Long-term Outcomes With Ibrutinib Treatment for Patients With Relapsed/Refractory Mantle Cell Lymphoma: A Pooled Analysis of 3 Clinical Trials With Nearly 10 Years of Follow-up

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The long-term outcome for patients with mantle cell lymphoma (MCL) has been improving; however, historical evidence indicates that progression-free survival (PFS) declines and high-risk factors accumulate with each successive line of chemoimmunotherapy (CIT).¹,² Median PFS with CIT declined by 70% from first-line (1L) (47.4 mo) to second-line (14.0 mo) and by 86% after third-line therapy (6.5 mo), emphasizing a need for therapies that will reverse or mitigate these trends.

Ibrutinib is a once-daily, oral inhibitor of Bruton’s tyrosine kinase, established as a standard-of-care for patients with relapsed/refractory (R/R) MCL.³⁻⁴ A previously published pooled analysis of 370 ibrutinib-treated patients with R/R MCL from 3 studies with up to 6.5 years’ follow-up (phase 2 PCYC-1104 [NCT01236391] and SPARK [NCT01599949], phase 3 RAY [NCT01646021]) showed that outcomes improved with earlier use of ibrutinib, with rapid and durable responses and median PFS >2 years when used at second line.³ Here, we present updated efficacy and safety outcomes of these patients with up to 9.7 years of follow-up, and explore whether ibrutinib treatment changes the trend of declining PFS reported with CIT retreatment.

Among the 370 enrolled patients, 87 patients who were benefiting from ibrutinib treatment at the end of the 3 studies were rolled-over to the open-label long-term extension study CAN3001 (NCT01804686). As previously described, disease evaluations were conducted per routine clinical practice and patients could continue treatment if they derived benefit, as assessed by the attending physicians. Positron emission tomography scans were not routine but were required to confirm complete response (CR). Only grade ≥3 adverse events (AEs) of special interest (major hemorrhage), and serious AEs (SAEs) were collected in CAN3001. PFS, duration of response (DOR), and overall survival (OS) were analyzed by number of prior lines of therapy (LOT; 1 and >1) and best overall response rate (ORR, CR, and partial response). The PFS for the regimen used before ibrutinib (denoted throughout as “estimated prior-line PFS”) was calculated as time from the first dose of the prior regimen to the first dose of ibrutinib, which was likely to overestimate rather than underestimate the true PFS. Progression of disease (POD) on frontline treatment was categorized as occurring within 24 months (POD24) or later (POD ≥24).

Baseline characteristics for the pooled dataset (N = 370) were reported previously.⁵ Briefly, patients had a median of 2 (range, 1–9) prior LOT, 99 (26.8%) received 1 prior LOT, 271 (73.2%) >1 prior LOT, and 162 (43.8%) ≥3 prior LOT. Among the 99 patients with 1 prior LOT (Suppl. Table S1), 44.4% were aged ≥70 years, 26.3% had high-risk simplified MCL international prognostic index (MIPI) score, 6.1% had blastoid MCL, and 43.4% had POD24. Of the 99 patients, 92 were treated with 1L CIT with or without bortezomib, and 7 patients received 1L autologous stem-cell transplantation. The following...
characteristics were more common in patients with POD24 versus POD ≥24: aged ≥70 years, high-risk MIPI, blastoid histology, bulky disease ≥5 cm, refractory disease, and mutated TP53 (Suppl. Table S1).

At data cutoff (March 2021), 24 (6.5%) patients were still receiving ibrutinib in the CAN3001 study; median ibrutinib exposure for these patients was 7.8 (range, 7.1–9.7) years. Of the total 370 patients, 115 (31.1%) were treated with ibrutinib for ≥2 years and 45 (12.2%) were treated for ≥5 years (Suppl. Figure S1). Overall, the most common reasons for discontinuation of ibrutinib were progressive disease (61.9%) and AEs (12.2%; Suppl. Figure S2).

Best outcomes with ibrutinib were noted in patients with 1 prior LOT and those achieving a CR (Table 1; Figure 1A). In ibrutinib-treated patients with 1 prior LOT (N = 99), median PFS was 25.4 months and median OS was 61.6 months (Figure 1B,C); ORR was 77.8%, with a CR rate of 37.4% and a median DOR of 35.6 months. Median PFS with 2L ibrutinib was even longer (57.5 mo) in patients who experienced extended response to frontline CIT (POD ≥24, Figure 1D); median DOR was not reached (NR). In patients who achieved a CR (N = 102), median PFS and DOR were 68.5 and 66.4 months, respectively, and median OS was NR with a 5-year OS rate of 83%. The durability of response in patients who achieved a CR was similar regardless of number of prior LOT.

