Ibrutinib for mantle cell lymphoma at first relapse: a United Kingdom real-world analysis of outcomes in 211 patients

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Summary

Ibrutinib is an established treatment for relapsed/refractory (R/R) mantle cell lymphoma (MCL) and clinical trial data supports use at second line compared to later relapse. We aimed to investigate outcomes and tolerability for ibrutinib when given second line in a real-world setting. Our multi-centre retrospective analysis included 211 R/R MCL patients, median age 73 years, receiving ibrutinib second-line within the United Kingdom's National Health Service. Overall response to ibrutinib was 69% (complete response 27%). The median progression-free survival (PFS) was 17·8 months (95% CI 13·1–22·2) and median overall survival (OS) 23·9 months (95% CI 15·0–32·8). Drug-related adverse event led to dose reduction in 10% of patients and discontinuation in 5%. In patients with progressive disease, accounting for 100 of 152 patients stopping ibrutinib, 43% received further systemic therapy. Post-ibrutinib rituximab, bendamustine and cytarabine (R-BAC) showed a trend toward improved survival compared to alternative systemic treatments (post-ibrutinib median OS 14·0 months, 95% CI 8·1–19·8, vs. 3·6 months, 95% CI 2·6–4·5, P = 0·06). Our study confirms the clinical benefit and good tolerability of ibrutinib at first relapse in a real-world population. Patients progressing on ibrutinib had limited survival but outcomes with R-BAC in select patients were promising.

Keywords: ibrutinib, mantle cell lymphoma, post-ibrutinib outcomes, clinical aspects.

Background

Mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin lymphoma which most commonly presents in older age and tends to follow an aggressive, multiply relapsing clinical course. Over the past 20 years therapeutic advances, including the emergence of several novel agents, have led to improved survival for MCL patients.[1,2] A crucial development has been ibrutinib, a first in class once a day Bruton's tyrosine kinase (BTK) inhibitor that demonstrated impressive response rates and a favourable side-effect profile in heavily pre-treated patients.[3]

Ibrutinib is now widely available as a treatment option in the relapsed, refractory setting but there remains no consensus on optimal timing within the treatment algorithm.[4] A pooled analysis of patients treated with ibrutinib in three clinical trials highlighted a significant benefit in progression-free survival (PFS) and overall survival (OS) for patients receiving ibrutinib at first relapse compared to those treated at later relapse (median PFS 25·4 months *versus* (vs.) 10·3 months) suggesting earlier use is most beneficial.[5–7] However, general applicability of trial findings to real-world populations enriched with frailer patients prone to drug toxicity is unknown, and uncertainties persist regarding post-ibrutinib outcomes. The largest study to date reported a median post-ibrutinib OS of only 5·8 months, although this may simply reflect a patient group where multiply-relapsed disease and short-lived responses to ibrutinib were common.[8]

Ibrutinib for relapsed MCL was made available on the National Health Service (NHS) in March 2015 for patients in England via the Cancer Drugs Fund. In January 2018, following National Institute for Health and Care Excellence (NICE) appraisal, reimbursement was approved in all United Kingdom (UK) patients if they had received only one previous line of therapy, effectively making this standard of care in the UK.[9]

In this retrospective cohort study, we have compiled and evaluated data on 211 patients with MCL receiving ibrutinib at first relapse treated on the NHS in the UK. We aimed to investigate PFS and OS benefit in a real-world patient group and provide insights on drug tolerability and survival outcomes following ibrutinib discontinuation. This is the first time post-ibrutinib outcomes have been reported in patients exclusively receiving treatment at first relapse.

Method

Centres across the UK were invited to contribute anonymised data to an NHS service evaluation (patient selection in Figure S1). To meet eligibility patients had to have relapsed or refractory MCL, received only one prior line of systemic therapy (excluding steroids or radiotherapy) and received at least 1 day of ibrutinib, which was commenced no earlier than 15th March 2015, when ibrutinib first became available

on the NHS for this indication, and no later than 30th June 2019. Centres were asked to submit data for all patients meeting eligibility criteria treated at their institution with any exceptions recorded. The database was locked in June 2020 for analysis.

Medical records were evaluated for clinical characteristics, pathology and radiology data and therapies used pre- and post-ibrutinib. Clinicians were asked to provide response and progression data according to Lugano classification.[10] Use of computer topography (CT) and positron emission topography (PET)/CT varied between institutions and bone marrow biopsy was not routinely performed to assess response meaning complete response is denoted by CR/CRu (complete response unconfirmed). Due to retrospective methodology, adverse events whilst on therapy were not graded and reporting was limited to episodes that required dose reduction or permanent cessation of ibrutinib.

