DOSE ADJUSTMENT OUTCOMES IN PATIENTS WITH WALDENSTRÖM MACROGLOBULINEMIA TREATED WITH IBRUTINIB

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Introduction: Ibrutinib has dramatically changed the Waldenström macroglobulinemia (WM) treatment landscape since its approval as single-agent or combination therapy with rituximab. In relapsed/refractory (R/R) WM, single-agent ibrutinib demonstrated sustained efficacy and safety with long-term follow-up of >5 years and superior progression-free survival (PFS) and longer time to next treatment in combination with rituximab versus rituximab alone. Evidence suggests that ibrutinib dose adjustments do not negatively affect hematologic response or time to discontinuation after adverse events (AEs). We examine ibrutinib dosing patterns and describe characteristics and outcomes in patients treated with ibrutinib for WM with/without dose reductions (DRs) after AEs.

Methods: This post hoc analysis used data from ibrutinib registrational trials where patients received ibrutinib 420 mg daily: (1) an open-label, single-arm, phase 2 trial (PCYC-1118; NCT01614821) of patients with R/R WM who received single-agent ibrutinib; and (2) 2 arms of a randomized, double-blind, placebo-controlled, phase 3 trial (iNNOVATE; NCT02165397) including patients with R/R and previously untreated WM who received ibrutinib plus rituximab (I+R) and patients who received single-agent ibrutinib after failure of prior rituximab-containing therapy. Median follow-up for PCYC-1118 and I+R and ibrutinib arms of iNNOVATE was 15, 50, and 58 months, respectively. Patients were categorized as with or without a DR due to an AE. Key outcomes included baseline demographics and clinical characteristics, PFS, and resolution and recurrence in the DR cohort.

Results: The analysis included 169 patients (113 [67%] male; median age 67 years [range, 36–90]), 29 (17%) with a DR and 140 (83%) without a DR. For the entire cohort (n=169), median follow-up was 45 months. Estimated 48-month PFS (95% CI) was 68% (59–76) for all patients in this analysis and 79% (57–91) and 65% (54–74) for patients with and without DR, respectively (Figure). Most DRs occurred within 12 months (62%; median time to first DR: 9 months [range, 1–41]). Causes of AEs leading to DR included hematologic (n=8), gastrointestinal and musculoskeletal (n=6 each), dermatologic and other (n=5 each), and cardiac and infection (n=2 each). Initial AEs resolved in 27/29 patients (93%) in the DR cohort. For patients with a DR, median time on study treatment from first DR until ibrutinib discontinuation was 25 months (range, 1–52). Fourteen patients (8%) had recommended DR per United States Prescribing Information (AE of special interest [AESI]; Gr 2 cardiac failure, Gr 3 cardiac arrhythmia, Gr 3–4 nonhematologic AEs, Gr 3–4 neutropenia with infection or fever, Gr 4 hematologic AEs). These AESIs resolved after first ibrutinib DR in 100% of patients; 12 patients (86%) had no recurrence/recurrence of initial AE at lower grade; 2 patients (14%) experienced recurrence at the

same/higher grade. Median time on study treatment after first DR due to an AESI was 28 months (range, 1–51).

Conclusions: In this analysis, most AEs resolved following DRs without negatively affecting efficacy outcomes in patients with WM treated with ibrutinib-based treatment with/without rituximab. Thus, ibrutinib DR can be an effective strategy to manage AEs while maintaining clinical efficacy for patients with WM.

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