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AML: DEVASTATING

WITH A FLT3 MUTATION: DISASTROUS

IN PATIENTS WITH AML,

A *FLT3-ITD* mutation drives progression and may lead to lower patient survival.[1-3]

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Prescribing information for: XOSPATA™ ▼ 40 mg film coated tablets (gilteritinib). **Indications:** Gilteritinib is indicated as monotherapy for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation. **Posology and administration:** Treatment with gilteritinib should be initiated and supervised by a physician experienced in the use of anti-cancer therapies. Before taking gilteritinib, relapsed or refractory AML patients must have confirmation of FMS-like tyrosine kinase 3 (FLT3) mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]) using a validated test. The recommended starting dose is 120 mg gilteritinib (three 40 mg tablets) orally once daily, with or without food, swallowed whole with water and should not be broken or crushed. Gilteritinib should be administered at about the same time each day. See *Special warnings and precautions for use* section on tests to be conducted prior to initiation e.g. blood chemistries, ECG & pregnancy test. Treatment should continue until the patient is no longer clinically benefiting from gilteritinib or until unacceptable toxicity occurs. Response may be delayed; therefore, continuation of treatment at the prescribed dose for up to 6 months should be considered to allow time for a clinical response. In the absence of a response (patient did not achieve a composite complete remission (CRc) after 4 weeks of treatment), the dose can be increased to 200 mg (five 40 mg tablets) once daily, if tolerated or clinically warranted. Gilteritinib may be re-initiated in patients following haematopoietic stem cell transplantation (HSCT), Planned HSCT: Interrupt treatment one week prior to administration of the conditioning regimen for HSCT. Treatment can be resumed 30 days after HSCT if engraftment was successful, the patient did not have grade ≥2 acute graft versus host disease and was in CRc. Elderly: No dose adjustment is required in patients ≥65 years of age. Gilteritinib is not recommended for use in patients with severe (Child-Pugh Class C) hepatic impairment. Please refer to SPC, section 4.2 for full instructions for use in hepatic & renal impairment. Paediatric population: The safety and efficacy of gilteritinib in children aged below 18 years has not yet been established. No data are available. Due to in vitro binding to $5HT_{2B}$, there is a potential impact on cardiac development in patients less than 6 months of age. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC. **Special warnings and precautions for use:** Differentiation syndrome: Gilteritinib has been associated with differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms and clinical findings of differentiation syndrome include fever, dyspnoea, pleural effusion, pericardial effusion, pulmonary oedema, hypotension, rapid weight gain, peripheral oedema, rash, and renal dysfunction. If differentiation syndrome is suspected, corticosteroid therapy should be initiated along with haemodynamic monitoring until symptom resolution. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, gilteritinib should be interrupted until signs and symptoms are no longer severe. Corticosteroids can be tapered after resolution of symptoms and should be administered for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. Resume gilteritinib at the same dose when signs and symptoms improve to Grade 2 or lower. Posterior reversible encephalopathy syndrome: There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving gilteritinib. PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, visual and neurological disturbances, with or without associated hypertension and altered mental status. If PRES is suspected, it should be confirmed by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of gilteritinib in patients who develop PRES is recommended. Prolonged QT interval: Gilteritinib has been associated with prolonged cardiac ventricular repolarisation (QT interval). QT prolongation can be observed in the first three months of treatment with gilteritinib. Therefore, ECG should be performed prior to initiation of treatment, on day 8 and 15 of cycle 1, and prior to the start of the next three subsequent months of treatment. Caution is warranted in patients with relevant cardiac history. Hypokalaemia or hypomagnesaemia may increase the QT prolongation risk. Hypokalaemia or hypomagnesaemia should therefore be corrected prior to and during gilteritinib treatment. Gilteritinib should be interrupted in patients who have a QTcF >500 msec.The decision to re-introduce gilteritinib treatment after an event of QT prolongation should be based on careful consideration of benefits and risks. Resume gilteritinib at a reduced dose (from 120 mg to 80 mg or from 200 mg to 120 mg) when QTcF interval returns to within 30 msec of baseline or ≤480 msec. Patients with QTcF interval increase by >30 msec on day 8 of cycle 1 should have a further ECG on day 9; if QTcF increase is confirmed gilteritinib dose should be reduced to 80 mg. If gilteritinib is re-introduced at a reduced dose, ECG should be performed after 15 days of dosing, and prior to the start of the next three subsequent months of treatment. In clinical studies, 12 patients had QTcF >500 msec. Three patients interrupted and re-initiated treatment without recurrence of QT prolongation. Pancreatitis: There have been reports of pancreatitis. Patients who develop signs