Ibrutinib versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma: an international, randomised, open-label, phase 3 study

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Lancet 2016; 387: 770–78

Published Online December 7, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00667-4

This online publication has been corrected. The corrected version first appeared at thelancet.com on Feb 18, 2016

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Summary

Background Mantle-cell lymphoma is an aggressive B-cell lymphoma with a poor prognosis. Both ibrutinib and temsirolimus have shown single-agent activity in patients with relapsed or refractory mantle-cell lymphoma. We undertook a phase 3 study to assess the efficacy and safety of ibrutinib versus temsirolimus in relapsed or refractory mantle-cell lymphoma.

Methods This randomised, open-label, multicentre, phase 3 clinical trial enrolled patients with relapsed or refractory mantle-cell lymphoma confirmed by central pathology in 21 countries who had received one or more rituximab-containing treatments. Patients were stratified by previous therapy and simplified mantle-cell lymphoma international prognostic index score, and were randomly assigned with a computer-generated randomisation schedule to receive daily oral ibrutinib 560 mg or intravenous temsirolimus (175 mg on days 1, 8, and 15 of cycle 1; 75 mg on days 1, 8, and 15 of subsequent 21-day cycles). Randomisation was balanced by using randomly permuted blocks. The primary efficacy endpoint was progression-free survival assessed by a masked independent review committee with the primary hypothesis that ibrutinib compared with temsirolimus significantly improves progression-free survival. The analysis followed the intention-to-treat principle. The trial is ongoing and is registered with ClinicalTrials.gov (number NCT01646021) and with the EU Clinical Trials Register, EudraCT (number 2012-000601-74).

Findings Between Dec 10, 2012, and Nov 26, 2013, 280 patients were randomised to ibrutinib (n=139) or temsirolimus (n=141). Primary efficacy analysis showed significant improvement in progression-free survival (p<0·0001) for patients treated with ibrutinib versus temsirolimus (hazard ratio 0·43 [95% CI 0·32–0·58]; median progression-free survival 14·6 months [95% CI 10·4–not estimable] *vs* 6·2 months [4·2–7·9], respectively). Ibrutinib was better tolerated than temsirolimus, with grade 3 or higher treatment-emergent adverse events reported for 94 (68%) versus 121 (87%) patients, and fewer discontinuations of study medication due to adverse events for ibrutinib versus temsirolimus (9 [6%] *vs* 36 [26%]).

Interpretation Ibrutinib treatment resulted in significant improvement in progression-free survival and better tolerability versus temsirolimus in patients with relapsed or refractory mantle-cell lymphoma. These data lend further support to the positive benefit–risk ratio for ibrutinib in relapsed or refractory mantle-cell lymphoma.

Funding Janssen Research & Development, LLC.

Introduction

Mantle-cell lymphoma, an incurable B-cell lymphoma, accounts for 6–8% of all non-Hodgkin lymphomas, with an annual incidence of 0·4 per 100 000 persons in the USA and Europe.[1] Mantle-cell lymphoma most often affects men older than 60 years, generally presents as late-stage disease, and has a median overall survival of 4–5 years.[2] Patients with relapsed disease respond poorly to chemotherapy and progress rapidly, resulting in a median overall survival of 1–2 years. Despite recent advances, and with the exception of a small patient population eligible for allogeneic stem cell transplantation, there is no globally recognised standard of care in relapsed mantle-cell lymphoma.[3–5]

Ibrutinib is a first-in-class, once-daily, oral, covalently binding inhibitor of Bruton's tyrosine kinase. Bruton's tyrosine kinase belongs to the cytoplasmic tyrosine kinase family (Tec kinases) and is important for B-cell receptor signalling and other pathways downstream of the B-cell receptor.[6] Ibrutinib binds to a cysteine residue (Cys481) in the active site of the ATP-binding domain of Bruton's tyrosine kinase, which then inhibits B-cell receptor signalling within the malignant B cell with downstream mitigation of cell growth, proliferation, survival, adhesion, and migration.[7–12]

Efficacy results from previous studies have shown significant single-agent activity of ibrutinib in the treatment of relapsed or refractory mantle-cell lymphoma. A single-arm phase 1b/2 study of ibrutinib in which patients with relapsed or refractory mantle-cell lymphoma were stratified by previous bortezomib exposure had an investigator-assessed overall response

Research in context

Evidence before this study

We searched PubMed and other relevant literature databases for English-language articles published between Jan 1, 2005, and Aug 1, 2015, to identify drugs used to treat mantle-cell lymphoma, including trials that have been published specifically on ibrutinib or mantle-cell lymphoma and trials that have been published specifically on temsirolimus in mantle-cell lymphoma. We used the search terms "mantle cell lymphoma", "ibrutinib", and "temsirolimus". Patients treated with ibrutinib have achieved high response rates and ongoing remissions in relapsed and refractory mantle-cell lymphoma, whereas temsirolimus has been shown to be superior to monochemotherapy in a randomised trial.

Added value of this study

Most of the patients in this study had advanced disease and progressive disease. Our findings show additional benefits of ibrutinib over the only other therapy approved for relapsed mantle-cell lymphoma in the European Union. Based on this first randomised trial of targeted therapies, ibrutinib is a standard targeted option for patients with relapsed or refractory mantle-cell lymphoma.

Implications of all the available evidence

We have proven that ibrutinib is active in patients with relapsed or refractory mantle-cell lymphoma who have had one or more previous rituximab therapy, and that it shows a significant improvement in progression-free survival compared with an approved comparator, temsirolimus, along with a favourable tolerability profile.

