REVIEW ARTICLE

“The End of the Golden Weather”: therapeutic strategies for mantle cell lymphoma relapsed or refractory to covalent BTK inhibitors

Brian T. Grainger[1] and Chan Y. Cheah[1,2,3]

[1]Department of Haematology, Sir Charles Gairdner Hospital; [2]Linear Clinical Research and [3]Medical School, University of Western Australia, Nedlands, WA, Australia

Correspondence: C.Y. Cheah
chan.cheah@health.wa.gov.au

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Abstract

Mantle cell lymphoma (MCL) is a subtype of non-Hodgkin lymphoma, often characterized by a pattern of continued relapse after front-line chemoimmunotherapy. Although patients are usually able to regain durable disease control with covalent Bruton’s tyrosine kinase inhibitors (cBTKi) at first relapse, it is now appreciated that such responses are often not sustained and the management of such patients represents a significant area of unmet need. There is an imperative to better understand resistance mechanisms and identify high-risk subsets of patients for whom cBTKi responses may be particularly short. Allogeneic stem cell transplant has an established role in appropriate candidates; however, contemporary consensus is to preferentially offer chimeric antigen receptor (CAR) T-cell therapy. In this Review, we consider the available data on both existing and emerging treatment options, including non-covalent BTK inhibitors, bispecific antibodies, antibody-drug conjugates and Bcl-2 inhibitors, and propose a treatment strategy, prioritizing clinical trials where available.

Introduction

Mantle cell lymphoma (MCL) is an uncommon subtype of non-Hodgkin lymphoma previously considered to have a poor prognosis and characterized by a pattern of continued relapse in the majority of patients.[1] The development of covalent Bruton’s tyrosine kinase inhibitors (cBTKi) has improved the management of relapsed and refractory (R/R) MCL over the last decade. Their utility in the setting of first relapse following front-line chemoimmunotherapy and autologous stem cell rescue is now well established,[2] including in real-world populations enriched for unfit and trial-ineligible patients.[3] The rates of complete response (CR) reported in phase II studies after a median of two prior lines of therapy were 21% with ibrutinib,[4] 43% with acalabrutinib,[5] and 77.9% with zanubrutinib.[6] Pooled analyses from longer term follow-up has demonstrated a median progression-free survival (PFS) of approximately 13 months, extending up to 26 months when these agents are used specifically in the setting of first relapse.[7,8]

However, approximately a third of MCL patients treated with cBTKi are refractory and the most durable results appear to be restricted to those who achieve an initial CR.[9] Moreover, up to 69% of patients who do respond at first will experience disease progression by two years on treatment. Effective management of patients whose disease has either relapsed or become refractory to cBTKi therapy (cBTKi R/R MCL) is arguably the greatest current unmet need in MCL.[10] Historically, such disease was often aggressive, resistant to further therapy and associated with poor patient outcomes, with a median life expectancy ranging between 2.9 and 8.4 months in various case series.[11,12] A multitude of ongoing trials are evaluating novel therapies in this context, but management remains challenging due to the paucity of effective agents with regulatory approval.[2]

Here, we review the treatment options currently available to patients with R/R MCL who have progressed following cBTKi. The established role of conventional chemotherapy, immunomodulatory therapy and allogeneic stem cell transplant is evaluated and contrasted with various emerging

agents (Tables 1 and 2) directed at a range of targets (Figure 1), including non-covalent BTKi and BTK degraders, antibody-drug conjugates, chimeric antigen receptor (CAR) T cells, bispecific antibodies, and other immune modulators.