and symptoms suggestive of pancreatitis should be evaluated and monitored. Gilteritinib should be interrupted and can be resumed at a reduced dose (reduced from 120 mg to 80 mg or from 200 mg to 120 mg) when the signs and symptoms of pancreatitis have resolved. Toxicity: If the patient experiences other Grade 3 or higher toxicity considered related to treatment, interrupt treatment until the toxicity resolves or improves to Grade 1. If deemed clinically appropriate gilteritinib can be resumed at a reduced dose (reduced from 120 mg to 80 mg or from 200 mg to 120 mg). Interactions: Co-administration of CYP3A/P-gp inducers may lead to decreased gilteritinib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of gilteritinib with strong CYP3A4/P-gp inducers should be avoided. Caution is required when concomitantly prescribing gilteritinib with medicinal products that are strong inhibitors of CYP3A,P-gp and/or breast cancer resistant protein (BCRP) (such as, but not limited to, voriconazole, itraconazole, posaconazole and clarithromycin) because they can increase gilteritinib exposure. Alternative medicinal products that do not strongly inhibit CYP3A, P-gp and/or BCRP activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for toxicities during administration of gilteritinib. Gilteritinib may reduce the effects of medicinal products that target $5HT_{2B}$ receptor or sigma nonspecific receptors. Therefore, concomitant use of gilteritinib with these products should be avoided unless use is considered essential for the care of the patient. Embryofoetal toxicity and contraception: Pregnant women should be informed of the potential risk to a foetus. Females of reproductive potential should be advised to have a pregnancy test within seven days prior to starting treatment with gilteritinib and to use effective contraception during treatment with gilteritinib and for at least 6 months after stopping treatment. Women using hormonal contraceptives should add a barrier method of contraception. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of gilteritinib. **Interactions:** Gilteritinib is primarily metabolised by CYP3A enzymes, which can be induced or inhibited by a number of concomitant medicinal products. See Special Warnings and Precautions for Use section above for further information on this and the effects of gilteritinib on products that target $5HT_{2B}$ receptor or sigma nonspecific receptors. *Gilteritinib as an inhibitor or inducer:* gilteritinib is not an inhibitor or inducer of CYP3A4 or an inhibitor of MATE1 *in vivo*. Gilteritinib is an inhibitor of P-gp, BCRP and OCT1 (organic cation transporter 1) *in vitro*. As no clinical data is available, it cannot be excluded that gilteritinib could inhibit these transporters at a therapeutic dose. Caution is advised during co-administration of gilteritinib with substrates of P-gp (e.g., digoxin, dabigatran etexilate), BCRP (e.g., mitoxantrone, methotrexate, rosuvastatin) and OCT1 (e.g., metformin). **Fertility, pregnancy and lactation:** Pregnancy: Gilteritinib is not recommended during pregnancy and in women of childbearing potential not using effective contraception. See Special Warnings and Precautions for Use section above for information on pregnancy testing and contraception. Breastfeeding: Breastfeeding should be discontinued during treatment with gilteritinib and for at least two months after the last dose. Fertility: There are no data on the effect of gilterinitib on human fertility. **List of adverse reactions:** *Prescribers should consult the SPC for full information on adverse events* **List of adverse reactions:** Very common (≥1/10): Dizziness, Hypotension, Cough, Dyspnoea, Diarrhoea, Nausea, Constipation, Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood creatine phosphokinase increased, Blood alkaline phosphatase increased, Pain in extremity, Arthralgia, Myalgia, Fatigue, Peripheral oedema and Asthenia. Common (≥1/100 to <1/10): Anaphylactic reaction, Electrocardiogram QT prolonged, Pericardial effusion, Pericarditis, Cardiac failure, Differentiation syndrome, Musculoskeletal pain, Acute kidney injury and Malaise. Serious adverse reactions: The most frequent serious adverse reactions noted from evaluation of 319 patients with relapsed or refractory AML who have received at least one dose of 120 mg gilteritinib were acute kidney injury, diarrhoea, ALT increased, dyspnea, AST increased and hypotension. Other clinically significant serious adverse reactions included differentiation syndrome, electrocardiogram QT prolonged and posterior reversible encephalopathy syndrome. **Overdose:** There is no known specific antidote for gilteritinib. In the event of an overdose, treatment should be stopped. Patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic and supportive treatment initiated, taking into consideration the long half-life estimated at 113 hours. **Cost (excluding VAT):** United Kingdom (UK): XOSPATA 40 mg film-coated tablets x 84: £14,188.00. **Legal classification:** POM. **Marketing authorisation number:** Great Britain (GB): PLGB 00166/0425. Northern Ireland NI: EU/1/19/1399/001. **Marketing authorisation holder:** GB: Astellas Pharma Ltd., 300 Dashwood Lang Road, Bourne Business Park, Addlestone, United Kingdom, KT15 2NX. NI: Astellas Pharma Europe B.V. Sylviusweg 62, 2333 BE Leiden, The Netherlands. **Date of preparation:** March 2023. **Document number:** MAT_UK_XOS_2023_00039. **Further information available from:** Astellas Pharma Ltd., Medical Information: 0800 783 5018.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Astellas Pharma Ltd. on 0800 783 5018.

