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# Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine and rituximab in 1 relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma

Rule, Simon

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1 **Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine and rituximab in**  
2 **relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma** G Fraser<sup>1</sup>, P Cramer<sup>2</sup>, F  
3 Demirkan<sup>3</sup>, R Santucci Silva<sup>4</sup>, S Grosicki<sup>5</sup>, A Pristupa<sup>6</sup>, A Janssens<sup>7</sup>, J Mayer<sup>8</sup>,  
4 NL Bartlett<sup>9</sup>, M-S Dilhuydy<sup>10</sup>, H Pylypenko<sup>11</sup>, J Loscertales<sup>12</sup>, A Avigdor<sup>13</sup>, S Rule<sup>14</sup>, D Villa<sup>15</sup>, O Samoilo<sup>16</sup>,  
5 P Panagiotidis<sup>17</sup>, A Goy<sup>18</sup>, MA Pavlovsky<sup>19</sup>, C Karlsson<sup>20</sup>, M Hallek<sup>21</sup>, M Mahler<sup>22</sup>, M Salman<sup>22</sup>, S Sun<sup>22</sup>,  
6 C Phelps<sup>22</sup>, S Balasubramanian<sup>23</sup>, A Howes<sup>24</sup> and A Chanan-Khan<sup>25</sup>

7 <sup>1</sup>Juravinski Cancer Centre, McMaster University, Hamilton, ON, Canada; <sup>2</sup>Department of Internal  
8 Medicine, Center of Integrated Oncology and German CLL Study Group, University of Cologne, Cologne,  
9 Germany; <sup>3</sup>Division of Hematology, Dokuz Eylul University, Izmir, Turkey; <sup>4</sup>IEP São Lucas/Hemomed  
10 Oncologia e Hematologia, São Paulo, Brazil; <sup>5</sup>Department of Cancer Prevention, Faculty of Public Health,  
11 Silesian Medical University, Katowice, Poland; <sup>6</sup>Regional Clinical Hospital, Ryazan, Russia; <sup>7</sup>Universitaire  
12 Ziekenhuizen Leuven, Leuven, Belgium; <sup>8</sup>Department of Internal Medicine, Hematology and Oncology,  
13 Masaryk University Hospital Brno, Jihlavská, Brno, Czech Republic; <sup>9</sup>Washington University School of  
14 Medicine, Siteman Cancer Center, St Louis, MO, USA; <sup>10</sup>Hôpital Haut-Lévêque, Bordeaux, Pessac, France;  
15 <sup>11</sup>Department of Hematology, Cherkassy Regional Oncological Center, Cherkassy, Ukraine; <sup>12</sup>Hematology  
16 Department, Hospital Universitario La Princesa, IIS-IP, Madrid, Spain; <sup>13</sup>Division of Hematology and Bone  
17 Marrow Transplantation, Chaim Sheba Medical Center, Tel-Hashomer and Sackler School of Medicine,  
18 University of Tel-Aviv, Tel-Aviv, Israel; <sup>14</sup>Department of Haematology, Plymouth University Medical  
19 School, Plymouth, UK; <sup>15</sup>Division of Medical Oncology, British Columbia Cancer Agency, Vancouver, BC,  
20 Canada; <sup>16</sup>Nizhny Novogorod Regional Clinical Hospital, Nizhny Novogorod, Russia; <sup>17</sup>1<sup>st</sup> Department of  
21 Propedeutic Medicine, National and Kapodistrian University of Athens, Athens, Greece; <sup>18</sup>John Theurer  
22 Cancer Center at Hackensack University Medical Center, Hackensack, NJ, USA; <sup>19</sup>Department of  
23 Hematology, Fundaleu, Buenos Aires, Argentina; <sup>20</sup>Department of Hematology, Karolinska University  
24 Hospital, Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; <sup>2</sup> Department I

25 *of Internal Medicine, University of Cologne, Cologne, Germany;* <sup>22</sup>*Janssen Research & Development,*  
26 *Raritan, NJ, USA;* <sup>23</sup>*Janssen Research & Development, Spring House, PA, USA;* <sup>24</sup>*Janssen Research &*  
27 *Development, High Wycombe, UK and* <sup>25</sup>*Mayo Clinic Cancer Center, Jacksonville, FL, USA.*

