Final author's draft of a paper accepted for publication in the Journal Leukemia DOI: "http://doi.org/10.1038/s41375-018-0023-2"

Ibrutinib versus temsirolimus: 3-year follow-up of patients with previously treated mantle cell lymphoma from the phase 3, international, randomized, open-label RAY study

S Rule[1]*, W Jurczak[2], M Jerkeman[3], C Rusconi[4], M Trneny[5], F Offner[6], D Caballero[7], C Joao[8], M Witzens-Harig[9], G Hess[10], I Bence-Bruckler[11], S-G Cho[12], C Thieblemont[13], W Zhou[14], T Henninger[14], J Goldberg[14], J Vermeulen[15] and M Dreyling[16]

[1]Plymouth University Medical School, Plymouth, UK; [2]Department of Hematology, Jagiellonian University, Krakow, Poland; [3]Skånes University Hospital, Lund University, Lund, Sweden; [4]Hematology Division, Hematology and Oncology Department, Niguarda Cancer Center, Niguarda Hospital, Milan, Italy; [5]Ist Dept Medicine, Charles University General Hospital, Prague, Czech Republic; [6]UZ Gent, Departement Oncologie, Ghent, Belgium; [7]Instituto Biosanitario de Salamanca, Hospital Clinico Universitario Salamanca, Salamanca, Spain; [8]Institutto Português de Oncologia de Lisboa, Portugal and Champalimaud Centre for the Unknown, Hematology, Lisbon, Portugal; [9]Klinikum der Ruprechts-Karls-Universität Heidelberg, Med. Klinik u. Poliklinik V, Heidelberg, Germany; [10]Department of Hematology, Oncology and Pneumology, University Medical School of the Johannes Gutenberg University, Mainz, Germany; [11]The Ottawa Hospital, General Campus, Ottawa, ON, Canada; [12]Seoul St. Mary's Hospital, Seocho-gu, Seoul, South Korea; [13]APHP, Saint-Louis Hospital, Hemato-oncology, Diderot University, Paris, France; [14]Janssen Research & Development, Raritan, NJ, USA; [15]Janssen Research & Development, Leiden, The Netherlands and [16]Department of Medicine III, Klinikum der Universität München, LMU, Munich, Germany.

*Correspondence:

Simon Rule, Department of Haematology, Derriford Hospital, Derriford Hospital, Plymouth, Devon, PL6 8DH | E-mail: Simon.Rule@nhs.net

Final author's draft of a paper accepted for publication in the Journal Leukemia DOI: "http://doi.org/10.1038/s41375-018-0023-2"

25 **Word count:** 1563/1500

26 **References:** 10/15

27 **Figures/Tables:** 2/2

28 **Running Title:** Phase 3 RAY Study 3-Year Follow-Up

Final author's draft of a paper accepted for publication in the Journal Leukemia DOI: "http://doi.org/10.1038/s41375-018-0023-2"

Mantle cell lymphoma (MCL) is an aggressive B-cell malignancy with a reported median overall survival (OS) of 3–5 years.[1] Most patients relapse after first-line therapy and have a poor prognosis.[1] Regulatory approval of ibrutinib has provided a much needed therapeutic option for patients with relapsed or refractory (R/R) MCL,[2] with ibrutinib becoming a preferred standard of care in current guidelines.[3,4] The randomized, open-label phase 3 RAY study (NCT01646021) was key in confirming the efficacy and safety of ibrutinib, with ibrutinib (*N*=139) showing significantly improved progression-free survival (PFS) versus temsirolimus (*N*=141) (primary analysis [20-month follow-up]: 14.6 vs 6.2 months, hazard ratio [HR] 0.43, 95% confidence interval [CI]: 0.32–0.58).[5] Here we report extended follow-up data from the final analysis of the RAY study.