AML=acute myeloid leukemia; FLT3=FMS-like tyrosine kinase 3; ITD=internal tandem duplication.

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SHORT REPORT

Haematological Malignancy - Clinical

Death from mantle cell lymphoma limits sequential therapy, particularly after first relapse: Patterns of care and outcomes in a series from Australia and the United Kingdom

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Summary

Mantle cell lymphoma (MCL) is a B-cell non-Hodgkin lymphoma characterised by a heterogeneous clinical course. Patients can often receive sequential treatments, yet these typically yield diminishing periods of disease control, raising questions about optimal therapy sequencing. Novel agents, such as chimeric antigen receptor T-cell therapies and bispecific antibodies, show promise in relapsed MCL, but are often reserved for later treatment lines, which may underserve patients with aggressive disease phenotypes who die early in the treatment journey. To assess the problem of patient attrition from lymphoma-related death limiting sequential treatment, we performed a multicentre retrospective cohort analysis of 389 patients treated at Australian and UK centres over a 10-year period. Deaths from MCL increased after each treatment line, with 7%, 23% and 26% of patients dying from uncontrolled MCL after first, second and third lines respectively. Patients with older age at diagnosis and early relapse after induction therapy were at particular risk of death after second-line treatment. This limitation of sequential treatment by lymphoma-related death provides support for the trial of novel therapies in earlier treatment lines, particularly in high-risk patient populations.

KEYWORDS
lymphoid malignancies, lymphomas, new drugs for lymphoma

INTRODUCTION

Mantle cell lymphoma (MCL) is a B-cell non-Hodgkin lymphoma characterised by dysregulation of cyclin genes, which contributes to oncogenesis. Despite therapeutic advances and the ability to induce long remissions, MCL is generally considered an incurable malignancy. Patients may receive multiple therapies throughout their treatment course; however, the journey is often characterised by progressively shorter periods of disease control.[1] New treatments are continually emerging, yet the optimal sequencing of these therapies is not defined. Most recently, novel targeted and immunotherapeutic agents have shown significant promise in inducing complete responses in patients with multiply relapsed disease. CAR T-cell therapies, such as brexucabtagene autoleucel and lisocabtagene maraleucel, are reported to achieve deep remission in the majority of patients failing bruton tyrosine kinase inhibitor (BTKi) therapy.[2,3] T-cell redirecting bispecific antibodies have similarly shown promise in this context.[4] Currently, however, the use of novel immunotherapeutics is mostly limited to later lines of treatment, which potentially misses an opportunity to utilise these effective agents in patients with more aggressive disease phenotypes.[5] In particular, patients who die early from uncontrolled MCL are underserved by this paradigm as they do not reach later treatment lines.

While real-world retrospective studies have been pivotal in defining areas of need in MCL,[6–10] very few examine patient attrition after each line of treatment. Where information is available, it suggests that a significant proportion of patients die from MCL prior to reaching a third line of therapy.[10,11] This is an important consideration when determining the optimal sequencing of novel therapies to obtain the most benefit from these agents. In this multicentre retrospective study, we aim to describe the longitudinal experience of 389 patients diagnosed with MCL over a 10-year period. We describe event rates following each line of therapy and subsequent treatment patterns, and focus on the proportion of patients not proceeding to a further treatment and the reasons for this.

