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Association Between Dose Reduction and Duration of Therapy in Patients Receiving Ibrutinib or Acalabrutinib for Chronic Lymphocytic Leukemia: A Medical Chart Review Study

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OBJECTIVE

To analyze the association between dose reduction (DR) due to adverse events (AEs) and duration of therapy in patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma who initiated treatment with ibrutinib or acalabrutinib in the first-line (1L) setting

CONCLUSIONS

In this real-world study, which was descriptive in nature, patients with CLL who initiated 1L treatment with ibrutinib and underwent a DR due to an AE of interest had a duration of therapy (DOT) of 35.7 months. Those who initiated acalabrutinib and underwent a DR due to an AE of interest had a DOT of 18.0 months

Findings from this and prior studies support ibrutinib DR strategies; however, additional studies with a larger population of patients and longer follow-up periods are needed to assess the effectiveness of DR for acalabrutinib and to evaluate the impact of the duration of acalabrutinib on treatment outcomes and on patients who require DR

https://www.congresshub.com/ASH2024/Oncology/Ibrutinib/Shadman

AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, and the review and approval of the publication. No honoraria or payments were made for authorship. Medical writing support was provided by Cindi A. Hoover, PhD, and Dimakatso Senthebane, PhD, and was funded by AbbVie.

MS: employment and stock with Bristol Myers Squibb; consulting/advisory role with AbbVie, ADC Therapeutics, AstraZeneca, BeiGene, Bristol Myers Squibb, Eli Lilly, Fate Therapeutics, Genentech, Genmab, Kite Pharma, MEI Pharma, MorphoSys/Incyte, Mustang Bio, Regeneron, and Pharmacyclics LLC, an AbbVie Company; research funding from AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb, Genentech, Genmab, MorphoSys/Incyte, Mustang Bio, TG Therapeutics, Vincerx, and Pharmacyclics LLC, an AbbVie Company. LR: consulting/advisory role with AbbVie, Ascentage, AstraZeneca, BeiGene, Curio, DAVA, Janssen, LOXO Oncology, Medscape, PeerView, Pfizer, Pharmacyclics LLC, an AbbVie Company, and TG Therapeutics; ownership interest with Abbott Laboratories; travel and grants from LOXO Oncology; research funding from AbbVie, Adaptive Biotechnologies, Aptose Biosciences, AstraZeneca, Dren Bio, Genentech, LOXO Oncology, Pfizer, and Qiu Puget Sound Biotherapeutics. JP: honoraria from Novartis. BS: employment with AbbVie; stock in AbbVie and Jazz Pharmaceuticals. S. Karve, EF, CS: employment with and stock in AbbVie. GSK: employment with AbbVie, Bristol Myers Squibb, and Pharmacyclics LLC, an AbbVie Company; stock in AbbVie, Bristol Myers Squibb, Dynavax, Inovio, and Moderna; travel/accommodations/expenses from AbbVie, Bristol Myers Squibb, and Pharmacyclics LLC, an AbbVie Company. S Karanth, RKG, JR: employment with RTI Health Solutions. DMS: consulting/advisory role with AbbVie, AstraZeneca, BeiGene, Bristol Myers Squibb, Celgene, CSL Behring, Eli Lilly, Epizyme, Genentech, Innate, and TG Therapeutics; research funding from ArQule, AstraZeneca, Iovance, Merck, Mingsight, and Novartis.

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Presented at the 66th ASH Annual Meeting and Exposition; December 7–10, 2024; San Diego, California [Ref DV #013147]

INTRODUCTION

- Bruton tyrosine kinase inhibitors (BTKis) including ibrutinib and acalabrutinib are first-line (1L) treatments for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL)[1,2]
- Through the course of CLL treatment, adverse events (AEs) may lead to treatment cessation in some patients, thereby leading to loss of treatment efficacy and disease progression[3,4]
- Dose reduction (DR) with ibrutinib is a reasonable strategy to address toxicity, and recent real-world studies suggest that ibrutinib DR can optimize treatment outcomes, reducing the rate of treatment failure regardless of cardiac or noncardiac AEs.[5] However, outcomes of DR with acalabrutinib are not well documented