Mechanisms of covalent Bruton's tyrosine kinase inhibitor resistance

The phenomenon of resistance to cBTKi in MCL is more complex than that seen in other B-cell lymphoproliferative disorders such as chronic lymphocytic leukemia (CLL) and Waldenstrom's macroglobulinemia (WM). Reported rates of primary resistance (defined as lack any response) in the phase II trial setting were 32% for ibrutinib,[4] 19% for acalabrutinib,[13] and 16.3% for zanubrutinib.[6] In those who achieved at least a partial response (PR) initially, rates of acquired or secondary resistance at 24 months ranged from 51% with acalabrutinib to 69% with ibrutinib. Similar outcomes were seen in pooled real-world data[14] with a median duration of response (DOR) of 21.8 months (95% Confidence Interval [CI]: 17.2-26.4), although prolonged responses up to a median of 55.7 months were observed in a subset of patients who achieved initial complete response (CR) and were treated at first relapse as opposed to later in their disease course. The underlying mutational landscape is diverse and not completely understood. The well-described cBTKi resistance-conferring genetic lesions seen in CLL such as the *BTK* C481S binding pocket variant and mutations in the downstream kinase *PLCG2* are uncommon in MCL[11,15] and pan-resistant 'dead-kinase' variants such as L528W are highly infrequent, although they have been reported.[16] Instead, cBTKi resistance in MCL is thought to reflect up-regulation of alternative B-cell receptor signaling pathways which serve to bypass BTK in promoting B-cell survival, antigen-driven clonal selection and humoral immunity.[15,17] The most common of these mutations are found in the downstream PI3K/AKT/mTOR pathway[18,19] and the alternative or non-canonical NF-κB pathway via mutations in *TRAF2*, *TRAF3* or *MAP3K14*.[20] Chromosome 9p21.1-p24.3 loss and/or mutations in components of the SWI-SNF chromatin-remodeling complex were present in all patients with primary resistance to the combination of ibrutinib and venetoclax in the AIM study along with two-thirds of patients with relapsed disease.[21] Cell cycle signaling dysregulation due to cyclin D1 overexpression is a defining feature of MCL and occurs as a result of the t(11;14) chromosomal translocation, which fuses *CCND1* and the immunoglobulin heavy chain gene. Additional mutations in the N-terminal region of the CCND1 protein (E36K, Y44D, C47S) promote stability by evading GSK3B-mediated phosphorylation and have been reported to invoke ibrutinib resistance in cell lines.[17,22,23] Finally, there is increasing appreciation of the epigenetic influence of the immune-depleted tumor microenvironment

