95% CI)	70% (59%, 84%)	31% (10%, 93%)	78% (66%, 91%)

Abbreviations and Definitions: Confidence interval (CI); double exposed (DE); double refractory (DR); hazard ratio (HR); not reached (NR); real-world time to treatment discontinuation (rwTTD): defined as the time from index to treatment discontinuation (end of current LOT), initiation of next LOT, or death; real-world time to next treatment (rwTTNT): defined as the time from index to the initiation of the next LOT or death; real-world progression-free survival (rwPFS): defined as the time from index to the date of progression event, initiation of next LOT, histologic transformation, or death; overall survival (OS): defined as the time from index to date of death

Figure 1: KM Curves – Real-World Progression-Free Survival and Overall Survival by DR Status

Progression Free Survival By Double-Refractory (DR) Status

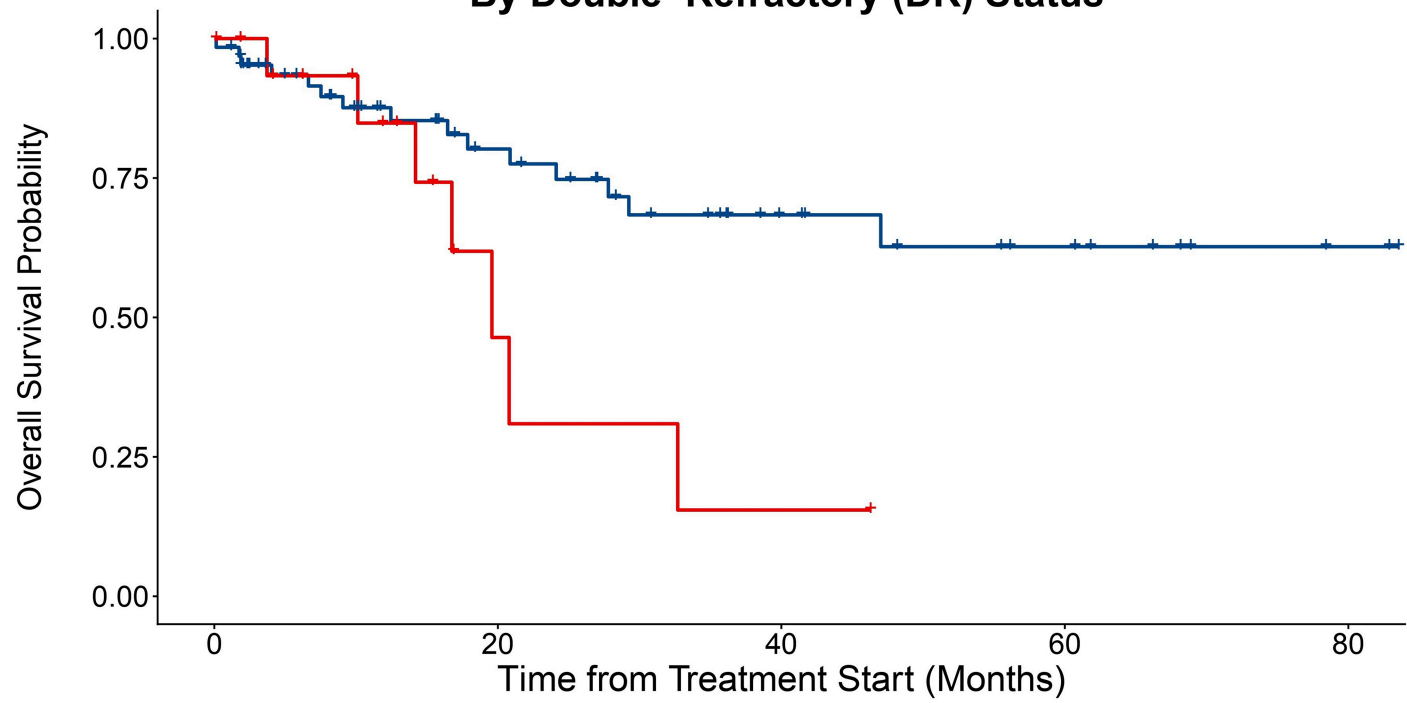


N at risk

Not DR	64	23	9	4	1
DR	17	1	1	0	0

Time from Treatment Start (Months)

Overall Survival By Double-Refractory (DR) Status



N at risk

Not DR	64	30	14	8	2
DR	17	3	1	0	0

Time from Treatment Start (Months)