At this final analysis, after an almost doubled median study follow-up of 38.7 months, 33 patients (24%) in the ibrutinib group and no patients in the temsirolimus group remained on initially randomized treatment. Crossover to ibrutinib from the temsirolimus group was permitted for patients who had confirmed disease progression. Fifty-five patients in the temsirolimus group (39%) received subsequent ibrutinib (42 were included in the formal study crossover; 13 received ibrutinib outside of the study). Disease progression or relapse was the most common reason for discontinuing treatment for both groups (ibrutinib, 78 patients [56%]; temsirolimus, 66 patients [47%]). Fewer patients in the ibrutinib group (12 [9%]) than in the temsirolimus group (39 [28%]) discontinued treatment due to adverse events (AEs); 8 patients in each arm discontinued due to death. Other reasons for discontinuation included refusing further treatment. Median duration of exposure was longer for ibrutinib than temsirolimus (ibrutinib, 14.4 months; temsirolimus, 3.0 months), as in the primary analysis.

Efficacy assessments at primary analysis by the Independent Review Committee showed high concordance with investigator assessment; at final analysis, all efficacy analyses were based on investigator assessment. With additional follow-up, median PFS remained significantly longer

for ibrutinib than temsirolimus (15.6 vs 6.2 months; HR 0.45 [95% CI: 0.35–0.60]; *P*<0.0001); consistent with the results of the primary analysis.[5] An exploratory *post hoc* analysis evaluated PFS by number of prior lines of therapy received (ibrutinib, 57 [41%] 1 prior line and 82 [59%] >1 prior line; temsirolimus, 50 [35%] 1 prior line and 91 [65%] >1 prior line). Median PFS for ibrutinib was significantly longer than temsirolimus regardless of the number of prior lines of treatment, and the difference in median PFS between ibrutinib- and temsirolimus-treated patients was greatest in those who received 1 prior line of therapy versus >1 (1 prior line, 25.4 vs 6.2 months, respectively, HR 0.40 [95% CI: 0.25–0.64]; >1 prior line, 12.1 vs 6.0 months respectively, HR 0.53 [95% CI: 0.38–0.73]; Figure 1a).

At the time of final analysis, 77 patients (55%) in the ibrutinib group and 83 (59%) in the temsirolimus group had died, with a trend toward improved OS in the patients randomized to receive ibrutinib versus temsirolimus (30.3 vs 23.5 months, respectively; HR 0.74 [95% CI: 0.54–1.02]; *P*=0.0621). Median OS was longer for ibrutinib than temsirolimus regardless of the extent of prior treatment. However, similar to PFS, a more pronounced OS difference was observed between ibrutinib and temsirolimus treatment in those patients who had received 1 prior line of therapy (1 prior line, 42.1 vs 27.0 months respectively, HR 0.74 [95% CI: 0.43–1.30]; >1 prior line, 22.1 vs 17.0 months respectively, HR 0.86 [95% CI: 0.59–1.25]; Figure 1b).

Overall response rate (ORR) in the final analysis was consistent with the primary analysis (77% for ibrutinib vs 47% for temsirolimus; odds ratio 4.27 [95% CI: 2.47–7.39]; *P*<0.0001), with a higher proportion of patients achieving a complete response (CR) with ibrutinib (23%) than with temsirolimus (3%). ORR results for ibrutinib were similar regardless of extent of prior treatment (75% vs 78% for 1 prior line and >1 prior line, respectively). However, the CR rate was two-fold higher in patients treated with ibrutinib who received 1 prior line of therapy than those who received >1 prior line: 33% and 16%, respectively. Overall median duration of response (DOR) was 23.1 months (95% CI: 16.2–28.1) with ibrutinib and 6.3 months (95% CI: 4.7–8.6) with

temsirolimus. Patients who achieved a CR on ibrutinib had a longer median DOR than patients who achieved a partial response (PR) (35.6 [*n*=32] vs 12.1 months [*n*=75]; Figure 1c). While DOR for patients achieving CR with ibrutinib remained consistent regardless of the extent of prior treatment (35.6 [*n*=19] vs 32.2 months [*n*=13] for 1 and >1 prior line of therapy, respectively), the DOR for patients achieving PR decreased with increasing lines of prior therapy (22.3 [*n*=24] vs 10.0 months [*n*=51], respectively, for those who had received 1 vs >1 prior line of therapy). Therefore, DOR for complete responders with only 1 prior line was more than three times longer than for partial responders with >1 prior line of therapy.

