P2070

Dose Adjustment Outcomes in Patients With Waldenström Macroglobulinemia Treated With Ibrutinib

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OBJECTIVE

To describe characteristics and outcomes of patients with Waldenström macroglobulinemia (WM) treated with ibrutinib with and without dose modifications due to an adverse event (AE)

CONCLUSIONS

Most AEs resolved following dose reductions without negatively affecting efficacy outcomes in patients with WM treated with ibrutinib-based therapy with or without rituximab

Ibrutinib dose reduction can be an effective strategy to manage AEs while maintaining clinical efficacy for patients with WM

https://www.congresshub.com/Oncology/EHA2024/Ibrutinib/Sarosiek

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 funded by AbbVie.

SS: research funding and honoraria from ADC Therapeutics, BeiGene, and Cellectar Biosciences. SPT: research funding from AbbVie/Pharmacyclics LLC, an AbbVie Company, BeiGene, Bristol Myers Squibb, Eli Lilly Pharmaceuticals, Janssen Oncology, and Ono Pharmaceuticals. MLP: research funding from Seres Therapeutics; consulting/advisory role with BeiGene, MustangBio, Novartis, Seres Therapeutics, and Symbiotix; stock in Notch Therapeutics, Pluto Immunotherapeutics, and Seres Therapeutics; honoraria from Frazier Healthcare Partners, Lygenesis, Nektar, Notch Therapeutics, Rheos Medicines, Seres Therapeutics, and Vor Biopharma; and intellectual property rights with Juno. M-AD: honoraria from Amgen, BeiGene, Bristol Myers Squibb, Janssen, and Takeda UK; research funding from AbbVie, AstraZeneca, BeiGene, Cellectar, Loxo, and Pharmacyclics LLC, an AbbVie Company; consulting fees from AbbVie, AstraZeneca, BeiGene, Cellectar, Janssen, Kite, Loxo, Mustang Bio, and Pharmacyclics LLC, an AbbVie Company. HMP: employment with and stock in AbbVie, Merck, and Seagen; patents with AbbVie and UC Berkeley. VG: employment with Everest Clinical Research; and other relationship with AbbVie. AB: employment with and stock in Janssen. AR and MP: employment with and stock in AbbVie. CB: research funding, honoraria, consulting/advisory role, and speakers bureau with AbbVie, Bayer, BeiGene, Celltrion, Incyte, Janssen, Morphosys, Novartis, Pfizer, Regeneron, and Roche.

Presented at the European Hematology Association (EHA) Hybrid Congress; June 13–16, 2024; Madrid, Spain

INTRODUCTION

- Ibrutinib has dramatically changed the treatment landscape for patients with Waldenström macroglobulinemia (WM) since its approval as single-agent or combination therapy with rituximab[1]
  - With up to 63 months follow-up (median 50 months), median progression-free survival (PFS) was not reached with ibrutinib + rituximab and was 20.3 months with placebo + rituximab[2,3]
  - With a median follow-up of 59 months, 79.4% of patients treated with single-agent ibrutinib achieved major response (defined as ≥50% reduction in serum immunoglobulin M [IgM])[4]
- Patients who continue ibrutinib-based treatment have better survival outcomes than those who discontinue within the first few years[5-8]
- Real-world evidence suggests that ibrutinib dose adjustments do not negatively affect hematologic response or time to discontinuation after adverse events (AEs)[9]
- In this post hoc analysis, we examine ibrutinib dosing patterns and outcomes in patients with WM with and without dose reductions (DRs) after AEs

METHODS

- This analysis used data from 2 ibrutinib registrational trials where patients received ibrutinib 420 mg/day
  - PCYC-1118 (NCT01614821) was an open-label, single-arm, phase 2 trial of patients with relapsed/refractory (R/R) WM who received single-agent ibrutinib[4]
  - iNNOVATE (NCT02165397) was a randomized, double-blind, placebo-controlled, phase 3 trial of patients with previously treated and untreated WM who received ibrutinib + rituximab (Arm A) versus placebo + rituximab (Arm B) and patients who received single-agent ibrutinib after failure of prior rituximab-containing therapy (Arm C)[2,3]
    - This post hoc analysis included patients from 2 arms of the iNNOVATE study: ibrutinib + rituximab (Arm A) and single-agent ibrutinib (Arm C), and PCYC-1118
    - The median follow-up for data used in this analysis was 14.8 months for PCYC-1118 (primary analysis) and 49.7 months for iNNOVATE (final analysis)
- Outcomes included baseline demographics and clinical characteristics for each arm separately and pooled for patients with and without DR