METHODS

Patients aged ≥18 years with MCL diagnosed between 1 January 2010 and 1 January 2020 were identified from local and multi-institutional databases at 11 Australian and 1 UK sites. Three hundred and four patients were identified from Australia and 85 from the United Kingdom. The study was undertaken by independent investigators collaborating via the Australasian Lymphoma Alliance, a working group of lymphoma clinicians and scientists. Data were sourced from a mixture of treatment settings, including local hospitals, major metropolitan services and quaternary referral centres. Data collected included baseline patient characteristics, stage, histological subtype, Mantle Cell Lymphoma Prognostic Index (MIPI), treatment and response details, dates of relapse or progression, date of death or last follow-up and cause of death. Responses were assessed according to Lugano 2014 criteria by local site investigators.[12]

Progression-free survival (PFS) was defined as the time from treatment commencement to progression or death from any cause. Overall survival (OS) was defined as the time from treatment commencement to death from any cause. Survival analyses were performed for each treatment phase individually using the Kaplan–Meier method with censoring at time of last follow-up. Median follow-up was calculated using the reverse Kaplan–Meier method. A subset of patients were the focus of comparative statistical tests, namely those that were free from death from MCL ($n = 127$) and those that died from MCL ($n = 23$) after second-line therapy. For the variables of interest, statistical tests were conducted to assess differences between these two groups. Categorical variables were compared using the chi-squared test, continuous variables using the Wilcoxon rank sum and survival analyses using the log-rank test. Multivariate analysis of clinically and statistically significant variables on univariate analysis was performed using logistic regression. All statistical analyses were performed using STATA v16 (College Station, TX). The study was conducted under the approval of the Peter MacCallum Cancer Centre Human Research Ethics Committee.

RESULTS

A total of 389 patients were included in the study, with a median age of 64 (range 40–90) years and median follow-up of 5.1 (range 0.1–11.4) years (Table 1). Eleven per cent had blastoid morphology; *TP53* and Ki67 expression data were not available. Treatment details, events and patient flow are presented in the consort diagram (Figure 1).

Treatment patterns and outcomes of first-line treatment

In total, 362 patients received induction treatment. Cytarabine-containing regimens were the most frequently utilised induction (43%), followed by R-CHOP (25%) and bendamustine–rituximab (12%). Fifty-eight patients (16%) were initially managed with a 'watch and wait' approach before receiving active therapy, with median time to treatment in this group of 343 days (range 16–2231 days). One hundred and seventy-seven (49%) patients received autologous stem cell transplant (ASCT) in first response. Twenty-seven patients (7%) received no induction treatment; 6 patients received initial palliative care and the remaining 21 were monitored and did not receive therapy with a median of 4.4 years of observation.

The overall response rate to induction therapy was 82%, with 66% of patients achieving complete response. Median PFS after induction therapy was 3.9 years and median overall survival was 8.5 years (Figure 2A,B). There were a total of

TABLE 1 Characteristics of treated patients and comparison of patients treated with second-line therapy.