28

29 **Corresponding author**

30 Graeme A.M. Fraser

31 699 Concession Street

32 Hamilton, ON L8V 5C2

33 Tel: 905-575-7820

34 Fax: 905-575-6340

35 Email: [fraserg@HHSC.CA](mailto:fraserg@HHSC.CA)

36

37 **CONFLICTS OF INTEREST**

38 GF: research support/honoraria: Janssen, Hoffmann-La Roche, Celgene; honoraria: Lundbeck, Abbvie.

39 PC: research grants/honoraria/travel support: F. Hoffmann-La Roche, Janssen-Cilag; research

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44 Mundipharma, Abbvie; speakers' fees: Janssen, Takeda, Roche, Abbvie; consulting fees: Janssen, Roche,

45 Gilead, Abbvie. JM: grants: Janssen, Roche. NLB: advisory board fees: Gilead, Seattle Genetics. M-SD:

46 fees: Janssen, Roche. JL: speakers' bureaus/advisory boards: Janssen, Gilead, Roche. AA: grant: Janssen.

47 SR: fees: Janssen, Pharmacyclics. DV: honoraria: Janssen, Lundbeck, Celgene, Genentech; research

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49 Johnson/Pharmacyclics, Takeda; consultancy/advisory board fees: Celgene. MAP: speaking/consulting  
50 honoraria: Novartis, Janssen. MH: honoraria/travel funds: Janssen; research funding/speakers'  
51 bureau/advisory role: Roche; advisory role: Gilead Sciences. MM, MS, SS, CP, SB, AH: employees of  
52 Janssen. AC-K: institutional funding for this clinical trial. All other authors: no competing interests.

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54

**55 Abstract**

56 We report follow-up results from the randomized, placebo-controlled, phase 3 HELIOS trial of  
57 ibrutinib+bendamustine and rituximab (BR) for previously treated chronic lymphocytic leukemia  
58 (CLL)/small lymphocytic lymphoma (SLL) without deletion 17p. Overall, 578 patients were randomized  
59 1:1 to either ibrutinib (420 mg daily) or placebo, in combination with 6 cycles of BR, followed by  
60 ibrutinib or placebo alone. Median follow-up was 34.8 months (range: 0.1–45.8). Investigator-assessed  
61 median progression-free survival (PFS) was not reached for ibrutinib+BR, versus 14.3 months for  
62 placebo+BR (hazard ratio [HR] [95% CI], 0.206 [0.159–0.265];  $P<0.0001$ ); 36-month PFS rates were 68.0%  
63 versus 13.9%, respectively. The results are consistent with the primary analysis findings (HR=0.203, as  
64 assessed by independent review committee, with 17-month median follow-up). Median overall survival  
65 was not reached in either arm; HR (95% CI) for ibrutinib+BR versus placebo: 0.652 (0.454–0.935;  
66  $P=0.019$ ). Minimal residual disease (MRD)-negative response rates were 26.3% for ibrutinib+BR and  
67 6.2% for placebo+BR ( $P<0.0001$ ). Incidence of treatment-emergent adverse events (including grade 3–4)  
68 were generally consistent with the initial HELIOS report. These long-term data support improved survival  
69 outcomes and deepening responses with ibrutinib+BR compared with BR in relapsed CLL/SLL.