RESULTS

- The analysis included 169 patients: 29 with DR and 140 without DR
- For the entire cohort, median follow-up was 45 months

Baseline Demographics

Characteristic	With DR n=29	Without DR n=140	Total N=169
Sex, n (%)			
Male	19 (66)	94 (67)	113 (67)
Female	10 (34)	46 (33)	56 (33)
Median age (range), years	68 (49–90)	67 (36–89)	67 (36–90)
Age ≥65 years, n (%)	18 (62)	77 (55)	95 (56)
Median time since diagnosis (range), months	94 (1–217)	58 (0.7–334)	61 (0.7–334)
Study treatment, n (%)			
Ibrutinib combination	17 (59)	58 (41)	75 (44)
Single-agent ibrutinib	12 (41)	82 (59)	94 (56)
Treatment history, n (%)			
Previously untreated	6 (21)	28 (20)	34 (20)
R/R	23 (79)	112 (80)	135 (80)
Median baseline IgM (range), g/L	43 (10–77)	35 (6–107)	35 (6–107)
Median baseline hemoglobin (range), g/L	102 (73–146)	105 (64–155)	105 (64–155)
Median bone marrow cellularity (range), %	65 (9–100)	70 (9–100)	70 (9–100)
MYD88^{L265P} mutation, n/N (%)[a]			
Yes	16/22 (73)	66/84 (79)	82/106 (77)
No	2/22 (9)	10/84 (12)	12/106 (11)
Missing	4/22 (18)	8/84 (10)	12/106 (44)
CXCR4^{WHIM} mutation, n/N (%)[a]			
Yes	7/22 (32)	26/84 (31)	33/106 (31)
No	11/22 (50)	50/84 (60)	61/106 (58)
Missing	4/22 (18)	8/84 (10)	12/106 (11)

[a]Mutation data collected in iNNOVATE only.

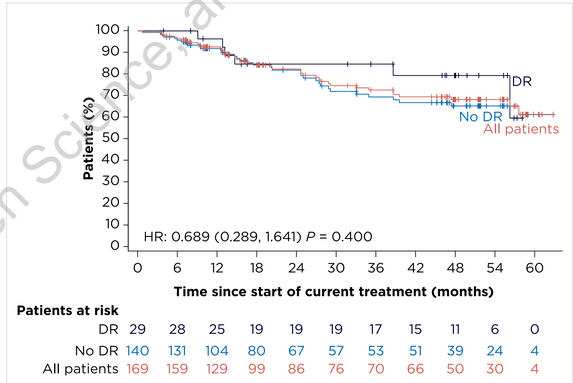
Study Treatment Exposure

Treatment Exposure	PCYC-1118	iNNOVATE
Median treatment duration (95% CI), months	11.7 (10.4–14.9)	47.7 (42.4–49.7)
Overall median follow-up (95% CI), months	14.8 (10.8–15.4)	49.7 (48.7–51.6)

Treatment Disposition

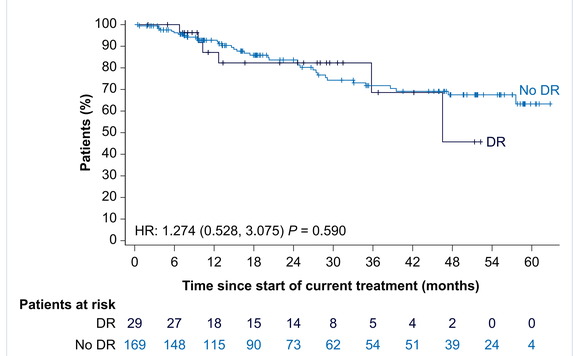
	With DR n=29	Without DR n=140
Patient discontinued treatment, n (%)	25 (86)	93 (66)
Reason for treatment discontinuation, n (%)		
Study conclusion	12 (41)	49 (35)
Progressive disease	4 (14)	19 (14)
Withdrawal by patient	2 (7)	11 (8)
AE	4 (14)	6 (4)
Unacceptable toxicity	2 (7)	2 (1)
Investigator and physician decision	1 (3)	2 (1)
Other	0	2 (1)
Death	0	1 (1)
Nonresponder	0	1 (1)