METHODS

Study Design and Patient Selection

- This retrospective, noninterventional medical chart review examined patients diagnosed with CLL/SLL who received 1L treatment with a BTKi (ibrutinib or acalabrutinib) in the United States between October 1, 2017, and September 30, 2022
- Patients were included if they met the following criteria:
  - Were aged ≥18 years at the time of CLL/SLL diagnosis
  - Had initiated 1L treatment with standard-dose ibrutinib (420 mg/day) or acalabrutinib (100 mg twice daily or 200 mg/day) after October 1, 2017
  - Had ≥12 months of potential follow-up since the start of the 1L therapy (except for instances of patient death)
- Patients were excluded if they met the following criteria:
  - Had participated in other clinical trials for CLL/SLL at any time
  - Had evidence of another cancer prior to the diagnosis of CLL/SLL
  - Had a history of Richter syndrome before BTKi initiation
  - Dates related to CLL/SLL diagnosis or BTKi therapy initiation were missing
- Data abstraction was performed by hematologist-oncologists at 142 community and academic oncology sites treating patients with CLL/SLL
- The study index date was defined as the date of first BTKi initiation
- A sampling quota was specified to ensure adequate representation of patients who experienced AEs (cardiac and noncardiac) on 1L treatment and subsequently had a DR or remained on standard dose

Study Variables and Analyses

- This analysis focused on patients treated with ibrutinib or acalabrutinib with DRs due to AEs of interest
  - AEs of interest included cardiac failure, atrial fibrillation, ventricular tachycardia, other cardiac arrhythmia, hypertension, cardiomyopathy, ischemic heart disease, febrile neutropenia, anemia, leukopenia, lymphopenia, neutropenia, pancytopenia, thrombocytopenia, diarrhea, abdominal pain, musculoskeletal pain, rash, and pneumonia
- Data on baseline demographics, clinical characteristics, and treatment patterns, including occurrence of AEs and subsequent dosing status (DR or remained on standard dose), were abstracted from medical records. All analyses presented here are descriptive
- Duration of therapy (DOT) with 1L therapy was calculated separately for ibrutinib and acalabrutinib cohorts using the following 2 approaches:
  - **DOT post-therapy initiation:** the time (in months) from index date to discontinuation or death, whichever occurred earlier
  - **DOT post-DR:** the time (in months) from first DR on 1L therapy to discontinuation or death, whichever occurred earlier
- DOT was analyzed using the Kaplan-Meier method. Patients without a recorded treatment discontinuation event were censored at the last available follow-up
- Multivariable Cox proportional hazards regression analyses were performed, adjusting for baseline patient characteristics including demographics, risk factors, genomic factors, and time from diagnosis to treatment (**Supplemental Methods**). Adjusted hazard ratios with 95% CIs were estimated
- To address signs of violation of the proportional hazard assumption, the restricted mean survival time (RMST) was assessed and average time on therapy was reported
  - RMST is defined as the area under the survival curve up to a specific time point and is a novel alternative measure in survival analyses that may be useful when proportional hazards assumptions cannot be made[6]
- All analyses were conducted using SAS statistical software (version 9.4 or later)