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71 **Running title:** 3-year update of BR+ibrutinib in relapsed CLL

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**76 INTRODUCTION**

77 Ibrutinib is an oral, once-daily inhibitor of Bruton's tyrosine kinase, an essential enzyme in the B-cell  
78 receptor signaling pathway [1-3]. The efficacy and safety of ibrutinib has been demonstrated in patients  
79 with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) in treatment-naïve and  
80 relapsed/refractory settings [4,5], leading to approvals for these indications [6,7]. Ibrutinib as a single-  
81 agent for previously treated patients with CLL/SLL was evaluated in a phase 1b/2 study (Study 1102 and  
82 its extension, Study 1103) and the phase 3 RESONATE study of ibrutinib versus ofatumumab [8,9]. Long-  
83 term follow-up data from these studies showed that continuing ibrutinib treatment leads to durable and  
84 deepening responses. The phase 1b/2 study (101 patients with previously treated CLL) reported an  
85 overall response rate (ORR) of 89% with 10% complete responses (CRs) and a median progression-free  
86 survival (PFS) of 52 months after 5-year follow-up, while the median overall survival (OS) remained  
87 unreached [9]. In the RESONATE™ study (195 previously treated CLL patients), the ORR was 91% (with  
88 9% CR/CRi [CR with incomplete bone marrow recovery]) at a median follow-up of 44 months versus 83%  
89 (2% CR/CRi) after median follow-up of 9.4 months [8].

90 Chemoimmunotherapy regimens such bendamustine and rituximab (BR) or fludarabine,  
91 cyclophosphamide and rituximab (FCR) are efficacious in patients with relapsed/refractory CLL, but their  
92 use is often limited by patient tolerability [10]. BR has been commonly used [11], largely based on a  
93 phase 2 study in relapsed/refractory CLL that showed an ORR of 59%, with 9% of patients achieving a CR,  
94 and a median PFS and OS of 15 and 34 months, respectively [12]. The BR regimen formed the backbone  
95 of the phase 1b study that led to the development of the HELIOS study [13]. In this phase 1b study  
96 (Study 1108) with 30 previously treated patients receiving up to six cycles of BR+continuous ibrutinib,  
97 the CR rate was 17% after a median of 15.8 months of follow-up, increasing to 40% at a median follow-  
98 up of 37.3 months [13].

99 In the phase 3 HELIOS trial of 578 patients with relapsed/refractory CLL, ibrutinib+BR ( $\leq 6$  cycles)  
100 significantly improved PFS at the initial analysis (median follow-up 17 months); median PFS was not  
101 reached in the ibrutinib arm versus 13.3 months in the placebo arm (hazard ratio [HR]=0.203, 95% CI:  
102 0.150–0.276;  $P < 0.0001$ ) [14]. The findings of HELIOS supported the approval of ibrutinib+BR in the US  
103 and EU for patients with relapsed/refractory CLL/SLL [6,7].

104 For traditional chemoimmunotherapy, minimal residual disease (MRD)-negative responses are  
105 prognostic for prolonged PFS [15] and may be a more potent predictor of PFS than the clinical response  
106 assessment according to International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guidelines  
107 [16]. Because of limited long-term follow-up data on novel targeted therapies, it is unclear if MRD-  
108 negative remissions are similarly prognostic in patients receiving these agents [17]. Evaluation of MRD  
109 status is of particular interest in ibrutinib-containing regimens, as MRD negativity represents a lower  
110 disease burden and is being investigated as a marker for treatment discontinuation with novel agents,  
111 which are usually administered until progression or unacceptable toxicity. HELIOS was the first study to  
112 evaluate MRD status in ibrutinib-treated patients. At 17-month median follow-up, the proportion of  
113 patients that achieved MRD negativity was higher with ibrutinib+BR versus placebo+BR (13% vs 5%;  
114  $P = 0.0011$ ) [14].

115 As ibrutinib is a continuously administered oral once-daily therapy, data addressing the safety profile of  
116 ibrutinib over time, longer-term outcomes, and efficacy in patient subgroups become increasingly  
117 relevant. We report updated data from HELIOS (3-year follow-up) to determine survival outcomes,  
118 evolution of responses and durability of remissions across patient subgroups, as well as long-term  
119 safety.