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See Online for appendix

rate of 68%, with a complete response rate of 21%, and a median duration of response of 17·5 months.[13] A longer-term follow-up (median 26·7 months) of this study reported a median progression-free survival of 13·0 months and median overall survival of 22·5 months, respectively.[14] A phase 2 single-agent study of ibrutinib in patients with relapsed or refractory mantle-cell lymphoma who had received a rituximab-containing regimen and had progressed after two or more cycles of bortezomib therapy had an overall response rate of 62·7%, with a complete response rate of 20·9%.[15]

Based on the phase 1b/2 results, ibrutinib at a dose of 560 mg per day has been approved in the USA, the European Union, and many other countries for patients with mantle-cell lymphoma who have received at least one previous line of therapy.

Temsirolimus is an inhibitor of the mTOR pathway that has been shown to be frequently activated in mantle-cell lymphoma.[16] In two phase 2 studies, temsirolimus at various doses achieved response rates of about 40% in relapsed mantle-cell lymphoma.[17,18] In the European Union, temsirolimus is approved based on a phase 3 study in relapsed or refractory mantle-cell lymphoma. Temsirolimus at the same dosing used in this study resulted in significantly longer progression-free survival versus investigator's choice single-agent therapy (4·8 months *vs* 1·9 months; hazard ratio [HR] 0·44 [97·5% CI 0·25–0·78]; p=0·0009). The overall response rate for temsirolimus was 22%, with a median overall survival of 12·8 months.[19]

This study (MCL3001) assesses the efficacy of these two approved targeted approaches in patients with relapsed or refractory mantle-cell lymphoma, was performed in collaboration with the European MCL Network, and was undertaken in the European Union, Latin America, and Asia-Pacific.

Methods

Study design and participants

This randomised, controlled, open-label, multicentre, phase 3 study compared the efficacy and safety of ibrutinib with temsirolimus in patients with relapsed or refractory mantle-cell lymphoma confirmed by central pathology. Between Dec 10, 2012, and Nov 26, 2013, patients with one or more previous rituximab-containing chemotherapy regimens were enrolled and randomised to oral ibrutinib 560 mg or intravenous temsirolimus 175 mg for a 3-week cycle followed by 75 mg (appendix). Eligible patients had at least one previous rituximab-containing chemotherapy regimen, documented relapse, or disease progression after the last anti-mantle-cell lymphoma treatment, measurable disease by Revised Response Criteria for Malignant Lymphoma,[20] and an Eastern Cooperative Oncology Group (ECOG) performance status[21] of 0 or 1. On July 30, 2014, the protocol was amended to include formal crossover of patients on the temsirolimus group to ibrutinib who have independent review committee-confirmed progression of disease. Key exclusion criteria included chemotherapy, radiation, or other investigational drugs within 3 weeks, antibody treatment or immunoconjugates within 4 and 10 weeks, respectively, and previous treatment with mTOR or Bruton's tyrosine kinase inhibitors. All inclusion or exclusion criteria are shown in the appendix. The study was done according to the principles of the Declaration of Helsinki and the Guidelines for Good Clinical Practice. All patients provided written informed consent.

Randomisation and masking

Central randomisation was used. Patients were randomly assigned (1:1) to oral ibrutinib or intravenous temsirolimus based on a computer-generated randomisation schedule. Randomisation was balanced by using

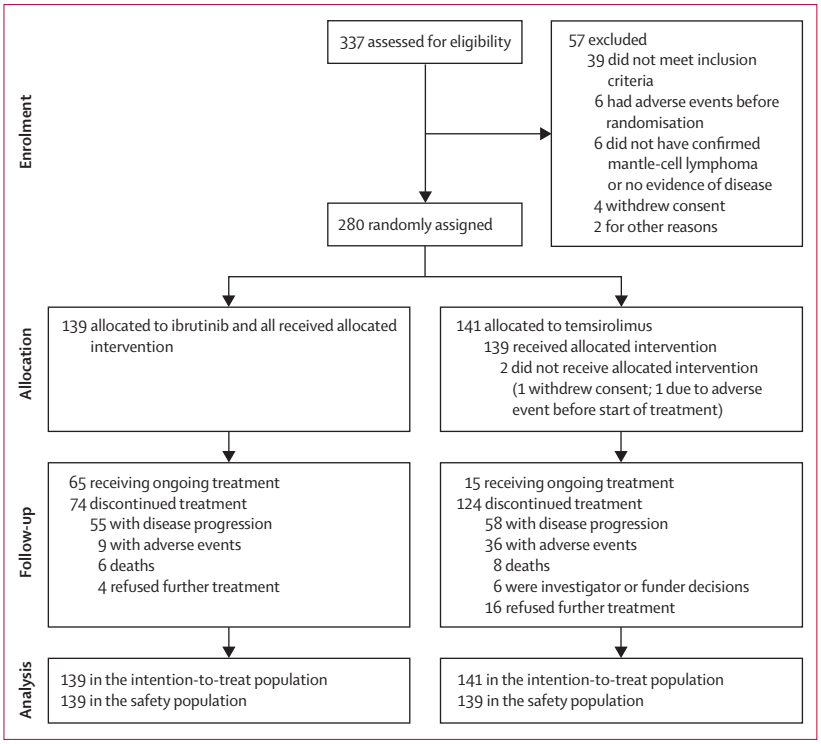

Figure 1: **Trial profile**
32 patients crossed over from temsirolimus but were analysed according to their original assignment.

randomly permuted blocks and stratified by number of previous lines of therapy (one, two, or three or more) and simplified mantle-cell lymphoma international prognostic index (sMIPI) score[22] (low risk [0–3] *vs* intermediate risk [4–5] *vs* high risk [6–11]). The randomisation scheme was implemented within the interactive web response system that determined treatment assignment and matching study drug kits. Patients randomly assigned to study treatment were not replaced by another patient in case of discontinuation for any reason. Patients and investigators were unmasked to treatment assignment.

Procedures

Patients in the ibrutinib group received 560 mg orally once per day. Patients in the temsirolimus group received 175 mg intravenously on days 1, 8, and 15 of the first cycle, followed by 75 mg on days 1, 8, and 15 of each subsequent 21-day cycle. Both groups continued treatment until disease progression or unacceptable toxic effects.