RESULTS

Patient Demographics and Clinical Characteristics

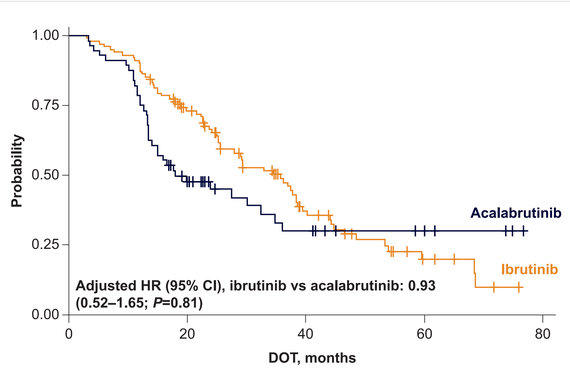
Characteristic	Ibrutinib N=102	Acalabrutinib N=56
Median age at index date (range), years	65.9 (37.3–87.1)	60.3 (27.4–77.9)
Sex, n (%)		
Men	61 (60)	38 (68)
Female	40 (39)	18 (32)
Not recorded or unknown	1 (1)	0 (0)
Predominant race, n (%)		
White	72 (71)	39 (70)
African American or Black	24 (24)	10 (18)
Asian	5 (5)	5 (9)
Middle Eastern or North African	1 (1)	2 (4)
Ethnicity, n (%)		
Hispanic, Latin American, or Latinx	14 (14)	10 (18)
Not Hispanic, Latin American, or Latinx	87 (85)	44 (79)
Unknown	1 (1)	2 (4)
Index year, n (%)		
2017–2019	41 (40)	24 (43)
2020–2022	61 (60)	32 (57)
Insurance status at index date, n (%)		
Commercial/private insurance	20 (20)	24 (43)
Medicare	64 (63)	25 (45)
Medicaid	17 (17)	7 (13)
Unknown	1 (1)	0 (0)
Healthcare setting type, n (%)		
Academic or teaching hospital	39 (38)	33 (59)
Community or nonacademic hospital	63 (62)	23 (41)
Geographic region, n (%)		
Northeast	18 (18)	13 (23)
South	53 (52)	13 (23)
Midwest	5 (5)	12 (21)
West	26 (26)	18 (32)
Community description of healthcare setting, n (%)		
Urban	64 (63)	46 (82)
Suburban	38 (37)	10 (18)
Median duration of follow-up from index date (range), months	35.1 (13.8–76.0)	32.6 (14.3–76.8)
Baseline comorbidities, n (%)		
Hypertension	31 (30)	23 (41)
Thyroid disease	19 (19)	1 (2)
Diabetes without end-organ damage	10 (10)	14 (25)
Chronic obstructive pulmonary disease	4 (4)	5 (9)
Congestive heart failure	1 (1)	6 (11)
Rai stage at index date, n (%)		
0–2	82 (80)	31 (55)
3–4	20 (20)	24 (43)
Not recorded or unknown	0 (0)	1 (2)
Genomic profiling status at index date, n (%)		
del(17p)	16 (16)	18 (32)
TP53 mutations/aberrations	10 (10)	11 (20)
Mutated IGHV	5 (5)	2 (4)
del(11q)	7 (7)	4 (7)
Median CCI score (range)	1 (0–5)	1 (0–5)
ECOG PS score at index date, n (%)		
0–1	83 (81)	46 (82)
2–3	13 (13)	10 (18)
Unknown	6 (6)	0 (0)

CCI, Charlson comorbidity index; ECOG PS, Eastern Cooperative Oncology Group performance status.

- Medical record data were abstracted for 102 patients treated with ibrutinib who had a DR due to an AE of interest (median age at index date: 65.9 years; 60% men) and 56 patients treated with acalabrutinib who had a DR due to an AE of interest (median age: 60.3 years; 68% men)
- Among patients treated with ibrutinib and acalabrutinib median follow-up from index date was 35.1 months (range, 13.8–76.0) and 32.6 months (range, 14.3–76.8), respectively
- Most patients received 1L therapy as a single agent (ibrutinib, 60.8%; acalabrutinib, 83.9%). Treatment characteristics of 1L therapy are shown in **Supplemental Table 1**
- The median time from index date to first recorded AE of interest and DR was 5.7 months and 6.7 months, respectively, for ibrutinib, and 4.3 months and 5.3 months, respectively, for acalabrutinib
  - Most patients had only 1 DR during 1L therapy (ibrutinib, 80.4%; acalabrutinib, 98.2%)
- For the first DR, the ibrutinib dose was reduced to 280 mg/day in 92.2% of patients, and acalabrutinib was reduced to 100 mg/day in 98.2% of patients (**Supplemental Table 2**)
- Per physician reports, the most common AEs leading to DR were hypertension (25.5%), diarrhea (21.6%), and rash (13.7%) with ibrutinib, and hypertension (28.6%), diarrhea (26.8%), and anemia (21.4%) with acalabrutinib

Duration of Therapy

Median DOT Post–Index Date Was 35.7 Months for Ibrutinib and 18.0 Months for Acalabrutinib[a]



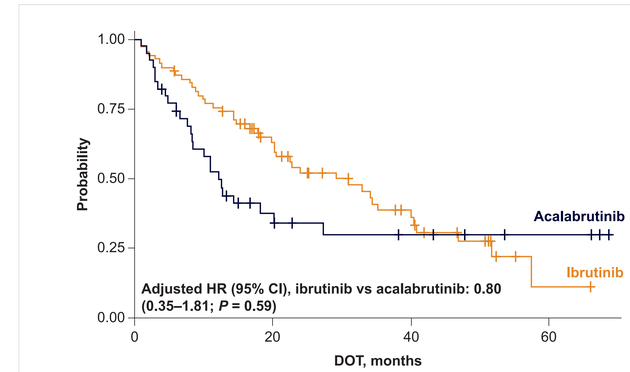
Patients at risk

Ibrutinib	102	67	24	6	0
Acalabrutinib	56	23	10	5	0

HR, hazard ratio.
[a]DOT post-therapy initiation was estimated from date of treatment initiation to discontinuation or death, whichever occurred earlier.