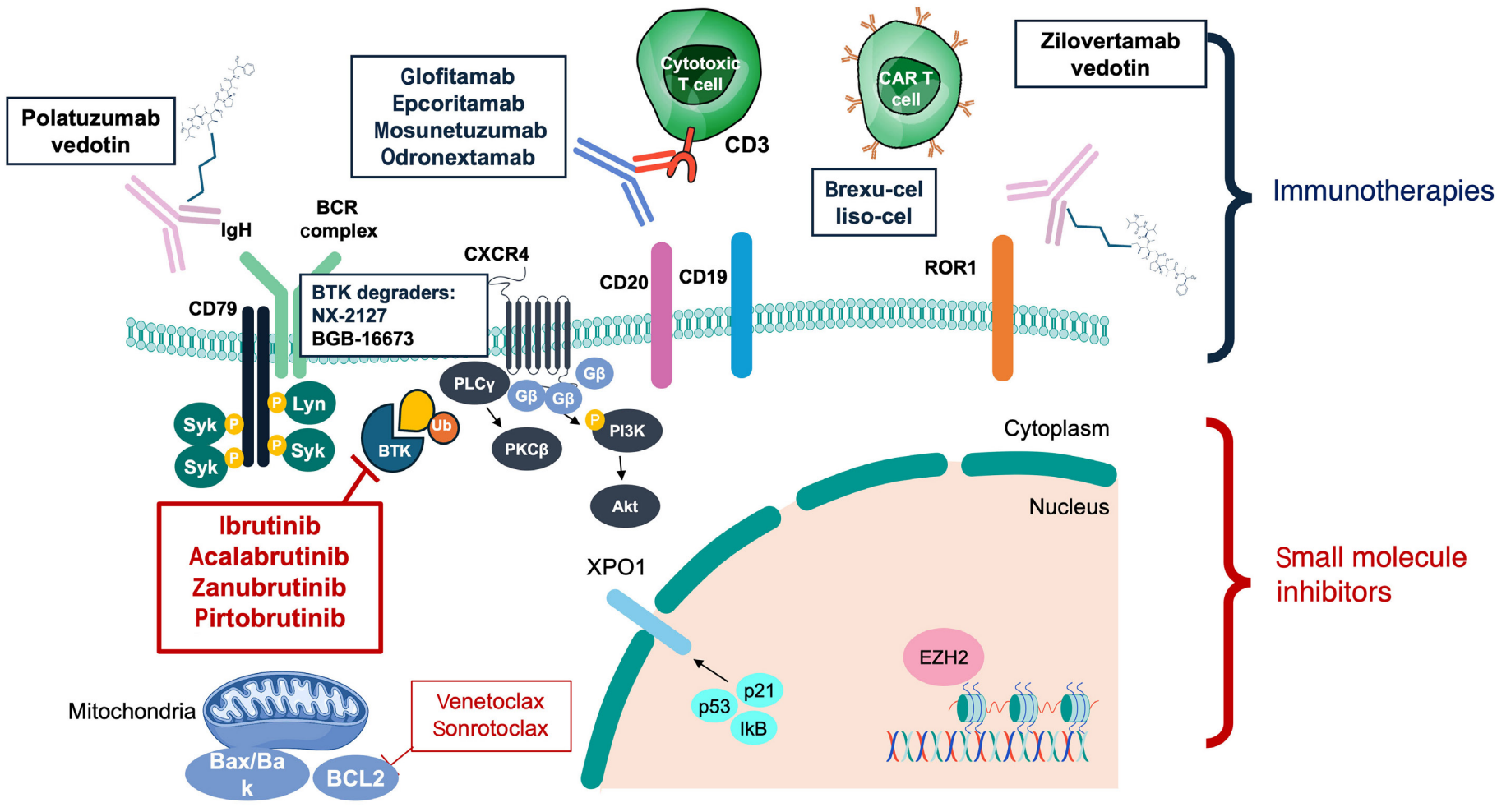

Figure 1. Mechanisms of action of selected targeted therapies. CAR T: chimeric antigen receptor T cell. (Adapted from Cheah *et al.*[82]).

in promoting cBTKi resistance in MCL.[18,24] Nodal tissue with transcriptomes characterized by low levels of expression of immune cytokines and stromal cells such as T helper and follicular dendritic cells are commonly seen in patients with clinical BTKi resistance.[24]

Risk factors for covalent Bruton's tyrosine kinase inhibitor failure

Covalant BTK inhibitors are now standard of care for MCL at first relapse following chemoimmunotherapy. Clinical assessment of the risk of cBTKi failure is, therefore, important to identify the subset of patients who will likely derive a limited duration of benefit allowing for early transition to the most appropriate next-line therapy, thus avoiding the accelerated progression seen with rapid cBTKi cessation.[25] Traditional adverse-risk features in MCL remain predictive in cBTKi treated patients with blastoid histology, Ki-67 expression ≥50% and *TP53* disruption, all identified as risk factors for cBTKi failure in *post hoc* analyses of the pivotal phase II trials.[8,13] A pooled analysis of patients treated with ibrutinib in the PCYC-1104, SPARK, and RAY trials[4,26] demonstrated that patients with TP53-mutated disease had significantly inferior median PFS (4·0 months *vs*. 12·0 months) and OS (10·3 months *vs*. 33·6 months) compared to those with wildtype *TP53*. Phase II data in zanubrutinib-treated patients confirmed inferior outcomes (complete response 67% *vs*. 82%, median PFS 14.7 months *vs*. not reached at approximately 3 years follow-up), although this is based on small numbers (54 participants with known *TP53* status).[6] Prior treatment exposure is also influential on cBTKi response with an objective response rate (ORR) of 78%, including 37% CR and a median PFS of 25 months in patients receiving single-agent ibrutinib in the second-line setting compared to ten months among patients receiving it after more than one prior line of treatment.[14]