Characteristic	All treated patients $N=362$	Patients who received second-line treatment $N=150$		
		Free from death from MCL ($n=127$)	Death from MCL before third-line treatment ($n=23$)	p-Value
Age at diagnosis Median years (Range)	64 (40–90)	63 (40–87)	72 (53–88)	**0.001**[a]
Female sex, *n* (%)	101 (28%)	29 (23%)	6 (26%)	0.7
Histology, *n* (%)				
Nodular	26 (11%)	12 (13%)	1 (6%)	0.2
Diffuse	18 (8%)	5 (5%)	6 (35%)	**0.001**
Pleomorphic	13 (6%)	5 (5%)	2 (11%)	0.2
Blastoid	26 (11%)	14 (15%)	2 (11%)	0.4
NOS	152 (65%)	56 (61%)	6 (35%)	**0.03**
Not available	127	35	6	
MIPI category at diagnosis, *n* (%)				
Low	58 (25%)	24 (29%)	0 (0%)	**0.01**
Int	73 (31%)	32 (38%)	3 (18%)	0.1
High	105 (45%)	28 (33%)	14 (82%)	**0.001**[a]
Unknown	126	43	6	
Initial watch and wait approach, *n* (%)	58 (16%)	25 (20%)	2 (9%)	0.2
Type of induction, *n* (%)				
ARA-C containing	168 (46%)	53 (42%)	5 (22%)	**0.04**[a]
R-CHOP-like	97 (27%)	42 (33%)	10 (43%)	0.2
Bendamustine–rituximab	44 (12%)	14 (11%)	4 (17%)	0.2
BTKi containing	23 (6%)	4 (3%)	1 (4%)	0.4
Other	30 (8%)	14 (11%)	3 (13%)	0.4
Complete response after induction, *n* (%)	238 (66%)	76 (60%)	11 (48%)	0.3
ASCT in first response, *n* (%)	177 (49%)	48 (38%)	4 (17%)	**0.003**[a]
Median PFS after induction, months (95% CI)	45 (41–54)	26 (20–34)	10 (6–19)	**0.001**
POD12, *n* (%)	85 (23%)	31 (24%)	12 (52%)	**0.007**
POD24, *n* (%)	144 (40%)	58 (46%)	18 (78%)	**0.004**[a]
Type of second-line therapy, *n* (%)	-			
Chemotherapy		40 (32%)	6 (26%)	0.3
BTKi monotherapy		56 (44%)	14 (61%)	0.07
BTKi combination		23 (18%)	2 (9%)	0.1
CD20 antibody alone		4 (4%)	0 (0%)	0.2
Radiotherapy		3 (2%)	0 (0%)	0.2
Other		1 (1%)	1 (4%)	0.08
Median PFS after second-line therapy, months (95% CI)	-	17 (12–35)	4 (1–8)	**0.001**

Bold values represent statistically significant values with $p<0.05$.

Abbreviations: ARA-C, cytarabine; ASCT, autologous stem cell transplant; BTKi, bruton tyrokine kinase inhibitor; MIPI, mantle cell lymphoma international prognostic index; NOS, not-otherwise specified; PFS, progression free survival; POD12, progression of disease within 12 months; POD24, progression of disease within 24 months; R-CHOP, rituximab, cyclosphosphamide, doxorubicin, vincristine, prednisolone.

[a]Included in multivariate analysis (Table S1).

204 events following commencement of induction treatment (56% of patients), consisting of 161 instances of progressive disease and 43 deaths (Figure 1). A total of 150 patients received a second-line therapy. Eleven patients progressed post-induction treatment but had not required a subsequent treatment at the time of data cut-off, with median