Among the 370 ibrutinib-treated patients, when comparing PFS achieved with ibrutinib to estimated prior-line PFS, half of all patients experienced longer PFS with ibrutinib versus prior LOT (Figure 1E); median PFS was 12.5 months for ibrutinib versus 10.9 months for prior LOT. Patients achieving longer PFS with ibrutinib than with the prior regimen were more likely to have low-risk simplified MIPI (29.1% versus 18.4%), nonbulky disease (<5 cm; 56.3% versus 45.7%), nonblastoïd histology (91.3% versus 85.4%), and wildtype TP53 (93.7% versus 80.2%; Suppl. Table S1). Overall, PFS with ibrutinib was ≥1 year longer than estimated prior-line PFS for 27.6% (n = 102) of patients; among these patients, the CR rate with ibrutinib was 66.7%. Among the subgroup of 99 patients with 1 prior LOT, median PFS with 2L ibrutinib was comparable to the estimated frontline PFS (25.4 versus 27.2 mo), regardless of age (Suppl. Figure S3A).

In patients with late relapses following frontline therapy (ie, POD ≥24; n = 56), median PFS with ibrutinib (57.5 mo) was approximately 15 months longer than estimated median frontline PFS (42.2 mo). In patients with early relapse following frontline therapy (ie, POD24; n = 43), median PFS on 2L ibrutinib was comparable to estimated median frontline PFS (13.8 versus 14.0 mo; Suppl. Figure S3B). Median DOR with 2L ibrutinib was 22.1 (95% CI, 10.6–35.6) months in patients with POD24, and NR (95% CI, 33.1–NR) in patients with POD ≥24.

There was no late unexpected toxicity with ibrutinib during extended follow-up. The incidence of grade ≥3 treatment-emergent AEs (TEAEs) and SAEs was highest during the first year of treatment and generally decreased over time (Suppl. Table S2). With up to 9.7 years of follow-up, the most frequent grade ≥3 TEAEs (in ≥5% of patients) included neutropenia (17.0%), pneumonia (13.5%), thrombocytopenia (12.4%), anemia (10.5%), atrial fibrillation (6.8%), and hypertension (5.1%). During the 2 additional years of follow-up since the last reported 2019 data cut, the overall AE profile remained largely unchanged, indicating that long-term use of ibrutinib may not lead to cumulative toxicities. Among hematologic TEAEs, there were no new onsets of grade ≥3 or serious neutropenia, anemia, or thrombocytopenia. No new grade ≥3 or serious TEAEs of atrial fibrillation were reported. The rate of secondary malignancies was 11.9% (44/370) versus 11.6% (43/370) reported in 2019. The most common type of secondary malignancy was nonmelanoma skin cancer. Since the 2019 report, 1 additional patient experienced a grade 5 TEAE of prostate cancer, which was considered unrelated to ibrutinib by the investigator.

This pooled analysis of ibrutinib treatment in R/R MCL with extended follow-up of nearly 10 years indicates that a notable number of patients had durable disease control for >5 years. Patients with only 1 prior LOT and those achieving a CR continued to have the best outcomes with ibrutinib. There was no emerging toxicity with additional follow-up.

A novel and interesting finding of this analysis is that treatment with single-agent ibrutinib in R/R MCL appears to have mitigated the historical trend of successive declines in median PFS with each line of CIT, regardless of age and prior LOT. Among the 370 ibrutinib-treated patients, median PFS with ibrutinib was slightly longer versus the prior regimen (12.5