Outcomes

The primary endpoint was progression-free survival, which was defined as the interval from date of randomisation to the date of disease progression (as assessed by the independent review committee) or date of death, whichever occurred first, irrespective of the use of subsequent antineoplastic therapy. Patients who were progression-free and alive were censored at the time of their last disease assessment, and patients who were alive with no post-baseline disease assessment were censored at randomisation. Complete response, partial response, and progressive disease were assessed by an independent review committee per revised Cheson criteria.[20] Secondary endpoints included overall response rate (complete response and partial response), overall survival, 1-year survival rate, duration of response, time to next treatment, safety, prespecified patient-reported outcomes, biomarkers and pharmacokinetics, and medical resource use rate.

Patient-reported outcomes were assessed using the Functional Assessment of Cancer Therapy—Lymphoma (FACT-Lym) questionnaire at baseline and until disease progression, death, or the clinical cutoff. Other malignancies and major bleeding events were defined as adverse events of special interest. Major bleeding was defined as any grade 3 or higher haemorrhage, any haemorrhage reported as a serious adverse event, and all grades of central nervous system haemorrhage.

Statistical analysis

About 280 patients (140 per treatment group) were to be randomised to observe 178 progression-free survival events. The study was designed to detect a hazard ratio (HR) of 0·64 for ibrutinib relative to temsirolimus (corresponding to a 57% improvement in median progression-free survival from 7 to 11 months under the exponential distribution assumption) with at least 85% power at a two-sided significance level of 0·05. No interim analysis was planned.

The primary efficacy analysis was done on the intention-to-treat population (all patients randomly assigned to groups). The Kaplan-Meier method was used to estimate the distribution of progression-free survival for each treatment group. The treatment effect of ibrutinib compared with temsirolimus based on progression-free survival was tested with a stratified two-sided log-rank test stratified by sMIPI and previous lines of therapy. The HR for ibrutinib relative to temsirolimus and its associated 95% CI were calculated based on the stratified Cox proportional hazards model by the stratification factors at randomisation. All time-to-event endpoints, including overall survival, were analysed using the same methods as progression-free survival. Overall response rate was analysed using the Cochran-Mantel-Haenszel χ^2 test adjusted for stratification. For patient-related outcomes, the proportions of patients improving and declining were calculated, and median time to clinically meaningful improvement and time to worsening were estimated. Clinically meaningful improvement was defined as a 5-point or greater increase from baseline, and worsening was defined as a 5-point or greater decrease from baseline.[23–25] Safety was analysed in patients who received at least one dose of study drug. An independent data monitoring committee monitored safety on a periodic basis. SAS version 9.2 was used for all statistical analyses. The trial is ongoing and is registered with ClinicalTrials.gov

(number NCT01646021) and with the EU Clinical Trials Register, EudraCT (number 2012-000601-74).

Role of the funding source

This study was funded by Janssen Research & Development. Funders were involved in the study design, data collection, data analysis and interpretation, and provided writing support. On behalf of the European MCL Network, lead investigators (MD, SR) had full access to the data and analyses for compilation of this report.

Results

280 patients were randomly assigned to ibrutinib (n=139) or temsirolimus (n=141; figure 1). Baseline demographics and disease characteristics (table 1) were generally well balanced and were consistent with known characteristics of mantle-cell lymphoma. Median age was 68 years (IQR 13), with 173 patients (62%) above 65 years. Most patients (208 [74%]) were male and most (232 [83%]) had stage IV disease. About two-thirds of the patients had intermediate-risk or high-risk disease according to sMIPI scores. Median number of previous lines of therapy was 2 (IQR 2). The median duration of exposure was 14·4 months (IQR 15·1) for ibrutinib versus 3·0 months (7·6) for temsirolimus, with a median relative dose intensity of 99·9% for ibrutinib versus 81·8% for temsirolimus (appendix). At the clinical cutoff, more patients in the ibrutinib group were continuing treatment compared with the temsirolimus group (65 [47%] *vs* 15 [11%]). Progressive disease was the most common reason for treatment discontinuation in both groups (ibrutinib, 55 [40%]; temsirolimus, 58 [41%]). Adverse events were reported as the primary reason of treatment discontinuation for nine patients (6%) in the ibrutinib group and 36 (26%) in the temsirolimus group (figure 1). The most common adverse event leading to discontinuation in the ibrutinib group was thrombocytopenia in two patients, whereas the most common adverse events leading to discontinuation in the temsirolimus group were pneumonia, atypical pneumonia, or pneumonitis in five patients. Based on the safety set, the number of patients with dose reductions due to adverse events was five (4%) of 139 for ibrutinib versus 60 (43%) of 139 for temsirolimus. At the time of reporting, 65 (47%) of 139 ibrutinib patients were still on treatment, compared with 15 (11%) of 141 temsirolimus patients. Additionally, more patients discontinued temsirolimus per investigator decision or patient refusal of treatment (ibrutinib, 4 [3%]; temsirolimus, 22 [16%]).