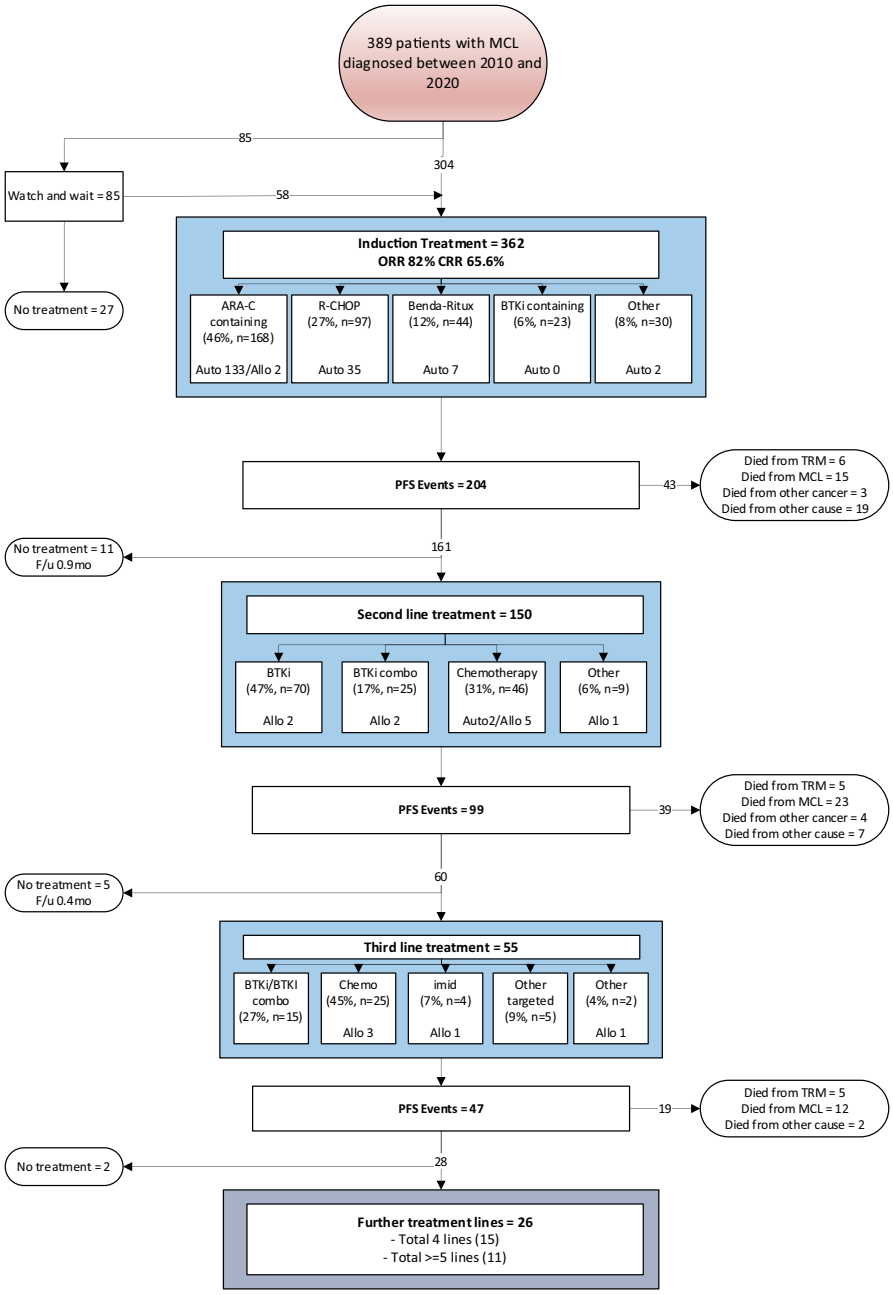

FIGURE 1 Consort diagram summarising patterns of treatment, relapse and survival. ARA-C, cytarabine; BTKi, bruton tyrosine kinase inhibitor; CRR, complete response rate; MCL, mantle cell lymphoma; ORR, overall response rate; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone; TRM, treatment-related mortality.

post-progression follow-up in this group of 0.9 months. Causes of death were MCL in 15 patients (35%), toxicity from treatment in 6 patients (14%), other malignancy in 3 patients (7%) and other causes in 19 (44%).

Outcomes following second-line treatment

Second-line treatments were administered in 150 patients and included BTKis in the majority (63%), 70 as monotherapy (47%) and 25 (17%) in combination (predominantly with venetoclax, $n = 17$). The remaining patients received cytotoxic chemotherapy (31%) or other various treatments (6%), including lenalidomide or single agent rituximab. Two patients received ASCT in second response, while 10 patients received allogeneic transplantation.

Median PFS after second-line treatment was 1.2 years and OS 2.5 years (Figure 2A,B). In patients who received chemotherapy as first line, the use of BTKi second line was associated with improved overall survival (Figure 2C; $p = 0.047$). Following second-line treatment, there were 99 events, consisting of 60 progression events and 39 deaths. Causes of death were predominantly due to MCL (23/39; 59%), with the remainder of deaths attributed to treatment-related