PFS was defined as the time from day 1 of ibrutinib therapy until investigator assessed progression or death from any cause (event) or last date of clinical review with no evidence of progression (no event). Patients consolidated with allogeneic stem cell transplant were not censored at date of transplant. Overall survival was defined as the time from day 1 of ibrutinib therapy until death from any cause. Post-ibrutinib OS was defined as the date of cessation of ibrutinib until death from any cause, as previously adopted by Martin et al.[8]

Kaplan-Meier survival analyses, Cox regression and log-rank tests were used for time to event analyses. The proportional hazard assumption for each covariable was tested by time-dependent Cox model. Baseline characteristics of patients progressing on ibrutinib were stratified according to post-ibrutinib management and compared using logistic regression. Statistical analyses were performed in IBM SPSS Statistics for Windows version 24 (IBM Corp., Armonk, NY, USA).

The prespecified primary objective was PFS, secondary objectives included OS, incidence of ibrutinib discontinuation due to toxicity, incidence of ibrutinib dose reduction due to toxicity and OS after ibrutinib discontinuation for patients with progressive disease.

All patient data were anonymised at source and treated according to the principles of the declaration of Helsinki and the UK Data Protection Act (1998).

Results

Baseline patient characteristics

Patient data were returned on 211 eligible patients from 38 centres, including 14 academic sites and 24 district general hospitals (DGHs). The median age of patients at the start of ibrutinib was 73 years (range: 33–96), 70% were male. When starting ibrutinib the Eastern Cooperative Oncology Group

(ECOG) performance status (PS) was 0–1 in 76% (147/193) and 2–4 in 24% (46/193); Simplified Mantle cell lymphoma international prognostic index (sMIPI) group was low in 13% (19/142), intermediate in 41% (58/142) and high in 46% (65/142); 4% (8/211) had central nervous system (CNS) involvement. All patients received only one prior line of systemic therapy. Twenty-eight percent (60/211) received high-dose cytarabine based frontline therapy and 25% (53/211) had consolidation with haematopoietic stem cell transplant (HSCT). For comprehensive baseline characteristics see Table I.

Median PFS with frontline therapy was 21·4 months (95% CI 15·5–27·4). Fifty-two percent (109/211) had progression of disease within 24 months of treatment (early POD), including 38 patients (18%) with primary refractory disease.

Response rates and survival analysis

The overall response rate (ORR) to ibrutinib in evaluated patients was 69% (124/179) with complete response (CR/CRu) 27% (49/179) and partial response (PR) 42% (75/179). Of 32 patients without response data available 28 patients (88%) remained on ibrutinib after 6 months. At data-lock median follow-up of survivors by reverse censoring was 24 months (range 9–61 months), 118 patients had died, 59 remained on ibrutinib and 32 were alive having stopped ibrutinib (reasons: progressive disease [$n = 17$], allogeneic (allo) HSCT [$n = 10$], drug toxicity [$n = 4$], patient choice [$n = 1$]).

The median PFS was 17·8 months (95% CI 13·1–22·2) and the median OS was 23·9 months (95% CI 15·0–32·8) (Fig 1). PFS with ibrutinib exceeded PFS with frontline therapy in 40% (68/170) of evaluable patients. Sub-group Kaplan-Meier analyses of PFS and OS according to age, ECOG PS and duration of response to frontline therapy are displayed in Fig 2.

PFS and OS were explored in a univariable non-stratified Cox regression model by baseline characteristics. Older age, ECOG PS ≥ 2, blastoid histology and shorter duration of response to frontline therapy (progression within 24 months) were significantly associated with inferior PFS (Table II). The same pattern with OS was observed and raised lactate dehydrogenase (LDH) ratios and high white cell count (WCC) were also adverse predictors.

Additional analyses of PFS and OS were performed using important prognostic variables in a multivariable Cox regression model (Table III). The model revealed blastoid histology to be a significant independent adverse predictor for PFS and OS. Raised LDH and ECOG PS ≥ 2 were significant adverse predictors of OS but not PFS, possibly due to reduced sample size as hazard ratios remained similar. Older age was not independently associated with OS, again possibly limited by sample size, but showed no association with PFS. Early progression of disease with frontline therapy was not independently significant.

Table I. Baseline characteristics.