120

## 121 **Subjects and Methods**

122 Study design and patients

123 Study design and participants have been previously described [14]. Briefly, HELIOS (Clinicaltrials.gov  
124 #NCT01611090) is a phase 3, randomized, placebo-controlled, double-blind study of 578 patients  
125 conducted at 133 sites in 21 countries between September 19, 2012, and January 21, 2014. Eligible  
126 patients were aged  $\geq 18$  years, had a diagnosis of CLL/SLL according iwCLL criteria [18],  
127 relapsed/refractory disease following  $\geq 1$  previous lines of systemic therapy, an Eastern Cooperative  
128 Oncology Group performance status of 0–1, measurable lymph node disease ( $>1.5$  cm) by computed  
129 tomography (CT) scan and adequate liver and kidney function. Patients with deletion 17p ( $\geq 20\%$  of  
130 blood or bone marrow cells examined by fluorescence in situ hybridization) were excluded due to  
131 known poor response to BR.

132 Patients were randomly assigned 1:1 to ibrutinib (420 mg daily)+BR or placebo+BR. BR was administered  
133 for up to six cycles (bendamustine: 70 mg/m<sup>2</sup> intravenously on days 2–3 in cycle 1 and days 1–2 in cycles  
134 2–6; rituximab: 375 mg/m<sup>2</sup> on day 1 of cycle 1 and 500 mg/m<sup>2</sup> on day 1 of cycles 2–6). After 6 months of  
135 BR with ibrutinib or placebo therapy, patients continued ibrutinib treatment or placebo alone until  
136 disease progression or unacceptable toxicity. Following the pre-specified interim analysis, the study was  
137 unblinded and placebo treatment was discontinued. Subsequently, adverse events (AEs) were collected  
138 only for patients continuing on ibrutinib, although patients originally treated with placebo were  
139 followed with regular disease evaluations and were able to crossover to ibrutinib at the time of  
140 progression and meeting iwCLL criteria for treatment.

141

#### 142 Endpoints and assessments

143 The primary endpoint was Independent Review Committee (IRC)-assessed PFS, for which results were  
144 reported previously [14]. Investigator-assessed endpoints were used for the follow-up analyses reported  
145 here. Key secondary endpoints were investigator-assessed PFS, OS and response rates, proportion of  
146 patients with MRD-negative responses ( $<1$  CLL cell per 10 000 leukocytes or  $<0.01\%$ ) confirmed by

147 central laboratory assessment of peripheral blood or bone marrow aspirate, and safety. PFS2 (time  
148 interval from randomization to disease progression on next-line treatment or death, or start of next  
149 antineoplastic therapy if no progressive disease [PD] was recorded) was also assessed.  
150 Assessment of tumor response was conducted in accordance with iwCLL 2008 criteria [18]. Prior to the  
151 interim analysis, CT scans were performed at baseline, then every 12 weeks for 2 years and every 6  
152 months thereafter. Following the interim analysis, disease evaluations based on the discretion of  
153 investigators continued every 3 months in both arms; for patients randomized into the ibrutinib arm  
154 who had not yet progressed, CT scans continued every 6 months until progression. Analysis of MRD was  
155 initially performed on bone marrow sampled at the time of radiological documentation of CR, with  
156 subsequent analyses of peripheral blood every 12 weeks. After the interim analysis, the protocol was  
157 amended to include MRD analysis for all patients with a partial response (PR) or better. Testing was  
158 performed at a central laboratory by flow cytometry using an eight-color panel of antibodies in keeping  
159 with the EuroFlow panel [19].

160

#### 161 Statistical analysis

162 Statistical analyses have been described previously [14]. Approximately 580 patients were randomized  
163 to observe 342 PFS events, to detect an HR of 0.7 for the ibrutinib+BR group relative to the placebo+BR  
164 group with 90% power at a one-sided significance level of 0.025, using a group sequential testing design.  
165 The distribution of time-to-event endpoints was estimated using the Kaplan-Meier method.

166 The analysis of PFS and OS using the long-term follow-up data was similar to those used for the primary  
167 analyses, except that investigator assessments were used for follow-up data. For patients in the  
168 placebo+BR group who crossed over to receive ibrutinib, no adjustment was made for OS analysis, i.e.,  
169 the OS is defined as the time interval from randomization to death irrespective of cause. For surviving  
170 patients, the OS is censored at the last date known to be alive. Separate analyses of OS corrected for

171 crossover were performed using the Inverse Probability of Censoring Weighting and the Rank Preserving  
172 Structural Failure Time Methods (Supplementary Figure S1). The MRD-negative response rate was  
173 compared between treatment arms using the Fisher's exact test; MRD assessments continued until  
174 crossover for the placebo+BR arm.