### Table 1.

| Endpoint | Overall (N = 370) | 1 Line (N = 99) | >1 Line (N = 271) |
|----------|------------------|----------------|------------------|
| **PFS, median (95% CI), mo** | | | |
| Patients with CR (n = 102) | 12.5 (9.8–16.6) | NR (38.0–NE) | NR (74.3–NE) |
| Patients with PR (n = 156) | 12.6 (10.3–16.6) | 24.2 (13.9–36.5) | 10.5 (8.3–12.9) |
| **Overall response rate, n (%)** | | | |
| CR | 258 (69.7) | 77 (77.8) | 181 (66.8) |
| PR | 102 (27.6) | 37 (37.4) | 65 (24.0) |
| SD | 156 (42.2) | 40 (40.4) | 116 (42.8) |
| PD | 43 (11.6) | 11 (11.1) | 32 (11.8) |
| NP/UN | 56 (15.1) | 8 (8.1) | 48 (17.7) |
| Missing | 6 (2.2) | 1 (1.0) | 7 (2.6) |
| **DOR, median (95% CI), mo** | | | |
| Patients with CR (n = 102) | 21.8 (17.2–26.4) | 35.6 (23.2–66.5) | 16.6 (12.9–21.3) |
| Patients with PR (n = 156) | 66.4 (49.5–NE) | 35.6 (23.2–66.5) | 65.6 (40.0–NE) |
| **OS, median (95% CI), mo** | | | |
| Patients with CR (n = 102) | 26.7 (22.5–38.4) | 61.6 (36.0–NE) | 22.5 (16.2–26.7) |
| Patients with PR (n = 156) | 23.6 (20.7–32.2) | 36.0 (21.8–55.6) | 22.6 (17.2–26.9) |

CI = confidence interval; CR = complete response; DOR = duration of response; LOT = line of treatment; NE = not estimable; NR = not reached; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PD = progressive disease; PR = partial response; SD = stable disease; UN = unknown.
Half of the patients experienced a longer median PFS with ibrutinib than with the prior regimen. More than one-quarter of patients experienced ≥1 incremental year of benefit with ibrutinib versus the prior regimen, which is not unexpected given the different mechanism of action of ibrutinib versus CIT.

Figure 1. Kaplan-Meier estimate of PFS and OS with ibrutinib. (A) PFS by best response (CR versus PR); (B) PFS by prior LOT; (C) OS by prior LOT; (D) PFS with ibrutinib versus estimated PFS on prior regimen; (E) PFS with ibrutinib in patients with one prior LOT by frontline POD status (POD24 versus POD ≥24). CR = complete response; LOT = line of treatment; OS = overall survival; PFS = progression-free survival; POD = progression of disease; PR = partial response.
POD status following frontline therapy was previously shown to be predictive of poor survival with CIT-based salvage therapies. In this analysis, outcomes with 2L ibrutinib were also impacted by frontline POD status, likely reflecting disease biology. Despite a much shorter PFS in ibrutinib-treated patients with frontline POD24 (median 13.8 mo) versus frontline POD ≥24 (median 57.5 mo), ibrutinib appeared to perform better in patients with POD24 than 2L CIT, based on historical reports (range, 3.5–9.7 mo). This finding is consistent with data from the MANTLE-FIRST study, in which 2L ibrutinib was associated with significantly improved PFS and OS versus CIT (including BR or R-BAC) in younger patients with frontline POD24. In the current pooled analysis, median PFS with ibrutinib was >4 years in patients with POD ≥24, which translated to a 15-month improvement versus frontline PFS. In this patient subgroup, ibrutinib reversed the trend of PFS decline reported with CIT retreatment.

The recent introduction of CAR-T therapy adds an additional sequencing option for patients who progress after 2L ibrutinib. In the phase 2 ZUMA-2 study, all patients were previously treated with BTKi (85% with ibrutinib, 24% with acalabrutinib, 9% with both). The median PFS with KTE-X19 in patients with POD24 versus POD ≥24 was 11.3 versus 29.3 months, respectively. Interestingly, the CAR-T cell expansion peak was higher in patients who received prior ibrutinib versus acalabrutinib alone, indicating the unique property of ibrutinib to enhance CAR-T cell expansion. The sequencing of ibrutinib and CAR-T in R/R MCL has potential to further improve the overall outcome in R/R MCL, regardless of POD status. Taken together, these findings support the long-term efficacy and safety of single-agent ibrutinib in R/R MCL. Ibrutinib represents a significant advancement in treating MCL and should be considered a standard-of-care 2L treatment option, regardless of a patient’s initial response to frontline therapy.

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AUTHOR CONTRIBUTIONS

All authors participated in research design or performance of research, acquired data, and contributed to interpretation of the results, were involved in drafting, reviewing, and subsequent revisions of the article. All authors approved the final version of the article for submission.

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