Characteristic	
Median age, years (range)	73 (33–96)
Male (*n* = 211)	147 (70%)
Performance status (*n* = 193)	
ECOG 0–1	147 (76%)
ECOG 2	36 (19%)
ECOG 3–4	10 (5%)
Lactate dehydrogenase ratio (*n* = 147)	
<1·0	75 (51%)
≥1·0	72 (49%)
White cell count (*n* = 197)	
$<10 \times 10^9/l$	137 (70%)
$\geq10 \times 10^9/l$	60 (30%)
Simplified MIPI group (*n* = 142)	
Low risk	19 (13%)
Intermediate risk	58 (41%)
High risk	65 (46%)
CNS disease (*n* = 211)	
Absent	203 (96%)
Present	8 (4%)
Histology* (*n* = 205)	
Non-blastoid	176 (86%)
Blastoid	29 (14%)
Ki67 immunohistochemistry* (*n* = 141)	
<30%	65 (46%)
≥30%	76 (54%)
Stage* (*n* = 208)	
I–II	14 (7%)
III–IV	194 (93%)
Frontline therapy (*n* = 211)	
R-CHOP	66 (31%)
High-dose cytarabine based regimen	60 (28%)
R-Bendamustine	45 (21%)
Chlorambucil ±R	15 (7%)
Fludarabine, cyclophosphamide ±R	9 (4%)
VR-CAP	5 (2%)
R-miniCHOP	4 (2%)
Other[¥]	7 (3%)
Stem cell transplant consolidation	
Autologous HSCT	50 (24%)
Allogeneic HSCT	3 (1%)

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisolone; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group performance status; HSCT, haematopoietic stem cell transplant; MIPI, mantle cell lymphoma international prognostic index; R, rituximab; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisolone. *recorded at diagnosis; [¥]rituximab, cyclophosphamide, vincristine, prednisolone *n* = 3; R-CHOP plus ifosfamide, etoposide and epirubicin *n* = 2; prednisolone, mitoxantrone, cyclophosphamide, etoposide, bleomycin, vincristine *n* = 1; etoposide *n* = 1.

In 8 patients with CNS involvement at start of ibrutinib the median PFS was 4·9 months (95% CI 0·0–10·5) and the median OS 5·5 months (95% CI 2·9–8·2).