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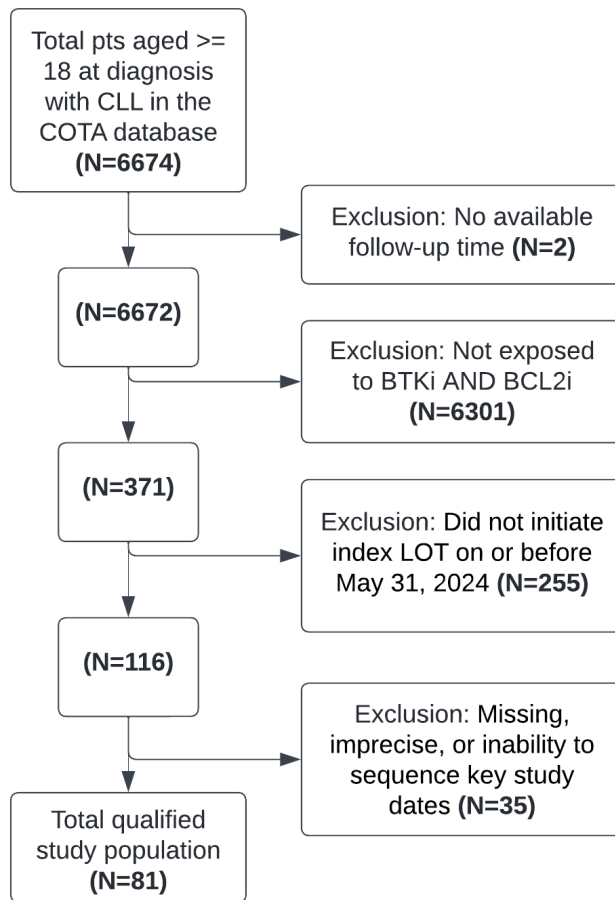
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Supplemental Table 1: Additional Characteristics by DR status

Supplemental Table 1: Additional Characteristics by DR status	DE (N= 81)	Subgroup: DR Status	
		DR (N= 17)	Non-DR (N= 64)
Year of Diagnosis, n (%)			
≤2014	60 (74.1)	12 (70.6)	48 (75.0)
2015-2018	17 (21.0)	5 (11.8)	12 (18.8)
2019-2024	4 (4.9)	0 (0.0)	4 (6.3)
Year of Index LOT Initiation, n (%)			
2016-2018	16 (19.8)	4 (23.5)	12 (18.8)
2019-2023	65 (80.2)	13 (76.5)	52 (81.3)
Follow up time from dx (months), median (IQR)	152.9 [104.7, 179.4]	134.6 [110.6, 154.2]	156.2 [104.4, 183.4]
Time from dx to index (months), median (IQR)	121.6 [83.9, 157.9]	116.6 [94.8, 139.7]	129.3 [82.3, 163.5]
ECOG Status, n (%)			
0-1	44 (54.3)	8 (47.1)	36 (56.2)
2+	1 (1.2)	0 (0.0)	1 (1.6)
Unknown	36 (44.4)	9 (52.9)	27 (42.2)
Prior Exposures, n (%)			
Refractory to cBTKi	44 (54.3)	17 (100.0)	27 (42.2)
Refractory to BCL2i	28 (34.6)	17 (100.0)	11 (17.2)
Prior exposure to CIT	46 (56.8)	13 (76.5)	33 (51.6)
Prior exposure to CIT and/or chemotherapy and/or anti-CD20	69 (85.2)	16 (94.1)	53 (82.8)
Molecular Markers, n (%)			
Del(17p)			

Negative	17 (21.0)	1 (5.9)	16 (25.0)
Positive	25 (30.9)	8 (47.1)	17 (26.6)
Unknown	39 (48.1)	8 (47.1)	31 (48.4)
IGHV			
Unmutated	15 (18.5)	3 (17.6)	12 (18.8)
Mutated	6 (7.4)	0 (0.0)	6 (9.4)
Unknown	60 (74.1)	14 (82.4)	46 (71.9)
TP53			
Negative	27 (33.3)	3 (17.6)	24 (37.5)
Positive	26 (32.1)	8 (47.1)	18 (28.1)
Unknown	28 (34.6)	6 (35.3)	22 (34.4)
Abbreviations: CI = confidence interval; DE = double exposed; DR = double refractory; dx = diagnosis; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; KM = Kaplan-Meier; LOT = line of therapy			

Supplemental Figure 1: Attrition Diagram



Supplemental Figure 2: Treatment Patterns Sankey Plot
Treatments Received by Line of Therapy (LOT)