The Mantle Cell Lymphoma International Prognostic Index (MIPI) is a well-established, prospectively validated prognostic score in MCL which stratifies patients into three risk groups (low, intermediate, and high) based on their predicted overall survival (OS).[27] The 2L BTKi MIPI[28] is a refinement of this index specific to their anticipated response to cBTKi therapy at first relapse after front-line rituximab-containing chemotherapy derived from multivariate real-world analysis. Variables predictive of PFS and OS were time to progression of disease (POD) on front-line therapy, baseline Ki67, and baseline MIPI. Patients identified as high risk (POD <6 months, Ki67 ≥30%, and intermediate-high MIPI) had a 2-year PFS of 14% (95% CI: 7-27), compared to 94% (95% CI: 44-100) in low-risk patients (POD >24, kI67 <30%, low MIPI). Blastoid or pleomorphic morphology was not independently statistically significant in this model, but the authors suggest this was expected because of its strong correlation with Ki-67.

Established therapies

Conventional agents

Two retrospective analyses have collated outcomes using several established therapeutic agents in the post-cBTKi setting, including chemotherapy, phosphoinositide 3-kinase inhibitors, lenalidomide and bortezomib. These have reported both low response rates and short duration of responses with an ORR of 29-32% and a median OS of 5.8-8.4 months.[11,12]

The largest real-world dataset of post-cBTKi treatment outcomes in the pre-CAR T era comes from the SCHOLAR-2 study, a retrospective, European multicenter study of 240 patients with R/R MCL who had predominantly experienced disease progression on cBTKi therapy (85.2%) but also included a small number who discontinued due to intolerance.[29] Patients received a median of one (range: 1-7) prior line of a heterogenous group of post-cBTKi therapies, with lenalidomide-containing regimens (17.4 %) and bendamustine plus rituximab (16.8%) being the most commonly administered. The median OS from initiation of first post-cBTKi therapy was 14.6 months (95% CI: 11.6-20.0). Of note, 37.9% patients received no further therapy after cBTKi discontinuation, although reasons for this and causes of death were not documented.

The single most active chemoimmunotherapy regimen in the post-cBTKi R/R MCL population is the combination of rituximab, bendamustine and cytarabine (R-BAC) based on a small retrospective cohort study of 36 patients[30] with an ORR of 83% and CR 60%. Median PFS was, however, modest at 10.1 months (95% CI: 6.9-13.3) and median OS was 12.5 months (95% CI: 11.0-14.0). Treatment-related toxicity was a significant issue, with toxicity-related dose reductions in nearly all patients over the age of 70 years, and 50% of patients experiencing an unplanned hospitalization event.

Allogeneic stem cell transplantation

Allogeneic stem cell transplantation (alloSCT) has a well-established place in the management of appropriately selected young, fit patients with MCL and offers the potential for cure. Pooled case series report OS and PFS rates at 3-5 years ranging from 50-80% and 40-60%, respectively; however, this is predominately based on historic data derived from its use in the setting of the first response.[31,32] Small datasets also suggest that patients with high-risk *TP53* disrupted disease can expect similarly favorable outcomes as their wild-type counterparts.[33] This durable disease control is, however, offset by not insignificant rates of treatment-related toxicity with reported incidences of chronic graft-*versus*-host disease (GvHD) of up to 60%[31] and non-relapse mortality (NRM) of between 10-20%.[34] Data specific to the post-cBTKi population are limited to two small retrospective studies – one of 22 patients describing a 1-year PFS of 76% and 5% NRM,[35] and another of 11 patients who received alloSCT following R-BAC, also with a 1-year PFS of 76%.[30] As

such, although contemporary guidelines recommend that appropriate consideration be given to alloSCT in the R/R MCL post-cBTKi,[2] its real-world applicability is complex and requires a thorough consideration of patient fitness, disease kinetics, and donor availability.[33,36] Furthermore, expanding experience with CAR T-cell therapy increasingly raises questions about appropriate sequencing in patients who would be candidates for both forms of cellular therapy in healthcare systems where such access is available.

