3728

Duration of Therapy in Patients With Waldenström Macroglobulinemia Undergoing Dose Reductions of First-Line Ibrutinib: A Real-World Analysis

Shayna Sarosiek, MD,[1] Monika Salkar, PhD,[2] Barnabie Agatep, MPH,[3] Barton Jones, MS,[3] Michelle Pacia, PharmD,[2] Chadi Saifan, MD,[2] Shaffee Bacchus, PharmD,[2] Sudeep Karve, PhD,[2] Jonas Paludo, MD[4]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]AbbVie, Inc., North Chicago, IL, USA; [3]Inovalon, Bowie, MD, USA; [4]Mayo Clinic, Rochester, MN, USA

OBJECTIVE

To characterize real-world long-term clinical and economic outcomes for patients with Waldenström macroglobulinemia (WM) with and without ibrutinib dose reduction (DR) following an adverse event (AE) in the first-line (1L) setting

CONCLUSIONS

This real-world evidence study suggests that implementing DRs to manage AEs can be a valuable strategy in supporting patients with WM to remain on 1L ibrutinib longer

These findings are consistent with previous studies, demonstrating that ibrutinib DRs help to improve tolerability while maintaining treatment efficacy

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. Editorial support was provided by Agnieszka Looney, PhD, and Anthony Yu, PharmD, MS, and was funded by AbbVie.

SS: consulting with BieGene and Cellectar; research funding from ADC Therapeutics. MS, MP, CS, SB, and SK: employment and stock or other ownership with AbbVie. BA and BJ: employment with Inovalon, which received consulting fees from AbbVie. JP: research funding from Biofourmis and Karyopharm, and advisory role at AbbVie.

References

1. Castillo JJ et al. *Leukaemia*. 2022;36:532–539.
2. Treon SP et al. *J Clin Oncol*. 2021;39:565–575.
3. Buske C et al. *J Clin Oncol*. 2022;40:52–62.
4. Sarosiek S et al. *Br J Haematol*. 2023;201:897–904.
5. Ogunbiyi O et al. *Blood*. 2021;138:4507.
6. Shadman M et al. *Hemasphere*. 2023;7:e24922b0.

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

Presented at the 66th ASH Annual Meeting and Exposition; December 7–10, 2024; San Diego, California [Ref DV# 013148]

INTRODUCTION

- Continuous single-agent ibrutinib treatment has been associated with extended progression-free survival in patients with Waldenström macroglobulinemia (WM)[1-3]
- Previous clinical studies have shown that ibrutinib dose reduction (DR) improved or resolved adverse events (AEs) in most patients, while hematologic responses were sustained[3]
- Ibrutinib DRs have proven effective in improving tolerability and treatment duration in patients experiencing AEs[4-6] and may be a valuable option for managing AEs while maintaining efficacy in patients with WM

METHODS

Data Source and Patient Selection

- In this retrospective observational study, data were obtained from Centers for Medicare & Medicaid Services (CMS)–sourced Medicare Fee-for-Service files, with Part A and Part B medical encounters and Part D prescription drug events
- Closed-claim records were used to identify patients diagnosed with WM who initiated first-line (1L) single-agent ibrutinib (420 mg/day) or 1L ibrutinib + rituximab from January 1, 2015, to September 30, 2022
- The study included patients with ≥1 qualifying (grade ≥3, based on ibrutinib US Prescribing Information) post-1L initiation AE (both prevalent and incident), as identified via International Classification of Diseases, Ninth Revision (ICD-9) or Tenth Revision (ICD-10) diagnosis codes

Study Outcomes

- Demographics, clinical characteristics, time to AE, and duration of therapy (DOT) were assessed in cohorts with and without DR
  - DOT was measured at the date of ibrutinib treatment initiation through treatment discontinuation (end of 1L treatment)
  - Treatment discontinuation was defined as receiving a subsequent systemic therapy after the 1L regimen, having a gap of ≥120 days with no systemic therapy following the last administration, or death while on the 1L regimen
    - Patients who did not have their treatment discontinued were censored at the end of follow-up or disenrollment, whichever occurred first

Healthcare Utilization and Direct Costs

- All-cause and WM-related healthcare resource use and costs were reported in the baseline period and during 1L treatment in the service categories of physician office, emergency department, durable medical equipment, supportive care, inpatient hospital, and pharmacy
  - WM-related costs were defined as those associated with a medical encounter in any setting of care with a qualifying diagnosis code of WM in any position of the claim processing
- Utilization and costs were reported as per-patient-per-month (PPPM) and summarized by total medical (inpatient and outpatient) and total healthcare costs (medical and pharmacy)
- All costs were adjusted to 2023 US dollars using the medical care component of the Consumer Price Index obtained from the US Bureau of Labor Statistics

Statistical Analyses

- Baseline characteristics were reported using descriptive statistics
- DOT was analyzed using Kaplan-Meier methodology
- A Cox proportional hazards model adjusted for patient demographics and clinical characteristics was used to identify factors associated with treatment discontinuation