Consistent with the primary analysis, the most common treatment-emergent AEs (TEAEs) of any grade were diarrhea (33%), fatigue (24%) and cough (23%) in the ibrutinib group, and thrombocytopenia (56%), anemia (44%) and diarrhea (31%) in the temsirolimus group. Despite longer treatment exposure in the ibrutinib group versus the temsirolimus group, the frequency of grade ≥3 TEAEs (75% vs 87%), serious AEs of any grade (57% vs 60%) and AEs leading to discontinuation (17% vs 32%) were lower in the ibrutinib group than in the temsirolimus group, respectively. The most common grade ≥3 TEAEs for both groups were hematological in nature and were less frequently reported in the ibrutinib group than the temsirolimus group, respectively: neutropenia (13% vs 17%), thrombocytopenia (9% vs 43%) and anemia (9% vs 20%) (Table 1). The rate of any grade bleeding was 40% and 33% in the ibrutinib and temsirolimus groups, respectively. The rate of grade ≥3 bleeding was 9% in the ibrutinib group and 5% in the temsirolimus group, with exposure-adjusted rates being lower in the ibrutinib group (0.455 events per 100 patient-months) versus the temsirolimus group (0.785 events per 100 patient-months). A higher rate of grade ≥3 atrial fibrillation was observed in the ibrutinib group (5%) versus the temsirolimus group (1%); exposure-adjusted rates were similar for both groups (0.272 events per 100 patient-months for ibrutinib; 0.221 events per 100 patient-months for temsirolimus).

With longer-term follow-up, the data support a sustained clinical benefit of ibrutinib. Median time to next treatment (TTNT) was longer for patients in the ibrutinib group versus the temsirolimus group (31. 8 vs 11.6 months; HR 0.33 [95% CI: 0.24–0.46]; *P*<0.0001). Moreover, median time from randomization to progression or death after subsequent therapy (PFS2) was longer for ibrutinib than temsirolimus (26.2 vs 15.4 months; HR 0.67 [95% CI: 0.50–0.90]; *P*=0.0079; Figure 1d).

Nearly half (*n*=29; 46%) of 63 patients randomized to ibrutinib who received subsequent anticancer therapy on study were treated with rituximab-based chemotherapy. In these 29 patients, following treatment with ibrutinib, the ORR with rituximab-based chemotherapy was 41% (24% CR [*n*=7]; 17% PR [*n*=5]); response was missing or not evaluable in 11 patients. Fifteen of these 29 patients were treated specifically with bendamustine-rituximab following ibrutinib (ORR 53%; 40% CR [*n*=6], 13% PR [*n*=2]); response was missing or not evaluable in six patients.

In conclusion, longer-term follow-up from the final analysis of the RAY study supports the initial report, demonstrating significant improvement in ORR and PFS with ibrutinib over temsirolimus in patients with R/R MCL. At the final analysis, OS showed a trend in favor of ibrutinib versus temsirolimus (30.3 vs 23.5 months; HR 0.74 [95% CI: 0.54–1.02], *P*=0.0621). In the initial analysis, number of previous lines of therapy was identified as a prognostic factor.[5] With longer follow-up this was evident, with patients who had received 1 prior line of therapy benefiting the most from the use of ibrutinib. More patients were able to achieve a CR (33% vs 16%), and those achieving a PR had a longer DOR (22.3 vs 10.0 months) when using ibrutinib after 1 versus >1 prior line of therapy. In ibrutinib patients with 1 prior line of therapy, this resulted in a doubling of PFS versus ibrutinib patients with >1 prior line of therapy (25.4 vs 12.1 months) and an almost 15-month improvement of OS versus temsirolimus patients with 1 prior line of therapy (42.1 vs 27.0 months). These data from the RAY study, irrespective of the number of prior lines