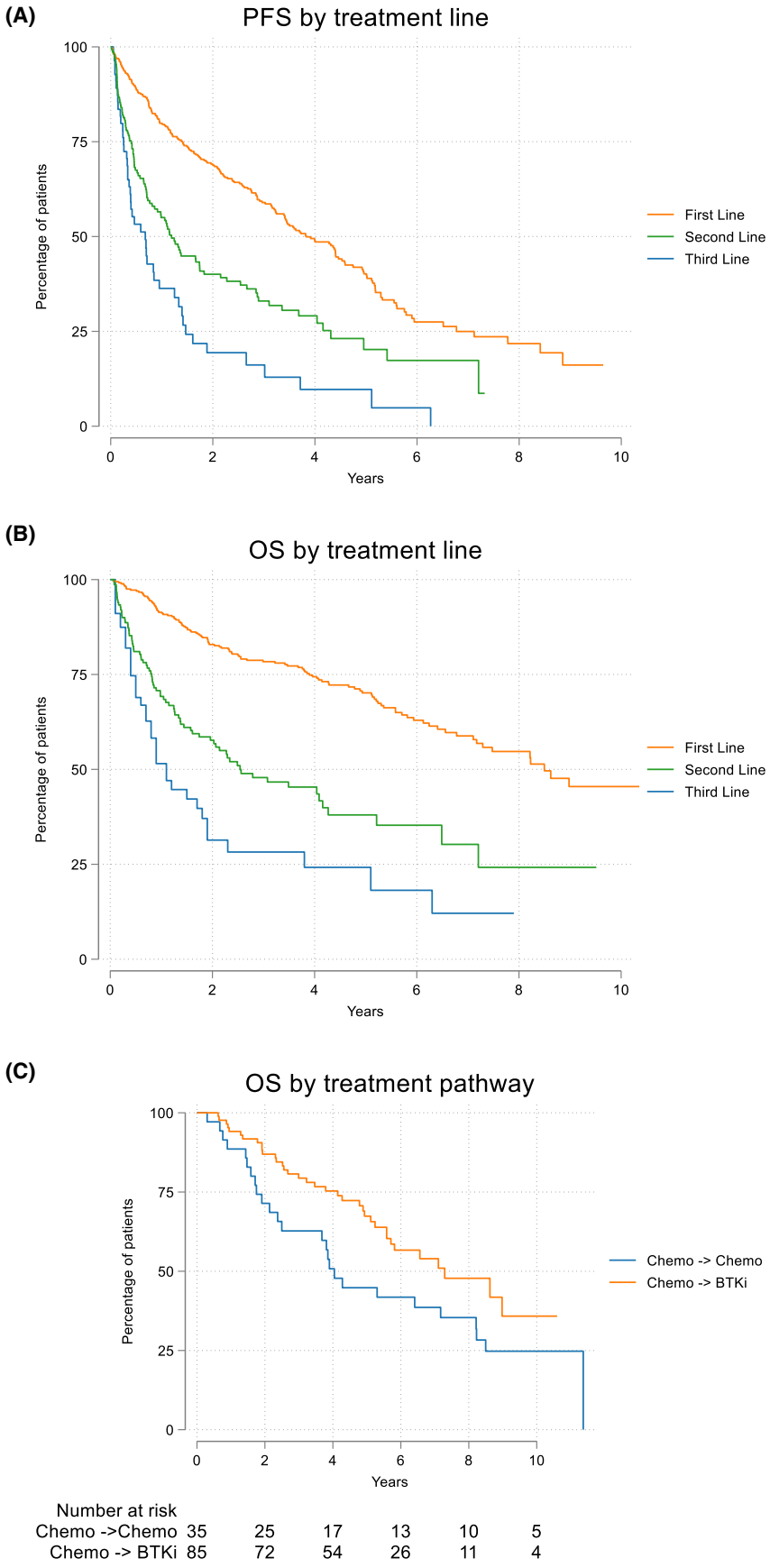

FIGURE 2 (A) Progression-free and (B) overall survival by treatment line. (C) Overall survival by the treatment pathway.

mortality in 5/39 (13%), other malignancies in 4/39 (10%) and other causes in 7/39 (18%).

Outcomes following subsequent therapies

Of the 60 surviving patients with progressive disease, 55 received third-line therapy, with 47 experiencing an event. Median PFS was 8.4 months and OS 14 months (Figure 2A,B). Deaths accounted for 19 of the 47 events (40%), and death from MCL was the most common cause (12/19; 63%). Twenty-six patients were able to receive a subsequent line of treatment with median PFS of 8.4 months.

Deaths from mantle cell lymphoma

As a proportion of all events occurring after a treatment line, deaths from MCL progressively increased with each therapeutic intervention (Figure S1). Following induction treatment, death from MCL accounted for 7.3% (14/204) of events. The vast majority of events post induction were progression events and most patients were able to receive a subsequent treatment (150/204; 74%). Following second-line treatment, the proportion of deaths from MCL accounted for 23% (23/99) of events and only 55% (55/99) of patients experiencing an event received a subsequent treatment. This was similar after third-line therapy, with 25% of patients experiencing death from MCL and 55% (26/47) receiving a subsequent treatment.