With a median follow-up of 20 months, ibrutinib treatment resulted in a 57% reduction in the risk of disease progression or death compared with temsirolimus (HR 0·43 [95% CI 0·32–0·58]; p<0·0001; figures 2 and 3). The median progression-free survival was 14·6 months (95% CI 10·4–not estimable) for the ibrutinib group and 6·2 months (4·2–7·9) for the temsirolimus group. At a 2-year landmark, the progression-free survival rate is 41% in the ibrutinib group versus 7% in the temsirolimus group. The preplanned subgroup analysis showed internal consistency across almost all subgroups (figure 3). Patients with blastoid histology appeared to have derived no statistically significant benefit; however, based on the small number of patients with this histology

	Ibrutinib (n=139)	Temsirolimus (n=141)	Total (n=280)
Age			
Median (IQR), years	67 (11)	68 (13)	68 (13)
≥65 years	86 (62%)	87 (62%)	173 (62%)
Sex			
Male	100 (72%)	108 (77%)	208 (74%)
Race			
White	115 (83%)	129 (91%)	244 (87%)
Asian	16 (12%)	5 (4%)	21 (8%)
Other, unknown	8 (6%)	7 (5%)	15 (5%)
ECOG performance status			
0	67 (48%)	67 (48%)	134 (48%)
1	71 (51%)	72 (51%)	143 (51%)
2	1 (1%)	2 (1%)	3 (1%)
Time from initial diagnosis to randomisation (months)			
Mean (SD)	49·98 (42·71)	51·17 (33·60)	50·58 (38·33)
Median (IQR)	38·90 (49·02)	46·23 (43·86)	42·56 (45·77)
<36 months	68 (49%)	58 (41%)	126 (45%)
≥36 months	71 (51%)	83 (59%)	154 (55%)
Time from end of last previous therapy to randomisation (months)			
Mean (SD)	15·43 (18·62)	16·34 (20·21)	15·88 (19·41)
Median (IQR)	8·25 (19·78)	7·03 (21·55)	7·23 (20·25)
Stage of MCL at study entry			
I	3 (2%)	2 (1%)	5 (2%)
II	7 (5%)	5 (4%)	12 (4%)
III	17 (12%)	14 (10%)	31 (11%)
IV	112 (81%)	120 (85%)	232 (83%)
Type of histology			
Blastoid	16 (12%)	17 (12%)	33 (12%)
Non-blastoid	123 (88%)	124 (88%)	247 (88%)
sMIPI			
Low risk (1–3)	44 (32%)	42 (30%)	86 (31%)
Intermediate risk (4–5)	65 (47%)	69 (49%)	134 (48%)
High risk (6–11)	30 (22%)	30 (21%)	60 (21%)
Previous lines of therapy			
Mean (SD)	2·1 (1·4)	2·2 (1·3)	2·2 (1·3)
Median (range)	2·0 (1–9)	2·0 (1–9)	2·0 (1–9)
1–2	95 (68%)	93 (66%)	188 (67%)
3–5	41 (29%)	45 (32%)	86 (31%)
>5	3 (2%)	3 (2%)	6 (2%)
Type of treatment indication			
Relapsed disease*	103 (74%)	94 (67%)	197 (70%)
Refractory disease†	36 (26%)	47 (33%)	83 (30%)

Data are n (%), mean (SD), or median (IQR). ECOG=Eastern Cooperative Oncology Group. MCL=mantle-cell lymphoma. sMIPI=simplified mantle-cell lymphoma international prognostic index. *Relapsed disease was defined as relapse or disease progression after achieving at least a partial response to the last regimen before study entry. †Refractory disease was defined as failure to achieve at least a partial response to the last regimen before study entry.

Table 1: **Baseline demographics and disease characteristics of the intention-to-treat population**

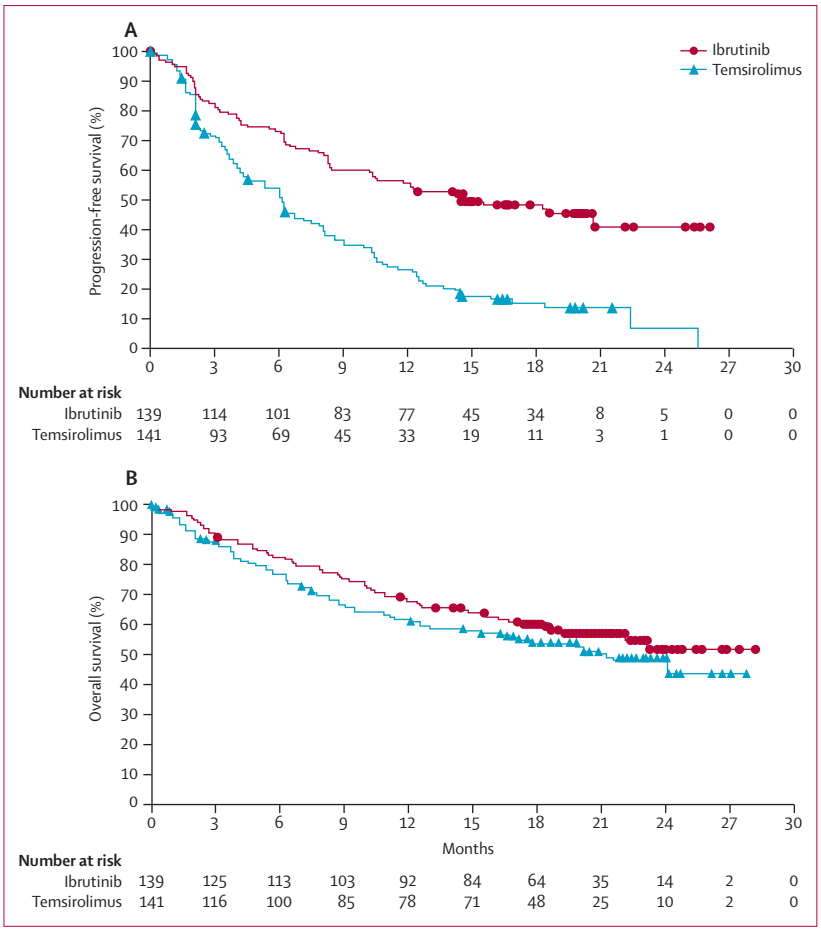

Figure 2: **Kaplan-Meier plots of progression-free survival and overall survival**
(A) Kaplan-Meier plot of progression-free survival by independent review committee assessment. (B) Kaplan-Meier plot of overall survival, intention-to-treat analysis set.