of therapy, compare favorably to the results from pivotal clinical trials of other single agents in R/R MCL (e.g. bortezomib, lenalidomide and temsirolimus), the use of which was associated with median PFS of 4–5 months, median OS of 13–19 months, and ORRs of 22–33%.[6-9] Given that these findings support earlier use of ibrutinib in the relapsed/refractory setting, a relevant clinical question is whether patients can be successfully treated after progression on ibrutinib. Here we show that patients could be successfully rescued post ibrutinib therapy with rituximab-based chemotherapy (ORR=41%), including bendamustine-rituximab (ORR=53%). Importantly, longer follow-up revealed no new late or cumulative toxicities, supporting the overall well-tolerated safety profile for ibrutinib.[5] The significant improvements in PFS2 provide further evidence that ibrutinib benefit is maintained beyond subsequent lines of treatment. Collectively, these results support the role of ibrutinib in the treatment of previously treated MCL. Emerging data suggest that ibrutinib may also have a role in treatment-naïve MCL,[10] with multiple phase 3 studies underway (e.g., ENRICH [EudraCT 2015-000832-13], SHINE [NCT01776840], and TRIANGLE [NCT02858258]).

Conflicts of Interest

SR has served as an advisor for Janssen, Pharmacyclics and Napp, and has received research funding from Janssen. WJ has received research funding from Janssen and Pharmacyclics. MJ has received research funding from Janssen, Celgene, Abbvie and Gilead. CR has served as an advisor for Italfarmaco, Teva, Janssen, Takeda and Roche. MT has served as an advisor and received research funding from Janssen. CJ has served as an advisor for Celgene, Janssen, Takeda, Amgen and Roche. MW-H has served as an advisor and received honoraria from Janssen. GH has served as an advisor and received honoraria from Roche, Pfizer, Janssen, CTI and Celgene, and received research support from Roche, Pfizer, Mundipharma,

Celgene and CTI. CT has served as an advisor for Bayer, Celgene, Janssen and Roche, and received research funding from Roche. MD has served as an advisor and received research funding from Janssen and Pfizer, and has received honoraria from Janssen. WZ is a contractor of Janssen. TH, JG and JV are employees of Janssen and own stocks in Johnson & Johnson. FO, DC, IB-B and S-GC have no conflicts of interest to disclose.

Author Contributions

All authors conceived and/or designed the work that lead to this submission, acquired data and/or played an important role in interpreting the results. All authors were involved in drafting or reviewing the manuscript, and all authors approved the final version of the manuscript.

Acknowledgements

This study was funded by Janssen Research & Development. Writing assistance was provided by Juan Sanchez-Cortes, PhD (PAREXEL, Hackensack, NJ, USA) and Natalie Dennis (PAREXEL, Worthing, UK) and was funded by Janssen Global Services, LLC. The authors would like to thank the contribution of Mark Wildgust and Lori Parisi for their support in the long-term reporting for this study. We also thank the patients who participated in this trial, their families and the investigators and coordinators at each of the clinical sites.