RESULTS

Patient Demographics and Clinical Characteristics Were Similar Between Patients With and Without DR

	DR Cohort n=55	No DR Cohort n=352
Age, mean ± SD [median], years	77.6 ± 7.3 [78.0]	77.5 ± 7.6 [77.0]
Sex, n (%)		
Women	27 (49)	130 (37)
Race/ethnicity, n (%)		
White	52 (95)	322 (91)
Black or African American	<11 (NA)	<11 (NA)
Asian	0 (0)	<11 (NA)
Hispanic or Latino	0 (0)	<11 (NA)
Unknown/other	<11 (NA)	16 (5)
Census region, n (%)		
Midwest	12 (22)	69 (20)
Northeast	16 (29)	101 (29)
South	13 (24)	93 (26)
West	14 (25)	88 (25)
Index year, n (%)		
2015–2019	40 (73)	216 (61)
2020	<11 (NA)	67 (19)
2021	<11 (NA)	<70 (<20)
2022	<11 (NA)	<11 (NA)
Original reason for Medicare entitlement code, n (%)		
Age	<50 (<90)	321 (90)
Disability	<11 (NA)	<35 (<10)
ESRD	0 (0)	<11 (NA)
Dual-eligibility status, n (%)		
Non-dual	50 (86)	313 (89)
Dual	<11 (NA)	38 (11)
Low income subsidy status for Medicare prescription drug coverage, n (%)		
Yes	<11 (NA)	41 (12)
No	<60 (<87)	311 (88)
CCI score, mean ± SD [median]	4. 1 ± 2.4 [3.0]	4.4 ± 2.8 [4.0]
Baseline comorbidities, n (%)		
Stroke	<11 (NA)	17 (5)
Myocardial infarction	0 (0)	<11 (NA)
Hypertension	37 (67)	238 (68)
Atrial fibrillation	<11 (NA)	46 (13)
Other cardiovascular conditions[a]	17 (31)	97 (28)
Renal dysfunction	<11 (NA)	45 (13)
Major bleeding events requiring hospitalization[b]	<11 (NA)	57 (17)
Infection requiring hospitalization[c]	<11 (NA)	51 (15)
Time between index treatment and AE, mean ± SD [median], months	5.8 ± 7.3 [3.0]	5.7 ± 8.1 [2.5]
Time between AE and DR, mean ± SD [median], months	9.3 ± 15.8 [3.5]	-

CCI, Charlson comorbidity index; ESRD, end-stage renal disease; NA, not applicable.
Cases occurring in <11 patients were masked per CMS data suppression policies.
[a]Other cardiovascular conditions included atrial flutter, cardiovascular event (transient ischemic attack, ischemic stroke including cerebrovascular accidents and cerebral ischemia, cardiac arrhythmias including atrial fibrillation and atrial flutter, and cardiac failure), congestive heart failure, peripheral vascular disease, pulmonary circulation disorders, stroke, valvular disease, and ventricular arrhythmias.
[b]Major bleeding events included gastrointestinal bleeding, intracranial bleeding, bleeding complication of a procedure, other bleeding, hematuria, and hemoptysis.
[c]Infections included pneumonia, meningitis/encephalitis, bacteremia/sepsis, cellulitis/soft tissue infections, endocarditis, pyelonephritis, and septic arthritis/osteomyelitis.

Patient Selection and Attrition

Diagnosis criteria:
Patients aged ≥18 years with ≥2 medical claims of WM and ≥1 medical or pharmacy claim of treatment for WM between January 1, 2015, to September 30, 2022. Start of treatment is index date
N=14,737

↓

Enrollment criterion:
≥12 months of continuous enrollment in Medicare Parts A, B, and D both before (baseline period) and after the index date (follow-up period)
N=1404

↓

Exclusion criteria:
Any claims indicating other types of cancer (ie, breast, prostate, kidney) or bleeding disorders, history of FL or MZL, receipt of treatment for FL and MZL, prior evidence of treatment with CYP3A4 inhibitors during the follow-up period, or enrollment in a clinical trial during the study duration
N=455

↓

Patients who received single-agent ibrutinib (420 mg/day) or ibrutinib + rituximab as 1L therapy after 2015 and experienced an AE[a]
N=407

↓

DR[b] cohort
Patients who had DR following AE
N=55

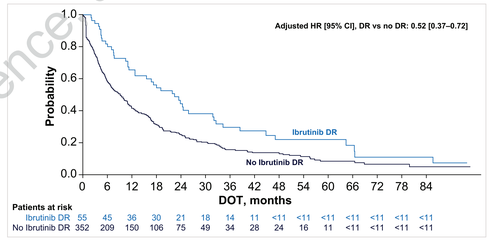
No DR cohort
Patients who did not have DR following AE
N=352

CYP3A4, cytochrome P450 3A4; FL, follicular lymphoma; MZL, marginal zone lymphoma.
[a]Post-initiation AEs identified through ICD-9 or ICD-10 codes, including both prevalent and incident AEs (qualifying AEs were grade ≥3 and based on ibrutinib US Prescribing Information).
[b]Ibrutinib DR was defined as reducing the starting dose after the first AE within 1-year of follow-up; patients without DR maintained ibrutinib at 420 mg/day for the 1-year period. Patients with DR in the absence of AEs or before any AE were excluded.