(ibrutinib, 16 [12%]; temsirolimus, 17 [12%]), interpretation of these results should be made with caution. Multivariate Cox regression analysis was done to assess effects of baseline factors on study outcome. Baseline ECOG performance status, sMIPI, blastoid histology, and number of previous lines of therapy were identified as significant prognostic factors ($p<0·05$) from this analysis (appendix). The results of the sensitivity analysis using progression-free survival by investigator (appendix) were consistent with the primary analysis results (HR 0·43 [95% CI 0·32–0·58]; appendix).

The overall response rate assessed by an independent review committee was significantly higher for ibrutinib (72%, n=100) than for temsirolimus (40%, n=57) (difference 31·5% [95% CI 20·5–42·5]; $p<0·0001$), with a complete response reported in 26 (19%) patients versus two (1%) patients, respectively (odds ratio [OR] 3·98 [2·38–6·65]). Investigator-assessed overall response rate was also significantly higher ($p<0·0001$) for ibrutinib (77%, n=107) than for temsirolimus (46%, n=65) (difference 30·9% [95% CI 20·1–41·7]; OR 4·38 [2·53–7·57]). Overall response rates were consistent with those assessed by the independent review committee. At time of clinical cutoff, median duration of response for the temsirolimus group was 7·0 months (4·2–9·9 [IQR 10·9]) and median duration of response was not reached for ibrutinib; 59 (59%) of the 100 responders in the ibrutinib group were continuing to respond. At 18 months, the estimated rate of duration of response was 58% (46–68) for ibrutinib and 20% (9–35) for temsirolimus (appendix).

After a median follow-up of 20·0 months, 59 patients (42%) in the ibrutinib group and 63 (45%) in the temsirolimus group had died. Median overall survival was not reached for ibrutinib versus 21·3 months for temsirolimus (HR 0·76 [95% CI 0·53–1·09]; p=0·1324; figure 2). This difference was not statistically significant; however, it should be noted that 32 (23%) temsirolimus patients crossed over to ibrutinib. The 1-year survival rates were 68% for ibrutinib and 61% for temsirolimus.

A post hoc sensitivity analysis of overall survival was done in which data from patients in the temsirolimus group who crossed over to receive ibrutinib during the study or who had received ibrutinib as subsequent therapy were censored at the date of the first dose of next-line ibrutinib treatment. The result was consistent with that recorded using the intention-to-treat analysis set (data not shown).

Subsequent anticancer therapy was given to 82 (58%) patients in the temsirolimus group and 44 (32%) in the ibrutinib group. The most common subsequent treatments were rituximab (n=21, 15%), bendamustine (n=15, 11%), and cyclophosphamide (n=12, 9%) in the ibrutinib group and rituximab (n=36, 26%), ibrutinib (n=32, 23%), bendamustine (n=22, 16%), and cyclophosphamide (n=19, 13%) in the temsirolimus group (appendix). Median time to next treatment was not reached with ibrutinib versus 11·6 months with temsirolimus ($p<0·0001$). Four patients who were assigned to the ibrutinib group received temsirolimus as subsequent therapy. After excluding patients who received crossover treatment with either drug, overall response rate on subsequent treatment was similar, with 20% response rate in both groups (ten of 50 patients in the temsirolimus group and eight of 40 patients in the ibrutinib group). More patients discontinued temsirolimus for adverse events, therefore potentially representing a less refractory population. The overall treatment effect might be better captured by progression-free survival 2 (defined as the time interval between the date of randomisation to the date of an event, where event is defined as progressive disease as assessed by the investigator after the next line of therapy, death from any cause, or start of subsequent therapy if no disease progression is noted[26]), which was longer for ibrutinib than for temsirolimus (HR 0·49 [95% CI 0·36–0·69]; $p<0·0001$; appendix). Effective subsequent salvage treatment might have affected post-progression survival in the temsirolimus group.

A greater proportion of patients treated with ibrutinib had a clinically meaningful improvement in lymphoma symptoms versus those treated with temsirolimus (86 [62%] *vs* 50 [35%]). Improvement in symptoms occurred more quickly with ibrutinib versus temsirolimus, with a median time to clinically meaningful improvement of 6·3 (IQR not estimable) weeks versus 57·3 (101·4) weeks, respectively (p<0·0001; figure 4). Similarly, a smaller proportion of patients treated with ibrutinib experienced a clinically meaningful worsening of lymphoma symptoms versus temsirolimus (37 [27%] *vs* 73 [52%]) and worsening of symptoms occurred later with ibrutinib versus temsirolimus (HR 0·27 [95% CI 0·18–0·41]; p<0·0001; figure 4).

Median treatment duration was four times longer for the ibrutinib group (14·4 months [IQR 15·1]) compared with temsirolimus (3·0 months [7·6]). Despite the time difference in exposure between the treatment groups, overall frequencies of most cumulative treatment-emergent adverse events were lower in the ibrutinib group relative to the temsirolimus group. Treatment-emergent adverse events were reported in 138 (99%) patients in both treatment groups, with grade 3 or higher treatment-emergent adverse events reported in 94 (68%) patients in the ibrutinib group and 121 (87%) in the temsirolimus group. In the study, treatment-emergent adverse events leading to treatment discontinuation occurred in nine (6%) patients in the ibrutinib group and 36 (26%) patients in the temsirolimus group. The most frequently reported (≥20% of patients) treatment-emergent adverse events in the ibrutinib group were diarrhoea (n=40, 29%), cough (n=31, 22%), and fatigue (n=31, 22%). In the temsirolimus group these were thrombocytopenia (n=78, 56%), anaemia (n=60, 43%), diarrhoea (n=43, 31%), fatigue (n=40, 29%), neutropenia (n=36, 26%), epistaxis (n=33, 24%), cough (n=31, 22%), peripheral oedema (n=31, 22%), nausea (n=30, 22%), pyrexia (n=29, 21%), and stomatitis (n=29, 21%; table 2).