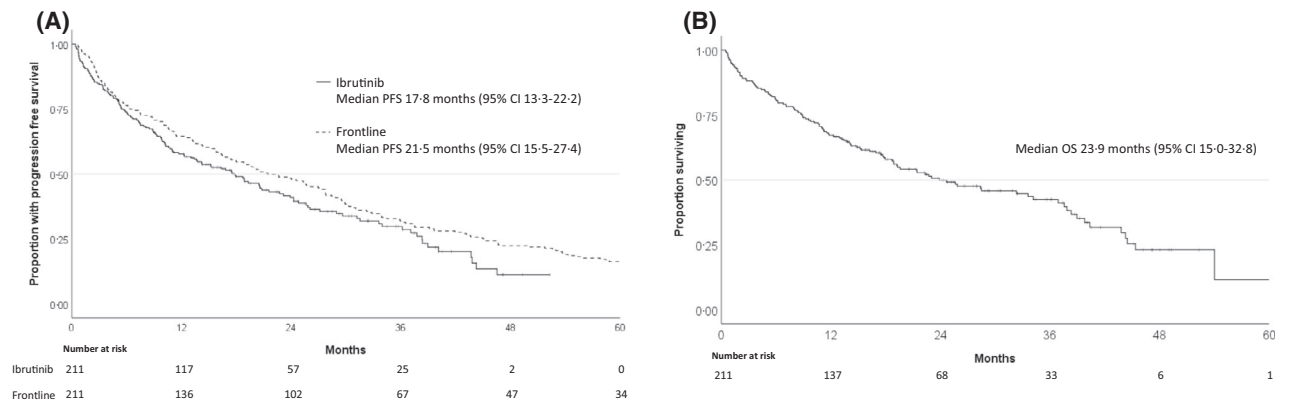**Fig 1.** Progression free survival (PFS) with ibrutinib versus PFS with frontline therapy (A) and Overall Survival (B).
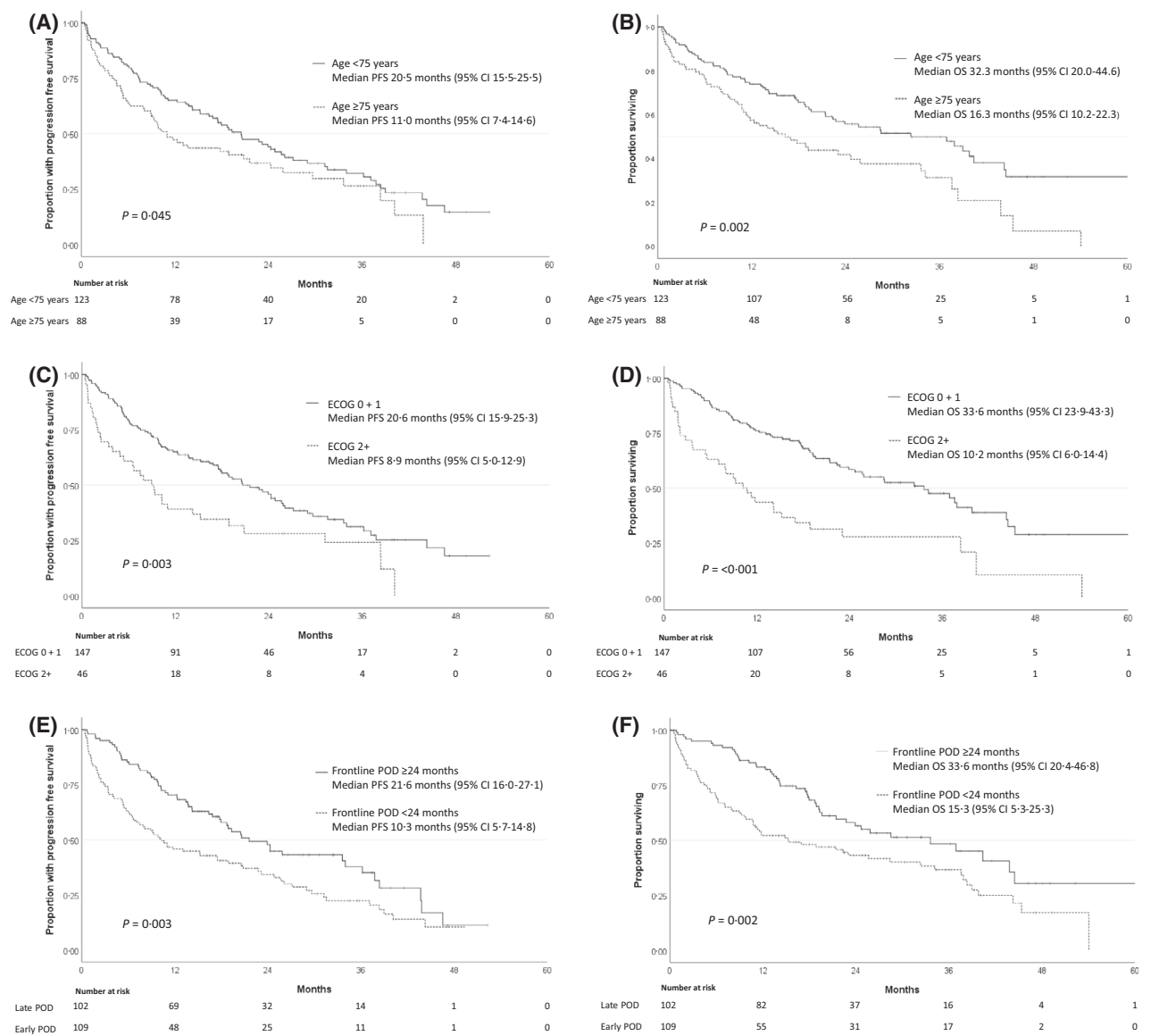

Fig 2. Progression free survival and overall survival stratified according to patient age (A,B), ECOG performance status (C,D) and duration of response to frontline therapy (E,F).

Table II. Univariable Cox regression analysis of PFS and OS according to baseline characteristics.