Estimated 48-Month PFS Rates Were Similar Among Patients With and Without DR in the Pooled Analysis



- Estimated 48-month PFS was 68% (95% CI, 59–76) for all patients in this analysis and 79% (95% CI, 57–91) and 65% (95% CI, 54–74) for patients with and without DR, respectively
- Among patients in the iNNOVATE trial receiving ibrutinib + rituximab, 48-month PFS was 94% (95% CI, 65–99) and 71% (95% CI, 57–81) in patients with DR versus without DR, respectively (**Supplementary Figure 1**)

No Significant Differences in PFS Were Observed Between DR and No DR Based on Time-Varying Covariate PFS in the Pooled Analysis



- When evaluating ibrutinib DR as a time-varying covariate from the pooled patient population, no significant differences in PFS were observed between DR and no DR (hazard ratio [HR]: 1.3; 95% CI: 0.53–3.08; $P = 0.59$). However, interpretation is limited due to the small sample size of the single-agent ibrutinib cohort
  - Similar results were observed in the ibrutinib + rituximab cohort (HR: 0.89; 95% CI: 0.19–4.05; $P = 0.88$) and in the single-agent ibrutinib cohort (HR: 2.14; 95% CI: 0.72–6.38; $P = 0.17$)

AEs Leading to Dose Modification in Pooled Ibrutinib-Treated Patients

AEs Leading to Dose Modification[a]	Pooled Ibrutinib-Treated Patients[b] N=169
Any AE leading to dose modification, n (%)	29 (17)
Initial DR, n (%)	
420 mg to 280 mg	27 (93)
420 mg to 140 mg	2 (7)
AEs leading to dose modification, n (%)[c]	
Hematologic	8 (5)
Gastrointestinal	6 (4)
Musculoskeletal	6 (4)
Dermatologic	5 (3)
Other	5 (3)
Cardiac	2 (1)
Infection	2 (1)
Grade of AE leading to dose modification, n (%)[c]	
Grades 1 and 2	15 (9)
Grades 3 and 4	18 (11)
Outcome of first AE leading to dose modification, n/N (%)[d]	
Initial AE resolved	27/29 (93)
No recurrence or recurred at lower grade	22/29 (76)
Recurred at same or higher grade	7/29 (24)

[a]Dose modification inclusive of dose hold and DR.
[b]Pool includes patients from long-term analysis of iNNOVATE and preliminary analysis of PCYC-1118.
[c]The same patient may be counted in more than 1 category due to multiple events.
[d]Denominator is patients with any AEs leading to dose modifications.

AEs With Recommended Dose Modifications in Pooled Ibrutinib-Treated Patients per Ibrutinib USPI[a]

AEs With Recommended Dose Modifications per USPI[a]	Pooled Ibrutinib-Treated Patients[b] N=169
Any AE leading to dose modification, n (%)	14 (8)
Initial DR, n (%)	
420 mg to 280 mg	11 (7)
420 mg to 140 mg	2 (1)
Outcome of first AE leading to dose modification, n/N (%)[c]	
Initial AE resolved	14/14 (100)
No recurrence or recurred at lower grade	12/14 (86)
Recurred at same or higher grade	2/14 (14)
Median time on study after DR per USPI (range), months	28 (1–51)

USPI, United States prescribing information.
[a]AEs for which DRs are recommended in the ibrutinib USPI (grade 2 cardiac failure, grade 3 cardiac arrythmia, grade 3–4 nonhematologic AEs [excluding cardiac failure and cardiac arrythmia], grade 3–4 neutropenia with infection or fever, and grade 4 hematologic AEs).[1]
[b]Pool includes patients from long-term analysis of iNNOVATE and preliminary analysis of PCYC-1118.
[c]Denominator is patients with any AE with recommended DR per USPI.

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