As an adverse event of special clinical interest, grade 3 or higher atrial fibrillation was reported in five (4%) patients of the ibrutinib group and two (1%) of the temsirolimus group. Major bleeding was reported in 14 (10%) patients in the ibrutinib group and in nine (6%) in the temsirolimus group. When adjusted for exposure, the event rate for any major bleeding treatment-emergent adverse event was 0·8 events per 100 patient-months for the ibrutinib group and 1·1 events per 100 patient-months for the temsirolimus group (appendix). New diagnoses of other malignancies were seen in five (4%) patients in the ibrutinib group and four (3%) in the temsirolimus group. Most malignancies were non-melanomatous skin cancers. When adjusted for exposure, frequencies were similar in both treatment groups.

Death during treatment or within 30 days of the last dose of study drug was reported in 24 (17%) patients in the ibrutinib group and 15 (11%) in the temsirolimus group. The most common cause of death in this period was disease progression in the ibrutinib group, whereas in the temsirolimus group adverse events were most common. During the first 6 months of treatment, eight (6%) patients in the ibrutinib group and 11 (8%) in the temsirolimus group had a treatment-emergent adverse event with an outcome of death.

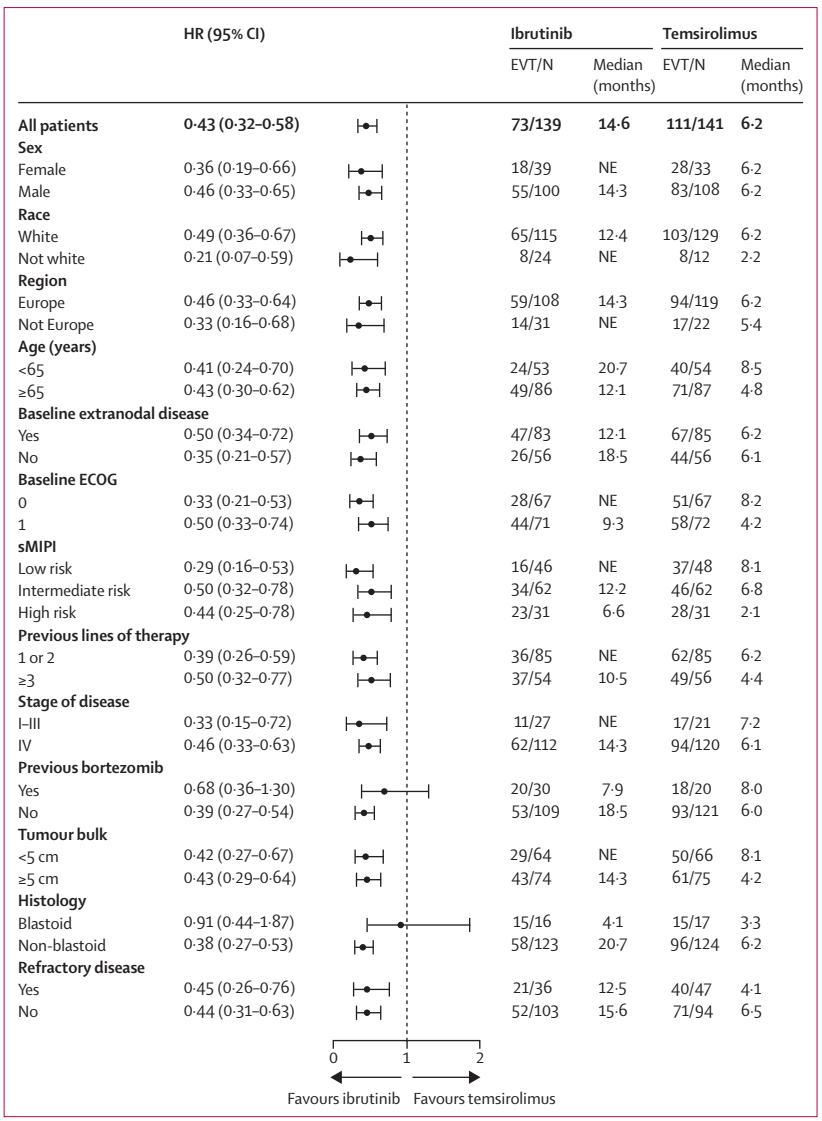

Figure 3: **Subgroup analysis for progression-free survival by independent review committee assessment**
EVT=event (progressed or died). ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. NE=not estimable. sMIPI=simplified mantle-cell lymphoma international prognostic index.

Discussion

This is the first randomised study comparing two of the targeted therapies approved for relapsed or refractory mantle-cell lymphoma, namely the Bruton's tyrosine kinase inhibitor ibrutinib and the mTOR inhibitor temsirolimus. A statistically significant advantage was shown for ibrutinib, with a median progression-free