Characteristics		Patients, n	PFS HR (95% CI)	PFS P value	OS HR (95% CI)	OS P value
Age (for an increase of 10 years)		211	1·21 (1·03–1·42)	**0·020**	1·38 (1·15–1·65)	**0·001**
ECOG PS	0 + 1 vs. ≥2	147 vs. 46	0·56 (0·38–0·83)	**0·003**	0·41 (0·27–0·62)	**<0·001**
LDH ratio	<1·0 vs. ≥1·0	75 vs. 72	0·69 (0·47–1·03)	0·066	0·54 (0·35–0·84)	**0·006**
WCC, ×10⁹/l	<10 vs. ≥10	137 vs. 60	0·79 (0·55–1·14)	0·209	0·66 (0·45–0·97)	**0·036**
sMIPI risk	Low + Int. vs. High	77 vs. 65	0·69 (0·46–1·03)	0·066	0·55 (0·35–0·85)	**0·007**
Histology	Blastoid vs. non-blastoid	29 vs. 176	2·26 (1·47–3·47)	**<0·001**	2·43 (1·54–3·81)	**<0·001**
Ki67	<30% vs. ≥30%	64 vs. 77	0·74 (0·48–1·12)	0·155	0·83 (0·52–1·31)	0·412
Frontline therapy						
HD cytarabine	Yes vs. no	60 vs. 151	0·87 (0·61–1·25)	0·451	0·69 (0·46–1·04)	0·075
HSCT consolidation	Yes vs. no	53 vs. 158	0·75 (0·51–1·10)	0·143	0·60 (0·39–0·94)	**0·025**
Response to frontline						
Early PODs	Yes vs. no	109 vs. 102	1·65 (1·18–2·31)	**0·003**	1·81 (1·25–2·62)	**0·002**

Bold value indicates statistical significance of P values =<0·05

CI, confidence interval; CR/CRu, complete response/complete response unconfirmed; ECOG PS, Eastern Cooperative Oncology Group performance status; Early POD, progression of disease within 24 months; HD, high-dose; HR, hazard ratio; HSCT, haematopoietic stem cell transplant; Int., intermediate; OS, overall survival; PFS, progression-free survival; PR, partial response; sMIPI, simplified mantle cell lymphoma international prognostic index.

Table III. Multivariable Cox regression analysis of PFS and OS according to baseline characteristics.

Characteristics		Patients, n	PFS HR (95% CI)	PFS P value	OS HR (95% CI)	OS P value
Age (for an increase of 10 years)		140	1·04 (0·83–1·30)	0·741	1·24 (0·96–1·60)	0·108
ECOG PS	0 + 1 vs. ≥2	110 vs. 30	0·65 (0·40–1·06)	0·085	0·58 (0·34–0·98)	**0·042**
LDH ratio	<1·0 vs. ≥1·0	71 vs. 69	0·72 (0·47–1·11)	0·136	0·53 (0·33–0·86)	**0·010**
WCC, ×10⁹/l	<10 vs. ≥10	95 vs. 45	0·717 (0·46–1·12)	0·143	0·62 (0·38–1·01)	0·053
Blastoid histology	Yes vs. No	20 vs. 120	2·95 (1·72–5·07)	**<0·001**	3·40 (1·89–6·14)	**<0·001**
Frontline early POD	Yes vs. No	66 vs. 74	1·48 (0·96–2·26)	0·073	1·19 (0·74–1·91)	0·476

Bold value indicates statistical significance of P values =<0·05

CI, confidence interval; Early POD, progression of disease within 24 months; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression-free survival; WCC, white cell count.

Ibrutinib dose reductions and discontinuation

Nine patients (4%) commenced ibrutinib at a dose less than 560 mg o.d. because of frailty. Thirty patients (15%) underwent 31 dose reductions during treatment. In 25 cases the indication involved clinician reported drug-related adverse events including bleeding (5/31), cardiac (3/31) and gastrointestinal events (3/31) (full details Table IV).

In total, 152 patients discontinued ibrutinib at data lock with the majority due to progressive disease (100/152, 66%). Other indications for treatment discontinuation included: consolidation with alloHSCT 11% (17/152), drug-related adverse event 7% (10/152), co-morbidities 4% (6/152), and death whilst on therapy 12% (18/152) (Table IV). Causes of death included: sepsis (5 cases), subdural haematoma (1 case), thrombotic stroke (1 case), pulmonary embolus (1 case), post-surgery complications (1 case), heart failure (1 case) and 8 were unknown.

For patients stopping ibrutinib for adverse events median age at start of therapy was 78 years (range 68–89) and median duration of treatment was 12 months (range 1–28 months). For patients who died whilst on ibrutinib the median age at start of treatment was 78 years (range 68–93) and ECOG PS was ≥2 in 60% (9/15). The median duration of ibrutinib at time of death was 9 months (range 1–44 months).

Of the 17 patients stopping ibrutinib for consolidation with alloHSCT, the median age was 55 years (range 33–65). There were nine PFS events and seven deaths during follow-up with the median PFS 34·0 months (95% CI 8·8–59·1) and 24-month overall survival 56·6%.

Table IV. Ibrutinib dose reductions during therapy and indications for stopping therapy.