Exploring specifically the 150 patients who embarked on second-line treatment, patients who died from MCL prior to receiving further therapy were older, had higher MIPI scores at baseline and were less likely to have received cytarabine containing first induction or ASCT (Table 1). This patient group also had significantly inferior outcomes after induction treatment, with PFS of 9.6 months versus 2.2 years and proportions of POD12 (progression of disease within 12 months) and POD24 (progression of disease within 24 months) were significantly higher. On multivariate analysis, only age and POD24 remained predictive of death from MCL (Table S1). Despite receiving similar second-line therapies, clinical deterioration and death occurred early at a median of 3.6 months.

DISCUSSION

Our data suggest that the majority of patients who progress after first-line chemoimmunotherapy are able to receive a subsequent treatment. Death from MCL prevents the initiation of further treatment in only a small minority of patients who progress after induction therapy. However, once a patient moves on to a second treatment, up to a quarter of patients may die from MCL without being able to receive further treatment, and a similar proportion after subsequent lines. Results from our cohort largely support those from a similar Nordic/European collaboration, in which 28% of patients embarking on second-line therapy died from MCL prior to receiving a third treatment.[11]

We argue that the high death rate from MCL after second-line treatment, often very early after treatment initiation, represents a particular area of need and provides a rationale to evaluate earlier use of novel agents that are associated with high rates of deep and durable response. We hypothesise the area of need will be even higher in patients who progress after front-line BTKi, which may become a new standard of care.[13] In patients embarking on second-line treatment, possible predictive factors for death from MCL included older age, a high baseline MIPI score, use of less intensive first-line induction regimen and a history of early disease progression (POD12 and POD24). In particular, older age and POD24 were significant on multivariate analysis. These factors may be useful in defining the patient group who may benefit the most from trials of novel treatments in the second line.

Our study is retrospective in nature and carries the caveats of this design. We did not have access to molecular studies, such as *TP53* mutations, which are an established mechanism to identify patients at risk of early treatment failure.[14] Further examination of prospective studies would be useful in this respect. Nonetheless, this longitudinal survey of patient treatment journeys serves to describe the treatment patterns in Australia and United Kingdom and highlight the considerable issue of high rates of lymphoma-associated death after first relapse, which may limit the applicability and ultimately the potential benefit of novel therapies if they were to only remain available in later lines of therapy.

AUTHOR CONTRIBUTIONS

Adrian Minson and Michael Dickinson conceived of the study, and Adrian Minson, Michael Dickinson and Eliza Hawkes designed the analysis. Adrian Minson performed the analysis, and Adrian Minson and Michael Dickinson wrote the paper. Eliza Hawkes, Nada Hamad, Pietro Di Ciaccio, Dipti Talaulikar, Matthew Ku, Sumita Ratnasingam, Chan Cheah, Costas K. Yannakou, Mark Bishton, Zi Yun Ng, Shivam Agrawal, Andrew McQuillan, Ashley Beekman, Anna Johnston, Emily Choong, Kimberly Wong and James McQuillan compiled patient data. All authors contributed to review and approval of the manuscript.

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CONFLICT OF INTEREST STATEMENT

AM has received travel support from Novartis, honoraria from Roche and research funding from Roche, AbbVie and Novartis. MD has received honoraria and consulting fees from Roche, BMS, Novartis, Kite, Gilead, NKARTA, AdiCet Bio, Interius, Janssen, and research funding from Roche, Novartis,

Kite, Gilead, MSD, Takeda and Celgene. EH served on an advisory board for Roche, Antengene, BMS, Gilead, Astra Zeneca, Janssen, Novartis, MSD, Specialist Therapeutics has received research funding from BMS, Merck, Astra Zeneca, Roche and travel funding from Astra Zeneca. CYC has received honoraria from BMS, Roche, Novartis, AstraZeneca, MSD, Janssen, Eli Lilly, TG therapeutics and Beigene and has received research funding from BMS and Roche. MB has received honoraria from Tevapharma, Celltrion, consulting fees from Lilly, Incyte, Roche and Beigene and travel support from Roche. PDC has received honoraria from Janssen. NH has served on an advisory board for Novartis. DT has received honoraria from Janssen, Beigene, Roche, EUSA, CSL, Amgen, Takeda, Novartis and Antengene, and research funding from Roche, Janssen and Takeda. The remaining authors declare no conflicts of interest.

ETHICS STATEMENT

The study was conducted under the approval of the Peter MacCallum Cancer Centre Human Research Ethics Committee.

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SUPPORTING INFORMATION

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

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