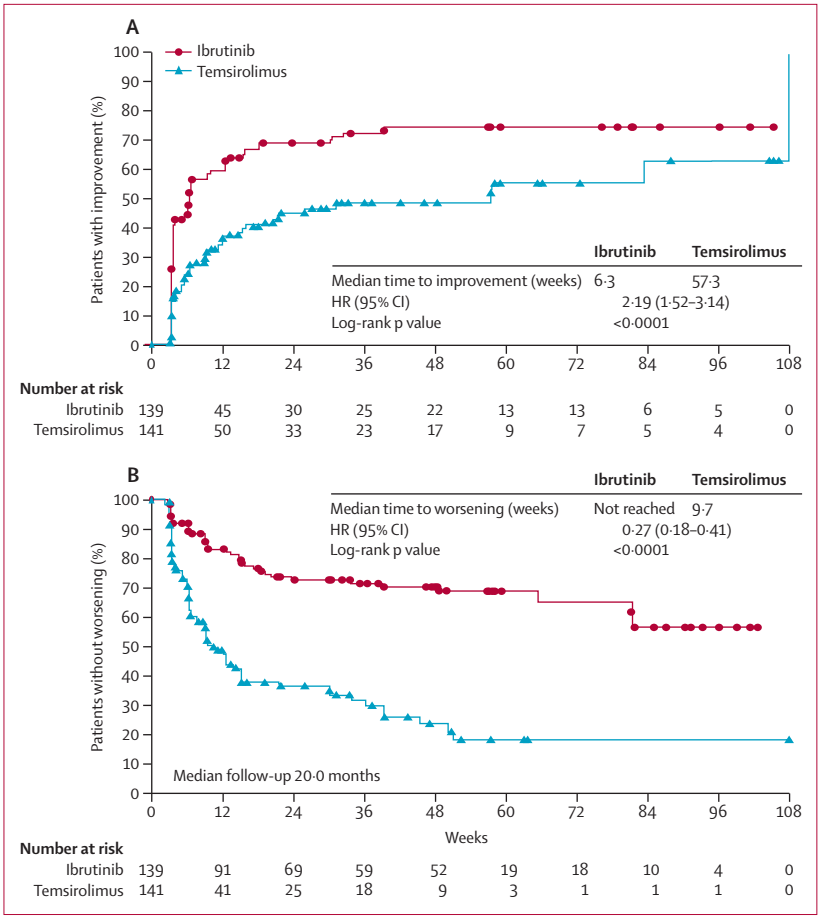

Figure 4: **Time to clinically meaningful improvement and time to worsening on the FACT-Lym lymphoma subscale in the intention-to-treat population**
(A) Time to clinically meaningful improvement on the FACT-Lym lymphoma subscale. (B) Time to worsening on the FACT-Lym lymphoma subscale. HR=hazard ratio.

	Ibrutinib (n=139)		Temsirolimus (n=139)	
	Any grade	Grade 3 or higher	Any grade	Grade 3 or higher
Haematological				
Thrombocytopenia	25 (18%)	13 (9%)	78 (56%)	59 (42%)
Anaemia	25 (18%)	11 (8%)	60 (43%)	28 (20%)
Neutropenia	22 (16%)	18 (13%)	36 (26%)	23 (17%)
Non-haematological				
Diarrhoea	40 (29%)	4 (3%)	43 (31%)	6 (4%)
Fatigue	31 (22%)	6 (4%)	40 (29%)	10 (7%)
Cough	31 (22%)	0	31 (22%)	0
Pyrexia	23 (17%)	1 (1%)	29 (21%)	3 (2%)
Nausea	20 (14%)	0	30 (22%)	0
Peripheral oedema	18 (13%)	0	31 (22%)	3 (2%)
Epistaxis	12 (9%)	1 (1%)	33 (24%)	2 (1%)
Stomatitis	4 (3%)	0	29 (21%)	5 (4%)

Data are n (%). Rates shown are not adjusted for differences in exposure (median treatment duration was 14·4 months for ibrutinib and 3·0 months for temsirolimus).

Table 2: **Common treatment-emergent adverse events (20% or more of patients) in the safety population**

survival of 14·6 months for ibrutinib and 6·2 months for temsirolimus. At 2 years, the progression-free survival rate is 41% in the ibrutinib group versus 7% in the temsirolimus group. Ibrutinib treatment also showed a significant improvement in overall response rate and improvement in time to next treatment, and was better tolerated.

The improvement in progression-free survival with ibrutinib was robust and showed high concordance between independent review committee-assessed and investigator-assessed outcomes. The independent review committee-assessed HR was 0·43 (95% CI 0·32–0·58; p<0·0001), with 184 independent review committee-confirmed progression-free survival events (ibrutinib 73, temsirolimus 111). The investigator-assessed HR was also 0·43 (95% CI 0·32–0·58; p<0·0001), with 182 progression-free survival events (ibrutinib 73, temsirolimus 109). Progression-free survival was also consistent in the preplanned subgroup analysis for most subgroups, although the benefit of ibrutinib was statistically not significant in patients with blastoid histology. However, the number of patients with this histology was low across the treatment groups, and interpretation of these results should be made with caution. Thus, analysis of data pooled from various studies is required to allow a more reliable interpretation of the role for ibrutinib in the treatment of patients with blastoid histology.

The patient-reported outcome data support the favourable benefit–risk data; ibrutinib was associated with greater and more rapid improvements, and also less worsening in lymphoma symptoms, as measured by the lymphoma subscale of the FACT-Lym. These results suggest that the superior efficacy results and preferable tolerability of ibrutinib are accompanied by better patient-reported lymphoma symptom responses, indicating significant clinical benefit for most patients with relapsed or refractory mantle-cell lymphoma.

Overall survival data showed a non-significant tendency towards improvement, despite the crossover of 32 (23%) patients from the temsirolimus group during the study. Subsequent treatments were required more frequently in the temsirolimus group than in the ibrutinib group. In fact, the crossover to an effective salvage treatment might have affected post-progression survival in the temsirolimus group. More patients died during treatment or within 30 days after the last ibrutinib dose, mostly due to disease progression. This is in light of the fact that more patients discontinued temsirolimus for adverse events after a median treatment duration of 3 months. Moreover, fewer patients died due to a treatment-emergent adverse event in the ibrutinib group versus the temsirolimus group in the first 6 months of treatment, and the number of treatment-emergent adverse events related to progressive disease in the ibrutinib group was low. Additionally, progression-free survival 2 results support the concept that the overall

benefit of ibrutinib is not negatively compromised by subsequent treatment.