175

## 176 **RESULTS**

### 177 Study population

178 The data represent outcomes of 6 months of combination therapy (ibrutinib+BR or placebo+BR)  
179 followed by over 2 years of continuous ibrutinib or placebo treatment. For consistency with the initial  
180 analysis, the treatment arms are referred to as ibrutinib+BR and placebo+BR. The median follow-up  
181 period at this analysis was 34.8 months (range: 0.1–45.8), with a median treatment duration of 34.7  
182 months (range: 0.2–43.3) for ibrutinib+BR and 14.3 months (range: 0.2–30.6) months for placebo+BR  
183 (Supplementary Table S1). Sixty-six percent (188/287) of ibrutinib-treated patients remained on  
184 treatment for  $\geq 24$  months.

185 Patient disposition is shown in Table 1. A total of 160 (55.4%) patients who had confirmed PD in the  
186 placebo+BR arm crossed over to ibrutinib. At the time of this analysis, patients received crossover  
187 therapy for a median of 16.9 months (range: 0.2–26.3). Patient demographics and baseline  
188 characteristics data were previously reported and were balanced between arms (Supplementary table  
189 S2) [14].

190

### 191 Efficacy

192 Investigator-assessed PFS was significantly longer with ibrutinib+BR (not reached vs 14.3 months for  
193 placebo+BR [HR (95% CI), 0.206 (0.159–0.265);  $P < 0.0001$ ]) (Figure 1a), and the 36-month PFS rate was

194 68.0% versus 13.9%, respectively. Median OS was not reached in either arm, but was significantly longer  
195 for the ibrutinib+BR arm (HR [95% CI], 0.652 [0.454–0.935];  $P=0.019$ ) (Figure 1b); the 36-month OS rate  
196 for each arm was 81.6% versus 72.9%, respectively. An analysis of OS that corrected for crossover from  
197 the placebo+BR arm to ibrutinib+BR confirmed the OS advantage of ibrutinib+BR (Supplementary Figure  
198 S1).

199 In assessed subgroups, including bulky disease, chromosomal deletions, ZAP70 elevation and  
200 immunoglobulin heavy-chain variable region (*IGHV*) mutation status, PFS outcomes favored ibrutinib+BR  
201 over placebo+BR (Figure 2a, Supplementary Figure S3). PFS at 36 months was significantly longer in  
202 ibrutinib-treated patients, whether they had one or multiple lines of therapy (Figure 2b). For patients  
203 who had one prior therapy, 36-month PFS was 70.2% in the ibrutinib+BR arm (95% CI: 61.3–77.5) and  
204 15.5% in the placebo+BR arm (95% CI: 8.3–24.7;  $P<0.0001$ ); for patients who had two or more prior  
205 therapies, 36-month PFS was 65.9% for ibrutinib+BR (95% CI: 56.8–73.5) and 11.2% with placebo+BR  
206 (95% CI: 6.5–17.4;  $P<0.0001$ ).

207 Median PFS2 was not reached in either arm but was significantly longer for patients assigned to  
208 ibrutinib+BR versus placebo+BR (HR [95% CI], 0.627 [0.445–0.881];  $P=0.0067$ ) (Supplementary Figure  
209 S2). Among 27 patients who discontinued ibrutinib+BR due to disease progression, 10 patients died  
210 (seven patients died due to PD, two due to AEs [pneumonia and cardiac arrest] and one of unknown  
211 causes following administration of subsequent CLL therapy). Eight patients received subsequent  
212 systemic CLL therapies, four in combination with rituximab.