DOT

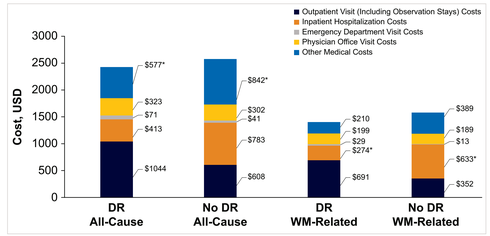
- In the DR cohort, DOT mean ± SD [median] was 26.2 months ± 23.1 [22] and was longer than in the no DR cohort (15.2 months ± 17.0 [9.3]; *P*=0.001)
- In the DR cohort, patients remained on ibrutinib for mean ± SD [median] 11.2 months ± 14.1 [6.0] from DR date until the end of 1L therapy
- In the adjusted analysis, patients with a DR had a 48% reduction in the risk of treatment discontinuation compared with those without a DR (adjusted HR [95% CI], 0.52 [0.37–0.72])

Median DOT Was Longer for Patients With DR Than for Those Without DR Following Treatment Initiation



HR, hazard ratio.

PPPM Healthcare Costs by Care Setting Differed Between Patients With and Without DR



*P<0.05.

Healthcare Utilization and Direct Costs

- During the 1L follow-up period, total direct healthcare costs were higher for patients without DR ($16,707) compared with those with a DR ($14,608; *P*<0.01)
- In both groups, WM-related costs constituted a similar proportion of the total cost
  - Specifically, total WM-related costs for patients without DR ($15,400) were higher than WM-related costs for patients with DR ($13,054; *P*<0.01)

Limitations

- Determination of an AE was based on the presence of a medical record with relevant ICD-9 or ICD-10 codes; thus, causal association between an AE and subsequent DR cannot be inferred from the claims databases
- AEs were identified following treatment initiation and may not be related to treatment use
- Reasons for DR and the grading of AEs were not documented in claims databases
- Omissions and inaccuracies are inherent in claims/electronic medical record data; administrative closed claims databases are designed for provider billing and reimbursement and do not capture complete medical history or physician notes. This may contribute to a potential misclassification of AEs, baseline comorbidities, and outcomes. However, any inaccuracies would likely affect all cohorts equally and, thus, should have had no impact on conclusions
- A claim or prescription for a medication does not necessarily indicate its use
- As DRs occurred post-index date, patients with a DR may have been subject to immortal time bias. Time-varying Cox proportional hazard models were used to mitigate potential bias introduced by this method
  - Multivariable model adjustment may have been subject to residual confounding due to unmeasured confounders

All-Cause Inpatient Hospitalization Rates Were Similar Among Patients With and Without DR

	DR Cohort n=55		No DR Cohort n=352	
	12-Month Baseline Period	Follow-Up (during 1L)	12-Month Baseline Period	Follow-Up (during 1L)
Healthcare resource utilization, PPPM				
All-cause inpatient hospitalizations, %	25	36	23	35
Hospital length of stay, mean ± SD, days	0.8 ± 0.8	0.4 ± 0.5	0.9 ± 1.0	0.8 ± 1.6
WM-related inpatient hospitalization, %	<11	29	4	28
All-cause 30-day readmission rates, %	NA	NA	17	7
WM-related 30-day readmission rates, %	NA	NA	NA	6
Emergency department visits, %	27	56	31	36
Outpatient visits, %	80	89	86	83
Other visits, %	63	67	53	60
Physician office visits, %	100	98	99	96
Number of unique medications, mean ± SD	0.08 ± 0.00	0.09 ± 0.11	0.08 ± 0.00	0.14 ± 0.27
Total healthcare costs, PPPM, mean ± SD [median]				
All cause total costs	$2641 ± $4964 [$1219]	$14,608 ± $5639 [$14,494]	$2231 ± $2828 [$1162]	$16,707 ± $5099 [$15,890]
All cause medical costs	$1835 ± $1864 [$1069]	$2427 ± $2486 [$1632]	$1929 ± $2590 [$980]	$2577 ± $4321 [$1347]
All cause pharmacy costs	$806 ± $4112 [$96]	$12,180 ± $4679 [$12,690]	$301 ± $1095 [$67]	$14,130 ± $2610 [$14,245]
WM-related total costs	$396 ± $872 [$61]	$13,054 ± $5076 [$13,256]	$446 ± $1193 [$77]	$15,400 ± $3948 [$14,925]
WM-related medical costs	$396 ± $872 [$61]	$1404 ± $2092 [$597]	$446 ± $1193 [$77]	$1576 ± $3369 [$414]
WM-related pharmacy costs	-	$11,651 ± $4341 [$12,663]	-	$13,824 ± $2283 [$13,958]

30-day readmission rates among those with an inpatient hospitalization during the period of 1L treatment. Sample sizes based on <11 patients were masked per CMS data suppression policies.