The results in our comparator group are consistent with the expected outcomes previously reported for temsirolimus, supporting the strength of this study. Witzig and colleagues[17] enrolled 35 patients (with a median of three previous lines of therapy) into a phase 2 study with a weekly dose of 250 mg for the treatment of relapsed or refractory mantle-cell lymphoma. The overall response rate was 38% with one (3%) complete response and 12 (35%) partial responses. Median overall survival was 12 months.[17] Subsequently, a phase 2 study assessed a flat dose of 25 mg weekly for the treatment of relapsed or refractory mantle-cell lymphoma.[18] In this phase 2 study, 29 patients were enrolled with a median of four previous lines of therapy. The overall response rate was 41% with one (4%) complete response and ten (37%) partial responses, and a median overall survival of 14 months. Direct comparisons between our study and these phase 2 studies are restricted by the different dosing regimens adopted. Temsirolimus was approved in the European Union for relapsed or refractory mantle-cell lymphoma on the basis of a phase 3 study of two different doses of temsirolimus randomised against an investigator's choice of a single drug therapy regimen.[19] In the phase 3 study, which enrolled more heavily pretreated patients than the current study, the 175 mg and 75 mg dose of temsirolimus (equivalent to that used in this study) showed a median progression-free survival of 4·8 months, an overall response rate of 22%, and a median overall survival of 12·8 months, which are inferior to those of the current study. However, the median progression-free survival for patients who received the 175 mg and 75 mg dosing in the phase 3 study increased to 7·4 months for patients who had fewer than three previous lines of therapy. Our median overall survival for patients randomised to temsirolimus was notably higher than seen in the previous studies. This finding could be the result of improvements in supportive care and the availability of new experimental drugs and treatment combinations for salvage therapy since the publication of the previous trials. Efficacy outcomes for temsirolimus are consistent with the expected outcomes of patients treated with other drugs used for mantle-cell lymphoma such as bortezomib and lenalidomide (eg, overall response rates were 33% and 28% with a median progression-free survival of 6·5 months and 4 months, respectively).[27,28] The responses in the ibrutinib group of this study (progression-free survival 14·6 months, overall response rate 72%, complete response 19%) are consistent with previous phase 2 studies. Ibrutinib was approved following a single-arm phase 1b/2 study[13] that enrolled 111 patients at the same dose (560 mg orally daily) as our study. Progression-free survival (13·0 months), overall response rate (68%), and complete response rate (21%) were very similar to our results. Similarly, in a subsequent phase 2 study in patients with relapsed or refractory mantle-cell lymphoma who had progressed after two or more cycles of bortezomib therapy, an overall response rate of 63% and a complete response rate of 21% were reported.[15]

Analysis of the safety profile of ibrutinib 560 mg per day in patients with previously treated mantle-cell lymphoma yielded findings that were consistent with the known safety profile of ibrutinib in other clinical settings. Whereas the frequency of all-grade treatment-emergent adverse events and serious adverse events was similar between treatment groups, the toxicity profile is especially in favour of ibrutinib when adjusted for exposure. Despite a median treatment duration four times higher for ibrutinib, grade 3 or higher adverse events and drug-related serious adverse events were reported more frequently in the temsirolimus group.

Although this was an open-label study, we do not believe this study design introduced bias. The primary endpoint was assessed by an independent review committee that was masked to study treatment. Patients who discontinued study therapy for reasons other than progressive disease (such as an adverse event) were not censored at start of subsequent treatment. Thus, the effect of the unmasked nature of this study on the assessment of the primary endpoint was minimised. We cannot exclude the possibility that the investigators might have been affected by the study group when reporting adverse events. However, given the improvement in toxicity profile seen for ibrutinib, we do not believe this potential bias could be responsible for our safety conclusions.

The results of this phase 3 trial confirm the efficacy and favourable safety profile of ibrutinib as shown in previous phase 2 studies. It also confirms the positive benefit–risk ratio for ibrutinib as an effective targeted approach in relapsed or refractory mantle-cell lymphoma. The demographic characteristics at baseline were reflective of the target patient population, supporting the application of these results to the general mantle-cell lymphoma population. Long-term follow-up will be reported at study conclusion (the end of the study will occur when 80% of the randomly assigned patients have died, or 3 years after the last patient is assigned to treatment, or the funder terminates the study, whichever comes first). Future research should investigate ibrutinib-based combination approaches for patients with relapsed or refractory mantle-cell lymphoma and in front-line therapy.[29]

Contributors

JB, MD, GH, WJ, MT, FO, CR, S-GC, SS, ST, JV, MW-H, JDG, RSS, and SR were responsible for study conception and design, provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript writing, and manuscript approval. NB and MJ were responsible for the provision of study materials or recruitment of patients, collection and assembly of data, data analysis and interpretation, manuscript writing, and manuscript approval. IB-B, DC, and CJ were responsible for the provision of study materials or patients, collection and assembly of data, manuscript writing, and manuscript approval. AR was responsible for the study conception and design, data analysis and interpretation, manuscript writing, and manuscript approval. CE was responsible for data analysis

and interpretation, manuscript writing, and manuscript approval. SB was responsible for study conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing, and manuscript approval.

Declaration of interests

MD reports grants and personal fees from Janssen and Pfizer outside the submitted work. CJ reports grants from Janssen during the conduct of the study and personal fees from Janssen outside the submitted work. GH reports grants and personal fees from Pfizer and Celgene, and personal fees from Janssen outside the submitted work. MT and MJ report grants from Janssen outside the submitted work. CR reports personal fees from Janssen Cilag and personal fees from Pfizer outside the submitted work. CE, NB, AR, SB, SS, ST, and JDG are employees of Janssen Research & Development and hold stock in Johnson & Johnson outside the submitted work. JV is an employee of Janssen Biologics and holds stock in Johnson & Johnson outside the submitted work. IB-B, JB, DC, WJ, FO, S-GC, MW-H, and RSS declare no competing interests. SR reports grants and personal fees from Janssen and personal fees from Roche and Pharmacyclics outside the submitted work.

Acknowledgments

This study was funded by Janssen Research & Development. Writing assistance was provided by Michelle Olsher (PAREXEL, Hackensack, NJ, USA) and was funded by Janssen Global Services, LLC. We thank the patients who participated in this trial, their families, and the investigators and coordinators at each of the clinical sites. The investigators are listed in the appendix.

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