Indications	Number (%)
Dose reductions during therapy (*n* = 207)	
All indications	31 (15%)
Drug-related adverse event	25 (12%)
Bleeding	5
Haematological adverse event	4
Cardiac adverse event	3
Gastrointestinal adverse event	3
Rash	3
Fatigue	2
Liver dysfunction	2
Arthralgia	1
Cramps	1
Infection	1
Drug interaction	1 (<1%)
Frailty	3 (1%)
Unknown indication	2 (1%)
Indications for stopping ibrutinib (*n* = 151)	
Progressive disease	100 (66%)
Allogeneic HSCT	17 (11%)
Drug-related adverse event	10 (7%)
Gastrointestinal adverse event	3
Cardiac adverse event	2
Bleeding	1
General toxicity	1
Haematological adverse event	1
Infection	1
Rash	1
Frailty	3 (2%)
Other cancer diagnosis	2 (1%)
Medical co-morbidities	1 (<1%)
Death during treatment	18 (12%)

Post-ibrutinib outcomes in patients progressing through ibrutinib

Baseline characteristics of patients discontinuing ibrutinib due to progressive disease (*n* = 100) are listed in Table V. Of the 98 patients with available data, 56 patients (57%) received no additional systemic therapy after ibrutinib cessation and 42 patients (43%) received at least one additional course of treatment. Baseline characteristics of these two groups showed distinct trends. In a univariable analysis, younger age, ECOG PS 0–1 at start of ibrutinib and non-blastoid histology were strongly associated with the use of post-ibrutinib therapy (Table V). Patients who received post-ibrutinib systemic therapy tended to have better treatment responses *versus* patients who did not receive post-ibrutinib therapy, as evidenced by median PFS to frontline therapy (16·5 months, 95% CI 9·9–23·0, vs. 10·5 months, 95% CI 8·7–12·2, log-rank $P = 0·028$) and median PFS with ibrutinib (11·7 months, 95% CI 7·3–16·1, vs. 3·4 months, 95% CI 1·8–5·0, $P = 0·006$).

At data-lock 81 of 100 patients with progressive disease had died. The median follow-up from date of ibrutinib discontinuation for survivors was 13 months (range 0–29 months). The median OS from ibrutinib discontinuation was 1·4 months (95% CI 0·6–2·2). Patients receiving further systemic therapy had significantly improved outcomes (median post-ibrutinib OS 11·6 months, 95% CI 6·8–16·5, vs. 0·4 months, 95% CI 0·2–0·5, $P=<0·001$) (Fig 3A).

Post-ibrutinib systemic therapy consisted of rituximab, bendamustine, cytarabine (R-BAC) in 50% (21/42), rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone (R-CHOP) in 12% (5/42), rituximab, bendamustine (R-B) in 10% (4/42), and assorted chemotherapy combinations in 24% (10/42). Five patients who received R-BAC were consolidated with alloHSCT, and one patient who received R-B, transplanted in first remission, was consolidated with donor lymphocyte infusion. Five patients received fourth line therapy: 2 received R-BAC, one patient received lomustine, etoposide, chlorambucil, dexamethasone (DECC), one received fludarabine and one patient received a bispecific monoclonal antibody on clinical trial.

In total, 23 patients with a median age 68 years (range 57–77) received post-ibrutinib R-BAC. This group was younger than patients receiving other post-ibrutinib therapy but had similar responses to ibrutinib (Table SI). Those receiving R-BAC displayed a trend toward improved survival compared to patients receiving other therapies (median post-ibrutinib OS 14·0 months, 95% CI 8·1–19·8, vs. 3·6 months, 95% CI 2·6–4·5, $P = 0·06$) (Fig 3B).

Discussion

The pooled trial analysis of 370 patients reported by Rule et al.[5] highlighted a significant benefit in PFS and OS for patients with MCL receiving ibrutinib at first relapse compared to later relapse and our study is the first to evaluate how real-world outcomes support these data. It is notable that despite representing an unselected group, the response rates reported in our study appear equivalent to those in the pooled analysis. The median PFS is modestly reduced (17·8 months vs. 25·4 months) but exceeds the outcomes observed for patients receiving ibrutinib at later relapses on clinical trials. The median OS, however, demonstrates marked divergence (23·9 months vs. 61·6 months). A discrepancy most attributable to marked differences in patient demographics, particularly age and performance status (median age 73 years vs. 67 years; ECOG PS ≥ 2 in 24% vs. 6%).