- Based on the RMST analysis, average DOT post–index date was 27.5 months for ibrutinib versus 22.6 months for acalabrutinib (P<0.01)
  - At 12 months, 88.2% of patients (95% CI, 80.2–93.1) who received ibrutinib and 75.0% of patients (95% CI, 61.5–84.4) who received acalabrutinib remained on therapy
- For patients treated with single-agent ibrutinib or ibrutinib + rituximab, median DOT was 34.4 months (95% CI, 25.3–38.4) versus 16.6 months (95% CI, 13.3–32.4) in patients treated with single-agent acalabrutinib or with acalabrutinib + obinutuzumab (**Supplemental Figure 1**)
- Based on the RMST analysis, average DOT post-DR was 20.1 months for ibrutinib versus 14.9 months for acalabrutinib (P=0.008)
- For patients treated with single-agent ibrutinib or with ibrutinib + rituximab, median DOT was 29.2 months (95% CI, 19.8–46.9) versus 11.0 months (95% CI, 6.6–27.3) in patients treated with single-agent acalabrutinib or with acalabrutinib + obinutuzumab (**Supplemental Figure 2**)
- Based on the RMST analysis, average time on therapy was 20.0 months for single-agent ibrutinib or ibrutinib + rituximab and 14.2 months for single-agent acalabrutinib or acalabrutinib + obinutuzumab (P<0.01)
  - At 12 months, 74.7% of patients (95% CI, 61.1–84.2) treated with single-agent ibrutinib or ibrutinib + rituximab and 48.0% of patients (95% CI, 30.1–63.8) treated with acalabrutinib remained on therapy (**Supplemental Table 3**)
- Based on the RMST analysis, average time on therapy was 25.2 months for single-agent ibrutinib or ibrutinib + rituximab and 20.4 months for single-agent acalabrutinib or acalabrutinib + obinutuzumab (P<0.01)
  - At 12 months, 85.9% of patients (95% CI, 76.5–91.7) treated with single-agent ibrutinib or ibrutinib + rituximab and 72.5% of patients (95% CI, 58.1–82.7) treated with single-agent acalabrutinib or acalabrutinib + obinutuzumab remained on therapy (**Supplemental Table 3**)

Median DOT Was 29.2 Months for Ibrutinib and 12.2 Months for Acalabrutinib After DR[a]



Patients at risk

Ibrutinib	70	36	15	1
Acalabrutinib	40	11	6	3

[a]DOT after DR was estimated from first DR to discontinuation or death, whichever occurred earlier.

Limitations

- Each cohort in this retrospective chart review study is representative of a specific group of patients; results may not be generalizable to the broader population of patients with CLL/SLL treated with ibrutinib or acalabrutinib
- Data were limited to information available in the patients' medical records that were available and accessible to physicians participating in the study
- Data abstraction was performed by physicians who entered data directly into an electronic data collection form; rigorous data validation mechanisms were incorporated into the electronic data collection form, but data entry errors cannot be completely ruled out
- Comorbidities and risk factors were not stratified during chart collection, resulting in imbalances in baseline characteristics between patient cohorts

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SUPPLEMENTAL METHODS

- Multivariable Cox proportional hazards regression analyses were adjusted for age, sex, race/ethnicity, index year, insurance status, healthcare setting, geographic region, disease stage, genomic profiling status at index date, Charlson comorbidity index score, smoking status, Eastern Cooperative Oncology Group performance status, number of adverse events (AEs), cardiac AEs, months from diagnosis to treatment initiation, and Bruton tyrosine kinase inhibitor (BTKi) monotherapy