References

1. Herrmann A, Hoster E, Zwingers T, Brittinger G, Engelhard M, Meusers P *et al*. Improvement of overall survival in advanced stage mantle cell lymphoma. *J Clin Oncol* 2009; **27**: 512–518.
2. IMBRUVICA® [US prescribing information]. Sunnyvale, CA, USA: Pharmacyclics, LLC; Horsham, PA, USA: Janssen Biotech, Inc.; 2017.
3. Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS *et al*. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. *N Engl J Med* 2013; **369**: 507–516.
4. Dreyling M, Campo E, Hermine O, Jerkeman M, Le Gouill S, Rule S, et al. Newly diagnosed and relapsed mantle cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; **28 (suppl_4)**: iv62-iv71.
5. Dreyling M, Jurczak W, Jerkeman M, Santucci Silva R, Rusconi C, Trneny M *et al*. Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international randomised, open-label, phase 3 study. *Lancet* 2016; **387**: 770–778.
6. Fisher RI, Bernstein SH, Kahl BS, Djulbegovic B, Robertson MJ, de Vos S, et al. Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma*. J Clin Oncol.* 2006; **24**: 4867–4874.
7. Goy A, Sinha R, Williams ME, Kalayoglu Besisik S, Drach J, Ramchandren R, *et al*. Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: phase II MCL-001 (EMERGE) study. *J Clin Oncol.* 2013; **31**: 3688–3695.
8. Hess G, Herbrecht R, Romaguera J, Verhoef G, Crump M, Gisselbrecht C, *et al*. Phase III study to evaluate temsirolimus compared with investigator's choice therapy for the

treatment of relapsed or refractory mantle cell lymphoma. *J Clin Oncol.* 2009; **27**: 3822–3829.

9. Jurczak W, Ramanathan S, Giri P, Romano A, Mocikova H, Clancy J *et al*. Comparison of two doses of intravenous temsirolimus in patients with relapsed/refractory mantle cell lymphoma. *Leuk Lymphoma.* 2017 Aug 3:1-9.
10. Wang ML, Lee HJ, Thirumurthi S, Chuang HH, Hagemeister FB, Westin JR *et al*. Chemotherapy-free induction with ibrutinib-rituximab followed by shortened cycles of chemo-immunotherapy consolidation in young, newly diagnosed mantle cell lymphoma patients: a phase II clinical trial. *Blood* 2016; **128**: Abstract 147.

Final author's draft of a paper accepted for publication in the Journal Leukemia DOI: "http://doi.org/10.1038/s41375-018-0023-2"