Comparison with historical real-world data from the UK highlights the positive impact of ibrutinib. The Haematological Malignancies Research Network (HMRN) registry, covering a UK-based population of 4 million, observed survival trends in patients diagnosed with MCL between 2004 and 2015.[11] Of patients receiving second-line therapy, the median OS from start of treatment was only 10 months. Poor

Table V. Baseline characteristics of patients progressing on ibrutinib stratified according to post-ibrutinib management.

Characteristic	Overall* (n = 100)	No post-ibrutinib systemic therapy (n = 56)	Received post-ibrutinib therapy (n = 42)	OR (95% CI)	P value
Median age, years (range)	73 (44–92)	74 (46–92)	70 (44–85)	0·94 (0·89–0·98)	**0·011**
At start of ibrutinib					
ECOG PS ≥ 2	26 of 91 (29%)	21 of 52 (40%)	4 of 37 (11%)	0·18 (0·05–0·58)	**0·004**
Blastoid histology	24 of 100 (24%)	18 of 56 (32%)	5 of 42 (12%)	0·29 (0·10–0·85)	**0·024**
CNS involvement	6 of 100 (6%)	5 of 56 (9%)	1 of 42 (2%)	0·25 (0·03–2·21)	0·212
sMIPI high risk	37 of 74 (50%)	23 of 41 (56%)	12 of 31 (39%)	0·49 (0·19–1·28)	0·146
Response to prior therapy					
Frontline early POD	67 of 100 (67%)	41 of 56 (73%)	26 of 42 (62%)	0·60 (0·25–1·40)	0·235
Frontline median PFS, mo.	13·5 (8·5–18·6)	10·5 (8·7–12·2)	16·5 (9·9–23·0)		
ORR to ibrutinib (CR/CRu)	53% (18%)	51% (10%)	57% (29%)		
Median PFS to ibrutinib, mo.	6·7 (4·9–8·4)	3·4 (1·8–5·0)	11·7 (7·3–16·1)		

Bold value indicates statistical significance of P values =<0.05.

CNS, central nervous system; CR, complete response; Early POD, progression of disease within 24 months; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; PFS, progression-free survival; sMIPI, simplified mantle cell lymphoma international prognostic index. *Post-ibrutinib management in 2 patients unknown.
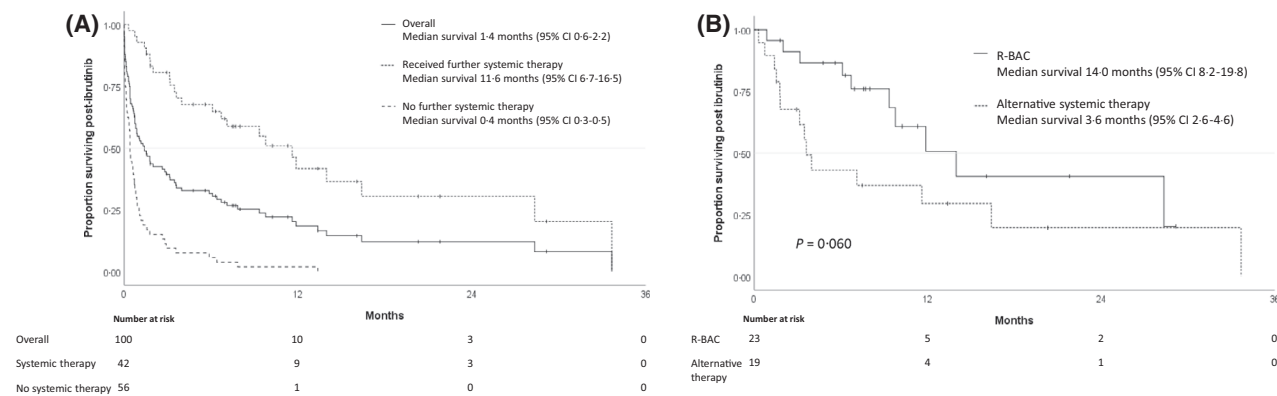
Fig 3. Post-ibrutinib overall survival for patients progressing on ibrutinib: received further systemic therapy versus no further systemic therapy (A) and received R-BAC versus alternative systemic therapies (B).

outcomes for older patients were notable, with median OS from date of diagnosis only 19 months for those aged ≥70 years. The high proportion of older patients in our study indicates widespread use of ibrutinib in the UK and the median OS from start of ibrutinib of 16 months for those age ≥75 years appears to represent an important breakthrough.

It has been observed that early POD following frontline therapy in younger MCL patients is an independent predictor for inferior survival at time of relapse, and this cohort had superior outcomes receiving second-line ibrutinib compared to chemotherapy.[12–13] In our study early POD was associated with inferior PFS and OS, but this association was lost in multivariable analysis indicating in our more heterogeneous population other variables were more predictive of survival.