Recently approved therapies

Chimeric antigen receptor T-cell therapy

Chimeric antigen receptor T-cell therapy is a rapidly developing form of genetically engineered cellular immunotherapy that offers the attraction of a single treatment and a track record of durable efficacy in other B-cell malignancies. In R/R MCL, mature data are currently available for two CAR T products.

Brexucabtagene autoleucel (brexu-cel, KTEX19) is a CD19-directed CAR T with an intracellular CD28 co-stimulatory domain which now has regulatory approval in the US, Europe, and Australia for patients with R/R MCL. The phase II ZUMA-2 study enrolled 76 heavily pre-treated patients with MCL (median 3 prior lines of therapy), including cBTKi.[37] A *post hoc* analysis of the pre-specified subgroup of 68 patients with prior cBTKi exposure comprised those who had been treated with ibrutinib (N=52), acalabrutinib (N=10), and both (N=6).[38] Response rates, outcomes and grade ≥3 treatment-emergent adverse events (TEAE) are presented in Table 1. The population was enriched for patients with high-risk features, including 68% with blastoid morphology, 63% Ki67 ≥30%, and 12% carrying a *TP53* mutation. A separate analysis of these subgroups showed comparable ORR and CR rates to the all-treated population, albeit with reduced median DOR (13.5 months) in the blastoid subgroup.

Although small sample sizes limit comparison, efficacy appeared lower in patients exposed to acalabrutinib (median duration of response 5.0 months [95% CI: 1.6 to not evaluable [NE]) compared to those who had received ibrutinib (28.2 months [95% CI: 10.4-46.7]). It has been hypothesized that this may reflect differences in peak immunomodulatory and proinflammatory cytokine levels, particularly IFN-g and IL-6 and their impact on CAR T-cell differentiation and sustained effector function with ibrutinib.[39,40]

Despite being highly effective, delivery of brexu-cel can be problematic due to the significant risk of treatment-related toxicity. The largest reported real-world dataset in MCL (N=168)[41] identified age ≥65 years, Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2, high-risk MIPI, blastoid or pleomorphic morphology and bulky disease were associated with grade ≥3 immune effector cell-associated neurotoxicity syndrome (ICANS). Twenty percent of patients required intensive care for a median of 3 days (range: 1-12), predominantly for vasopressor support.

Liscabatagene maraleucel (liso-cel) is another CD19-directed CAR T, which differs from brexu-cel in that it utilizes 4-1BB as a co-stimulatory molecule and the product features fixed ratios of CD4:CD8 T cells. The TRANSCEND

Table 1. Therapies for patients with covalent Bruton's tyrosine kinase inhibitor relapsed/refractory mantle cell lymphoma recently approved by the US Food and Drug Administration.

Therapy	Ref	Design	N	Median age in years (range)	Median prior lines of therapy (range)	cBTKi exposed %	Response, % (95% CI)		Outcomes in months (95% CI)		Median follow-up in months (range)	Major, grade ≥3, treatment-emergent toxicities (%)
							ORR	CR	OS	PFS		
Brexucabtagene autoleucel	38	Phase II	68	65 (38-79)	3 (1-5)	100	91 (81.8- 96.7)	68 (55.2-78.5)	46.6 (24.9-NR)	25.8 (9.6-47.6)	35.6 (25.9-56.3)	Neutropenia (85) Thrombocytopenia (51), Anemia (50) CRS (15) NE (31)
Lisocabtagene maraleucel	43	Phase I	83	68.5 (36-86)	3 (1-11)	94	83	72	18.2 (12.9-36.3)	15.3 (6.6-24.9)	16.1 (0.4-60.5)	Neutropenia (33–58) Infection (15) CRS (1) NE (9)
Pirtobrutinib	36	Phase I/II	152	70 (46-88)	3 (1-9)	100	49.3 (41.1-57.6)	15.8	23.5 (17.1-NR)	5.6 (5.3-9.2)	24	Neutropenia (13.3) Infections (19.9) Bleeding (2.4) AFib (3.6)

Ref: reference; N: number; cBTKi: covalent Bruton's tyrosine kinase inhibitors; CI: Confidence Interval; ORR: objective response rate; CR: complete response; OS: overall survival; PFS: progression-free survival; CRS: cytokine release syndrome; NR: not reported; NE: neurologic event; AFib: atrial fibrillation.