Supplemental Table 1. Treatment Characteristics of 1L Therapy

	Ibrutinib N=102	Acalabrutinib N=56
Agents, n (%)		
Acalabrutinib		47 (84)
Acalabrutinib, bendamustine		1 (2)
Acalabrutinib, obinutuzumab		4 (7)
Acalabrutinib, rituximab		3 (5)
Acalabrutinib, venetoclax, fludarabine, rituximab, duvelisib, prednisone		1 (2)
Ibrutinib	62 (61)	
Ibrutinib, bendamustine, prednisone	1 (1)	
Ibrutinib, obinutuzumab	9 (9)	
Ibrutinib, rituximab	23 (23)	
Ibrutinib, venetoclax	1 (1)	
Ibrutinib, venetoclax, obinutuzumab	6 (6)	
Median time from initial CLL diagnosis to index date (range), months	0.5 (0.0–24.9)	0.7 (0.0–22.8)
Frequency of administration of BTKi at index date, n (%)		
1 intake per day	94 (92)	26 (46)
2 intakes per day	6 (6)	30 (54)
3 intakes per day	2 (2)	0 (0)
Number of DRs, n (%)		
1	82 (80)	55 (98)
2	20 (20)	1 (2)
Median time from index date to first DR (range), months	6.7 (0.5–32.7)	5.3 (0.5–23.8)
Median time from index date to first AE occurrence (range), months	5.7 (0.0–44.1)	4.3 (0.3–23.8)
Median time from first AE to DR (range), months	0.4 (0.0–15.9)	0.3 (0.0–17.2)
New total dose after first DR, n (%)		
100 mg/day		55 (98)
140 mg/day	3 (3)	
280 mg/day	94 (92)	
Frequency of administration after first DR, n (%)		
1 intake per day	95 (93)	43 (77)
2 intakes per day	4 (4)	13 (23)
Reason for first DR, n (%)[a]		
AEs	102 (100)	56 (100)
Physician preference	41 (40)	16 (29)
Patient preference	32 (31)	13 (23)
Pharmacokinetic considerations	21 (21)	7 (13)
AEs leading to first DR, n (%)		
Hypertension	26 (25)	16 (29)
Diarrhea	22 (22)	15 (27)
Rash	14 (14)	5 (9)
Anemia	13 (13)	12 (21)
Musculoskeletal pain	12 (12)	5 (9)
Neutropenia	10 (10)	7 (13)
Febrile neutropenia	10 (10)	5 (9)
Abdominal pain	8 (8)	3 (5)
Pneumonia	6 (6)	1 (2)
Atrial fibrillation	5 (5)	9 (16)
Thrombocytopenia	5 (5)	4 (7)
Cardiac failure	5 (5)	3 (5)
Leukopenia	3 (3)	4 (7)
Ischemic heart disease	2 (2)	0 (0)
Pancytopenia	1 (1)	2 (4)
Ventricular tachycardia	1 (1)	2 (4)
Cardiomyopathy	1 (1)	1 (2)
Lymphopenia	1 (1)	1 (2)

1L, first-line; CLL, chronic lymphocytic leukemia; DR, dose reduction.
[a]Patients could have >1 reason for DR reported.

Supplemental Table 2. Treatment Characteristics of 1L Therapy in Subgroup of Patients Receiving Common Treatment Regimens Who Experienced a Post-AE DR

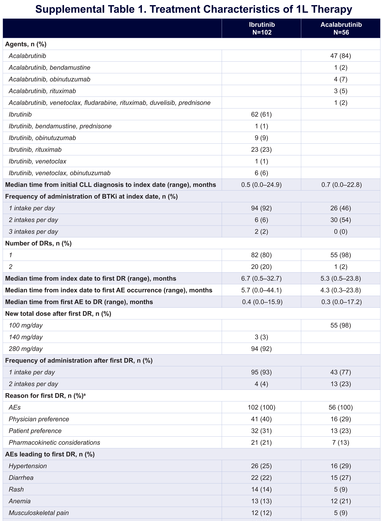
	Single-Agent Ibrutinib and Ibrutinib + Rituximab n=85	Single-Agent Acalabrutinib and Acalabrutinib + Obinutuzumab n=51
Agents, n (%)		
Acalabrutinib	0 (0)	47 (92)
Acalabrutinib, obinutuzumab	0 (0)	4 (8)
Ibrutinib	62 (73)	0 (0)
Ibrutinib, rituximab	23 (27)	0 (0)
Time from initial CLL diagnosis to index date, months		
Median (range)	0.5 (0.0–24.9)	0.8 (0.0–22.8)
Frequency of administration of BTKi at index date, n (%)		
1 intake per day	77 (91)	25 (49)
2 intakes per day	6 (7)	26 (51)
3 intakes per day	2 (2)	0 (0)
Number of DRs, n (%)		
1	70 (82)	50 (98)
2	15 (18)	1 (2)
DR 1		
Time from index date to DR, months		
Median (range)	6.6 (0.5–31.7)	4.8 (0.5–18.9)
Unknown, n (%)	20 (24)	6 (12)
Time from index date to occurrence of first AE, months		
Median (range)	6.0 (0–44)	3.8 (0.3–21.2)
Time from first AE to DR, months		
Median (range)	0.4 (0.0–15.9)	0.5 (0.0–17.2)
Unknown, n (%)	30 (35)	16 (31)
New total daily dose after DR, n (%)		
100 mg/day	0 (0)	50 (98)
140 mg/day	2 (2)	0 (0)
280 mg/day	78 (92)	0 (0)
Frequency of administration after DR, n (%)		
1 intake per day	78 (92)	40 (78)
2 intakes per day	4 (5)	11 (22)
Reason for DR, n (%)		
AEs	85 (100)	51 (100)
Patient preference	30 (35)	12 (24)
Physician preference	34 (40)	12 (24)
Pharmacokinetic considerations	18 (21)	4 (8)
AEs leading to DR, n (%)		
Hypertension	23 (27)	13 (25)
Diarrhea	16 (19)	14 (27)
Rash	12 (14)	5 (10)
Anemia	11 (13)	12 (24)
Febrile neutropenia	10 (12)	5 (10)
Neutropenia	7 (8)	7 (14)
Musculoskeletal pain	7 (8)	4 (8)
Abdominal pain	6 (7)	2 (4)
Pneumonia	6 (7)	1 (2)
Cardiac failure	5 (6)	3 (6)
Atrial fibrillation	4 (5)	9 (18)
Thrombocytopenia	4 (5)	3 (6)
Leukopenia	3 (4)	4 (8)
Ischemic heart disease	2 (2)	0 (0)
Ventricular tachycardia	1 (1)	2 (4)
Pancytopenia	1 (1)	2 (4)
Lymphopenia	1 (1)	1 (2)
Cardiomyopathy	0 (0)	1 (2)