213 The investigator-assessed ORR was 87.2% for ibrutinib+BR and 66.4% for placebo+BR ( $P<0.0001$ ). CR/CRi  
214 rates were 38.1% versus 8.0% (Figure 3a), which showed continued improvement over time versus the  
215 investigator-assessed CR/CRi rates of 21.4% and 5.9%, respectively, in the initial analysis [14]. Overall,  
216 211 patients in the ibrutinib+BR arm and 76 patients in the placebo+BR arm were evaluated for MRD;  
217 MRD-negative response rates in peripheral blood or bone marrow combined for the intent-to-treat

218 population were 26.3% (76/289) for ibrutinib+BR and 6.2% (18/289) for placebo+BR ( $P<0.0001$ ) (Figure  
219 3b). The majority of patients (67.1%) in the ibrutinib+BR arm who achieved MRD negativity had a CR/CRi  
220 as their best response; 32.9% patients had a PR as their best response. Of these MRD-negative patients  
221 in the ibrutinib+BR arm with PR as their best response, the CR criteria not met are listed in  
222 Supplementary Table S3. In the placebo+BR arm, 8/18 MRD-negative patients (44.4%) had PR as their  
223 best response. Patients who did not achieve CR/PR or who progressed prior to MRD testing being  
224 implemented for all responding patients had a shorter PFS (Figure 4a–b). Among MRD-evaluated  
225 patients, ibrutinib+BR showed a more sustained PFS over placebo+BR at each level of MRD (MRD-  
226 negative status  $<0.01\%$ , HR [95% CI], 0.121 [0.036–0.408],  $P<0.0001$ ; MRD  $\geq 0.01\%$  to  $<1\%$ , HR [95%CI],  
227 0.153 [0.063–0.374],  $P<0.0001$ ; or MRD  $\geq 1$  to  $<10\%$ , HR [95%CI], 0.110 [0.035–0.348],  $P<0.0001$ ) (Figure  
228 4a–b). In patients receiving ibrutinib+BR, the 36-month PFS rate for MRD-negative patients was 88.6%  
229 (95% CI: 76.8–94.6); for those with residual disease (MRD  $\geq 0.01\%$ ), it was 60.1% (95% CI: 52.6–66.8). In  
230 the placebo+BR arm, the 36-month PFS rate in MRD-negative patients was 54.5% (95% CI: 29.2–74.2)  
231 and 11.2% (95% CI: 7.1–16.3) for patients with residual disease. A multivariate analysis revealed no  
232 difference in OS according to MRD status in responding patients.

233

## 234 Safety

235 Following the interim analysis, patients who were randomized to placebo+BR stopped treatment and  
236 either crossed over to receive next-line treatment with ibrutinib or remained in follow-up until  
237 progression. Per protocol, safety data were collected for 30 days after the last dose of study medication  
238 (placebo or BR). Therefore, only safety data for patients randomized to ibrutinib+BR are presented  
239 (Table 2); comparison between the two treatment arms up to the interim analysis has previously been  
240 published [14]. Treatment-emergent AEs (TEAEs) observed in over 10% of patients, and their prevalence  
241 over time, are listed in Table 3. The prevalence of TEAEs decreased over time after year 1, except for

242 muscle spasms and hypertension, which remained stable (Table 3).The proportion of patients with all-  
243 grade AEs in the ibrutinib+BR arm was 98.3%, with 78.7% of patients reporting grade 3 or 4 events.  
244 Grade  $\geq 3$  AEs reported in  $\geq 2\%$  of patients are presented in Supplementary Table S4; the most common  
245 grade  $\geq 3$  AEs were neutropenia (53.7%), thrombocytopenia (15.0%), pneumonia (14.3%) and febrile  
246 neutropenia (12.5%), consistent with the initial analysis [14]. Serious TEAEs (i.e., life-threatening,  
247 requiring hospitalization or resulting in persistent/significant incapacity) occurred in 176 (61.3%)  
248 patients in the ibrutinib+BR arm; the most common were pneumonia (13.6%) and febrile neutropenia  
249 (10.1%). Serious atrial fibrillation (AF) or flutter was reported for 4.9% of patients (compared with 2.8%  
250 reporting AF in the initial analysis) [14]. There were 28 (9.8%) TEAEs leading to death in the ibrutinib+BR  
251 arm (compared with 19 [6.6%] reported in the initial analysis) [14], of which the most frequent were  
252 infections; a complete list of causes are included in Supplementary Table S5.