Despite an older patient population tolerance to ibrutinib appears good, with discontinuation linked to drug-related adverse events similar to those reported in clinical trials. This is in contrast to real-world evidence from the United States where 21% of patients stopped ibrutinib due to drug-related adverse events.[14] The difference may relate to the restricted availability of effective alternative therapy in the UK, particularly other BTK inhibitors, which encourages clinicians to manage toxicity without stopping ibrutinib. The death rate during ibrutinib therapy was high relative to trials but similar to real-world data for ibrutinib in chronic lymphocytic leukaemia and likely relates to competing risks of death, with advanced age and poor performance status noted in many affected patients.[15]

The post-ibrutinib outcomes reported in our study require careful consideration. That only 43% of patients

progressing on ibrutinib received further systemic therapy appears low, especially compared to 70% in the cohort reported by Martin et al.[8] The reasons for this discrepancy likely relate to the older patient population and limited treatment options available compared to a cohort treated primarily at academic centres with access to clinical trials. Of interest, the rate of subsequent treatment in our study is similar to that reported in the HMRN registry, where only 39% of MCL patients received third line therapy, suggesting the general availability of ibrutinib has not altered this UK approach. In addition, with this historical HMRN cohort, where 16% received ibrutinib at third line or later, the median OS from the start of third line was only 7 months, indicating that the poor outcomes observed in this setting are not specific to ibrutinib. Promisingly, patients who received post-ibrutinib R-BAC in our study showed a strong trend to improved OS, a finding consistent with a recent study illustrating high response rates to R-BAC post BTK inhibitor (ORR 83%, CR/CRu 60%).[16]

It was not possible to access data on ibrutinib use at national level but as our series provides a balanced representation of academic centres and DGHs results should reflect all institutions where the drug is prescribed in the UK. Steps taken to mitigate inherent bias of retrospective methodology mean the extent of adverse events were only partially explored and inconsistent timing of response assessments mean data was not suitable for time-dependent analysis and should be interpreted carefully alongside prospective data. PFS data were similarly hindered but as the kinetics of progression in MCL is invariably rapid and easy to determine we believe results are representative of the real-world.

These limitations notwithstanding our findings consolidate the central role of ibrutinib in MCL therapy and support use at first relapse. However, with a third of patients progressing within 12 months and no survival plateau improved strategies are required. Studies have assessed giving ibrutinib alongside complimentary novel agents including lenalidomide, umbralisib and palbociclib.[17–19] To date, these have reported increased toxicity without an obvious benefit in outcome, but the combination with the BCL2 inhibitor venetoclax appears promising with phase II study reporting a CR rate of 72% and median PFS of 29 months.[20–21] A phase III trial comparing venetoclax plus ibrutinib with ibrutinib monotherapy is ongoing (SYMPATICO, NCT03112174). Second generation BTK inhibitors acalabrutinib and zanubrutinib have FDA approval in relapsed MCL and whilst evidence of improved efficacy is lacking, reduced off target effects offer potential for improved tolerability.[22]

MCL progressing through ibrutinib continues to represent a major clinical challenge. Our results further establish a role for R-BAC, but achieving durable responses appears dependent on consolidation with cellular therapies. This has traditionally been restricted to a minority of younger patients able to tolerate alloHSCT[23] but the impressive results for chimeric antigen receptor T-cell therapy in post BTK inhibitor MCL suggest this approach may soon be superseded.[24] However, it is not established if early results will translate into long-term disease-free survival and trial data may be difficult to replicate in real-world populations.

In summary, our study confirms the clinical benefit of ibrutinib monotherapy for MCL at first relapse. Comparison with historical data indicates a particular benefit in older patients and overall tolerability appears to be good. In the post-ibrutinib setting, OS is relatively short but treatment with R-BAC in select patients is promising. Developing ibrutinib combination therapies for high risk patients and more effective salvage therapies remains a priority.

Author contributions

RM, DL, NC and SR contributed to study design, data collection, data analysis and manuscript drafting. AAK contributed to data analysis and manuscript drafting. TAE, SB, AA, TC, HG, AM, SD, SH, OM, AR, DD, MRW, PM, GF, NP, RP, JL, MB, WO and RJ contributed to data collection and manuscript drafting.

Conflict of interest

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Flow chart displayingpatient identification for study.

Table SI. Baseline characteristics of patients receiving post-ibrutinib R-BAC versus patients receiving alternative systemic therapy.

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