Supplemental Table 3. DOT With 1L Therapy in Subgroup of Patients Limited to Common Treatment Regimens Who Experienced a Post-AE DR

	DOT Post–Therapy Initiation[a]		DOT Post-DR[b]	
	Single-Agent Ibrutinib and Ibrutinib + Rituximab n=85	Single-Agent Acalabrutinib and Acalabrutinib + Obinutuzumab n=51	Single-Agent Ibrutinib and Ibrutinib + Rituximab n=56	Single-Agent Acalabrutinib and Acalabrutinib + Obinutuzumab n=35
Kaplan-Meier estimates				
Patients who discontinued or died, n (%)	56 (66)	32 (63)	34 (61)	22 (63)
Patients censored (no recorded treatment discontinuation event), n (%)	29 (34)	19 (37)	22 (39)	13 (37)
Median (95% CI), months	34.4 (25.3–38.4)	16.6 (13.3–32.4)	29.2 (19.8–46.9)	11.0 (6.6–27.3)
Patients still on therapy (%)				
At 6 months, (95% CI)	95.3 (87.9–98.2)	92.2 (80.4–97.0)	85.7 (73.4–92.6)	70.4 (51.9–82.8)
At 12 months, (95% CI)	85.9 (76.5–91.7)	72.5 (58.1–82.7)	74.7 (61.1–84.2)	48.0 (30.1–63.8)
At 24 months, (95% CI)	65.0 (53.6–74.2)	39.5 (25.6–53.1)	52.0 (37.4–64.7)	34.5 (18.7–51.0)
At 36 months, (95% CI)	47.8 (36.1–58.5)	32.3 (18.5–46.9)	39.1 (25.0–52.9)	29.6 (14.3–46.8)
	P=0.179		*P*=0.135	
Restricted mean survival time				
Mean (SE), months	25.2 (1.0)	20.4 (1.5)	20.0 (1.3)	14.2 (1.8)
	P=0.006		*P*=0.008	
Multivariable Cox PH regression analysis[c]	0.725 (0.37–1.42)	(reference)	0.919 (0.36–2.32)	(reference)
	P=0.347		*P*=0.859	

DOT, duration of therapy; PH, proportional hazards; SE, standard error.
[a]DOT estimated from date of treatment initiation to earliest of discontinuation or death. [b]DOT estimated from first DR to earliest of discontinuation or death. [c]Adjusted for age, sex, race/ethnicity, index year, insurance status, healthcare setting, geographic region, disease stage, high-risk prognostic factors, Charlson comorbidity index score, smoking status, Eastern Cooperative Oncology Group performance status, number of AEs, cardiac AE, months from diagnosis to treatment initiation, and BTKi monotherapy.

Supplemental Figure 1. DOT Post-Therapy Initiation in a Subgroup of Patients Receiving Common Treatment Regimens Who Experienced a Post-AE DR



Supplemental Figure 2. DOT Post DR in a Subgroup of Patients Receiving Common Treatment Regimens Who Experienced a Post-AE DR