253 Overall, the incidence of AEs of interest, including cytopenias, bleeding and infections, reduced during  
254 the course of the follow-up period (Table 4). Most AEs occurred within the first 12 months, with a sharp  
255 decrease in onset of new events after 12 months. Bleeding events (all grades) were reported in 34.5% of  
256 patients in the ibrutinib+BR arm (Table 4) versus 31% of patients in the initial report [14]; most were  
257 grade 1/2 events. No new major hemorrhage events or deaths due to bleeding or major hemorrhage  
258 events were reported during extended follow-up.

259 Ibrutinib therapy is generally well tolerated, but has been associated with AF. A detailed review of AF  
260 following ibrutinib treatment in HELIOS and other randomized clinical trials investigating ibrutinib has  
261 been recently published [20]. During extended follow-up, eight additional patients in the ibrutinib+BR  
262 arm developed AF/flutter, for a total of 29 patients (10.1%). The majority of AF events (17/29) during  
263 the entire study duration in the ibrutinib+BR arm were grade 1/2. While dose interruption was normal in  
264 these cases, none required dose reductions and none were fatal; four (1.4%) led to treatment  
265 discontinuation.

266 Patients randomized to placebo+BR who crossed over to the ibrutinib+BR arm did not demonstrate any  
267 difference in type or incidence of AEs compared with patients originally randomized to ibrutinib+BR  
268 (Supplementary Table S6).

269

## 270 **DISCUSSION**

271 The HELIOS study was conducted in patients with relapsed/refractory CLL/SLL and is the first trial to  
272 show a survival benefit with ibrutinib-based therapy versus a standard chemoimmunotherapy regimen,  
273 even in the context of a crossover design. These results support the continued use of ibrutinib, with  
274 maintenance of superior PFS and OS versus the placebo+BR arm and an increase in ORR and CR rates  
275 over time. It is notable that longer-term follow-up revealed a significant improvement in survival for  
276 ibrutinib+BR-treated patients compared with placebo+BR, despite the possibility of crossover after  
277 progression. Additionally, deeper responses were reported with continuous ibrutinib therapy, with rates  
278 of investigator-assessed CR/CRi and MRD-negative response rising to 38% and 26%, respectively  
279 (compared with IRC-assessed rates of 21% and 13% at the primary analysis) [14]. This finding is  
280 consistent with the phase 1b study 1108 of ibrutinib+BR, in which CR rates increased from 17% to 40%  
281 with 15.7 to 35.4 months of follow-up, respectively [13].

282 Among those tested for MRD, patients in the ibrutinib+BR arm demonstrated prolonged PFS compared  
283 with those in the placebo+BR arm at the same MRD level. Caution is warranted in interpreting the MRD  
284 analyses due to the relatively small numbers of MRD-tested patients in the placebo+BR arm and the  
285 potential that longer-term follow-up will be required to fully understand the prognostic significance of  
286 specific MRD levels in ibrutinib+BR-treated patients.

287 The evolution of ORR and of CR rates following ibrutinib monotherapy in study 1102 for treatment-naïve  
288 (ORR, 71% to 84%, CR 13% to 23%, at 22 months to 3 years of follow-up) or previously treated (ORR,  
289 71% to 90%, CR 2% to 7% from 26 months to 3 years of follow-up) CLL/SLL patients demonstrates that

290 ibrutinib is associated with durable and deep responses as treatment continues [21]. The results from  
291 the HELIOS study have further shown that in patients with relapsed/refractory disease, an induction-  
292 type period of ibrutinib+BR therapy followed by continued ibrutinib treatment produces better  
293 responses than BR therapy alone and improves outcomes as the duration of therapy increases [14]. The  
294 extended follow-up further confirmed that the positive effects on PFS of continuing ibrutinib following  
295 ibrutinib+BR are maintained irrespective of the number of prior lines of therapy or the presence of poor  
296 prognostic factors.