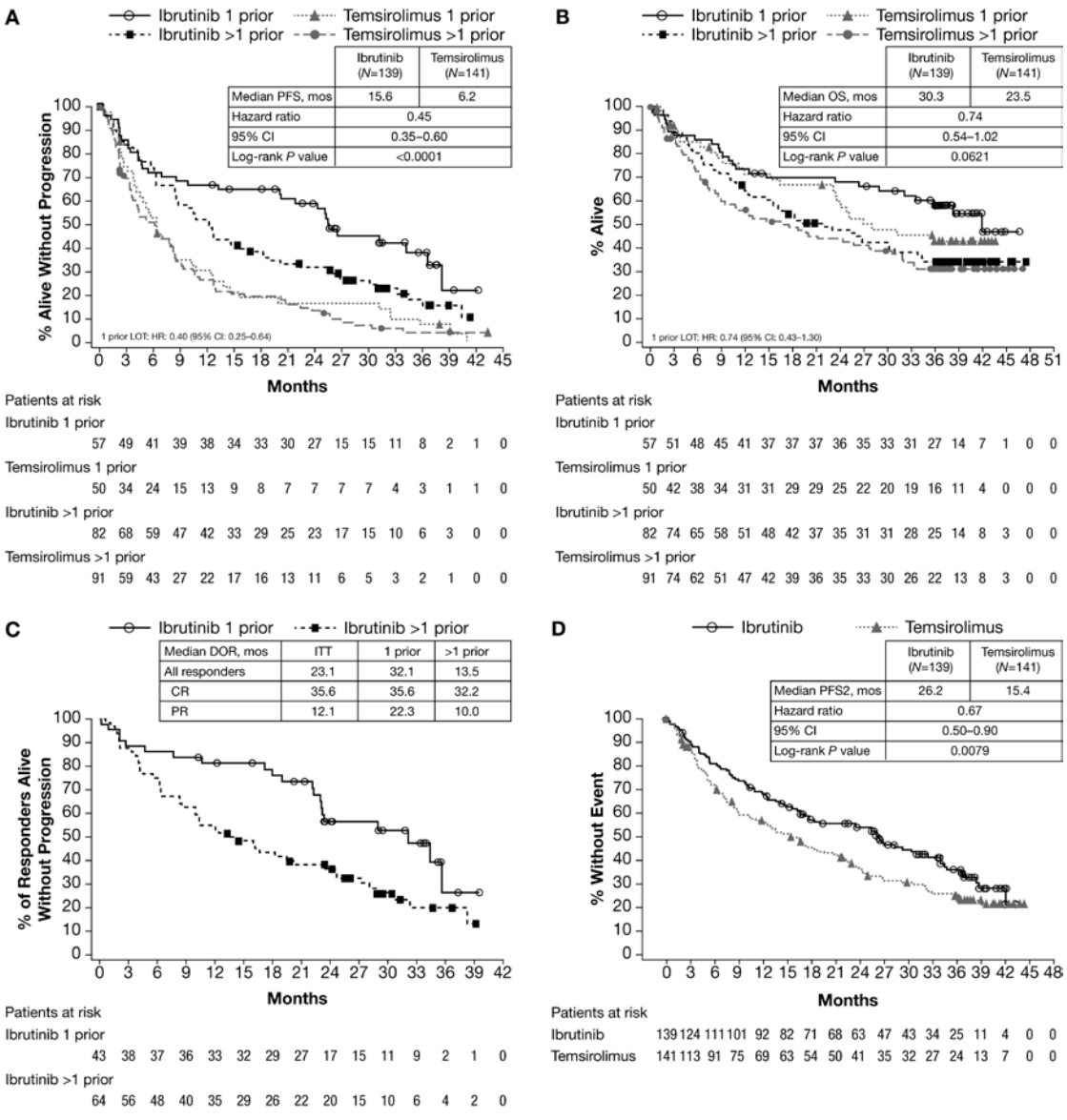
Tables

Table 1. Treatment-emergent adverse events (AEs) in ≥20% of patients in either treatment group

Safety population	**Ibrutinib (*N*=139)**		**Temsirolimus (*N*=139)**	
AE, %	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Hematological				
Thrombocytopenia	18.0	9.4	56.1	43.2
Anemia	19.4	8.6	43.9	20.1
Neutropenia	15.8	12.9	26.6	17.3
Non-hematological				
Diarrhea	33.1	3.6	30.9	4.3
Fatigue	23.7	5.0	28.8	7.2
Cough	23.0	0.7	22.3	0.0
Upper respiratory tract infection	20.1	2.2	11.5	0.7
Pyrexia	18.7	0.7	20.9	2.2
Nausea	14.4	0.0	21.6	0.0
Peripheral edema	13.7	0.0	23.7	2.2
Epistaxis	9.4	0.7	23.7	1.4
Stomatitis	2.9	0.0	20.9	3.6

Figures

Figure 1. Efficacy end points in 3-year follow-up in RAY study: (**a**) Progression-free survival for ibrutinib and temsirolimus by prior line of therapy; (**b**) Overall survival for ibrutinib and temsirolimus by prior line of therapy; (**c**) Duration of clinical response by prior line of therapy in patients randomized to ibrutinib; (**d**) Time to second progression or death for ibrutinib and temsirolimus.



CI, confidence interval; CR, complete response; DOR, duration of response; ITT, intent-to-treat; OS, overall survival; PFS, progression-free survival; PR, partial response.
Dosing schedule: daily 560 mg of oral ibrutinib (starting on cycle 1, day 1) or 175 mg of intravenous temsirolimus (starting on cycle 1, days 1, 8, 15; then 75 mg on days 1, 8, 15 of all subsequent cycles) until disease progression or unacceptable toxicity.