297 It remains unclear whether ibrutinib+BR provides benefits beyond those observed with ibrutinib  
298 monotherapy. In the RESONATE trial, which investigated ibrutinib monotherapy in patients with CLL, the  
299 3-year PFS and OS rates for ibrutinib were 59% and 74%, respectively. In our study, 3-year PFS and OS  
300 rates for the ibrutinib+BR arm were 68% and 82%, respectively. However, cross-trial comparisons are  
301 notoriously difficult to interpret and firm conclusions generally impossible to reach due to potential  
302 differences in study designs and treatment populations (e.g., HELIOS did not enroll patients with  
303 deletion 17p); an indirect treatment comparison of the HELIOS and RESONATE trials (ibrutinib+BR vs  
304 ibrutinib arms respectively) following adjustment for known confounders has recently been published  
305 [22]. At a median follow-up of 17 and 19 months, respectively, there was no difference in median PFS or  
306 OS, suggesting that addition of BR to ibrutinib does not improve outcomes compared with single-agent  
307 ibrutinib. An ongoing study directly comparing BR, ibrutinib+rituximab and ibrutinib alone in treatment-  
308 naïve CLL patients (clinicaltrials.gov NCT01886872) will provide more insights into the relative efficacy of  
309 chemoimmunotherapy versus ibrutinib alone or with rituximab.

310 Importantly, the extended follow-up data supported the manageable safety profile of ibrutinib, allowing  
311 for continued dosing following the initial induction with BR. The pattern and incidence of AEs and TEAEs  
312 was similar to the initial analysis when treatment extended beyond 17 months [14], and was  
313 comparable with the safety profile reported in other clinical trials of ibrutinib in CLL patients

314 [5,14,21,23]. Eight additional patients in the ibrutinib+BR arm reported AF/flutter during follow-up,  
315 consistent with reviews and meta-analyses documenting an increased risk of developing AF in ibrutinib-  
316 treated patients versus comparator treatments [20,24] and an elevated risk over time [20]. It has  
317 previously been reported that 5–9% of CLL/SLL patients receiving ibrutinib are affected [25]. The  
318 incidence of bleeding events increased slightly with continued follow-up in the ibrutinib+BR arm;  
319 however, there were no new major hemorrhagic events or bleeding-related deaths. These long-term  
320 follow-up data support improved survival outcomes with ibrutinib+BR compared with BR alone in  
321 relapsed CLL/SLL. In addition, continued ibrutinib monotherapy following the end of  
322 chemoimmunotherapy results in continuing improvement in the depth of remission.

323

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329 Supplementary information is available at *Leukemia's* website

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431 **Figure Legends**

432 **Figure 1.** Three-year follow-up of investigator-assessed (a) progression-free survival and (b) overall  
433 survival.

434 BR, bendamustine and rituximab; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS,  
435 progression-free survival.

436 **Figure 2.** Investigator-assessed PFS by (a) prognostic factors and (b) prior lines of therapy.

437 BR, bendamustine and rituximab; CI, confidence interval; EVT, event; *IGHV*, immunoglobulin heavy-chain  
438 variable; HR, hazard ratio; LDi, longest diameter; NE, not evaluable; PFS, progression-free survival.

439 **Figure 3.** Cumulative response rates over time (investigator-assessed) for (a) complete response and (b)  
440 MRD status. Note: The term “induction therapy” refers to BR. The induction phase is defined as the first  
441 six cycles of the study, when BR is given along with study drug (ibrutinib or placebo) as combination  
442 therapy. The end of the induction phase is the last dose of B or R + 30 days.

443 BR, bendamustine and rituximab; CR, complete response; CRi, CR with incomplete bone marrow  
444 recovery; MRD, minimal residual disease.

445 Note: Percentages are based on number of patients in the intent-to-treat analysis set in each treatment  
446 arm.

447 **Figure 4.** Investigator-assessed PFS by MRD level for (a) ibrutinib+BR and (b) placebo + BR arms.

448 BR, bendamustine and rituximab; MRD, minimal residual disease; PFS, progression-free survival.