NHL 001 investigators[42,43] reported promising clinical activity and a notably low incidence of treatment-related toxicity events among 88 patients with R/R MCL, of whom 83 (94%) were cBTKi exposed but only 47 (53%) were said to be refractory. The median number of previous lines of therapy was 3 (range: 1-11); 23% had *TP53* mutations and 8% had secondary central nervous system (CNS) lymphoma. Outcomes presented in Table 1 show comparable efficacy to brexu-cel and a relatively favorable toxicity profile with overall low incidences of grade ≥3 CRS (1%), neurologic events (9%), and infection (15%). Approval by the US Food and Drug Administration (FDA) for use in R/R MCL after ≥2 prior lines of therapy (including cBTKi) was granted in May 2024. The low rates of neurologic toxicity and potential for outpatient delivery make this likely to be an attractive option applicable to a larger proportion of MCL patients than brexu-cel.

Society guidance from the American Society for Transplantation and Cellular Therapy (ASTCT), the Centre for International Blood and Marrow Transplant Research (CIBMTR), and the European Group for Blood and Marrow Transplantation (EBMT) increasingly recommend that CAR T be favored in appropriate candidates over other potential therapies in patients with cBTKi R/R MCL; however, treatment-related toxicity, the need for administration in specialist centers and associated geographic constraints pose barriers to application for a large proportion of the patient group in need. While eligibility criteria vary between jurisdictions, common considerations include good performance status (typically ECOG ≤2), adequate cardiorespiratory and renal function, bone marrow reserve, and the absence of uncontrolled infection.[2,44]

Allogeneic CAR T-cell therapy involves the manufacture of CAR T cells using peripheral blood derived from healthy donors rather than the patient, with a strong focus on gene-editing technologies such as CRISPRCas9. This aims to overcome the time-consuming and highly personalized manufacturing processes associated with autologous CAR T, allowing for scalable mass production.[45] Several phase I clinical trials (e.g., NCT05643742 and NCT04637763) are currently enrolling patients with R/R B-cell lymphoma including MCL, with initial results showing promising efficacy and manageable toxicity profiles,[46] although long-term follow-up data are awaited.

Pirtobrutinib

Pirtobrutinib, formerly LOXO-305, is a first-in-class non-covalent BTKi. This new class of agent is distinct from their covalent counterparts in that they reversibly bind the BTK enzyme distant from the C481 residue targeted by the cBTKi family,[47,48] although efficacy has also been observed in patients who do not have the *BTK* C481S resistance-conferring mutation. Pirtobrutinib was granted accelerated approval by the FDA in January 2023 for use in patients with R/R MCL after ≥2 previous therapies, including a cBTKi. This was primarily based on data from the phase I/II BRUIN study, which was updated in May 2023 (see Table 2).[36,49,50] The median DOR was 21.6 months (95% CI: 9.2-27.2) at a median follow-up of 24.2 months. The ORR for all cBTKi pre-treated patients was 49.3% (95% CI: 41.1-57.6), including a CR in 15.8%, although in those who had discontinued cBTKi because of disease progression (rather than intolerance), the ORR was lower at 43.0%. Extended follow-up data[51] have demonstrated a favorable safety profile with fatigue (32%) and diarrhea (31%) being the most common TEAE. Dose reduction or

Table 2. Emerging therapies for patients with relapsed-refractory B-cell non-Hodgkin lymphoma, which have included patients with mantle cell lymphoma.

Therapy	Ref	Design	N	Patients with MCL N (%)	Median age in years (range)	Response, % (95% CI)		Major, grade >3, treatment-emergent toxicities (%)
						ORR	CR	
Glofitamab	53	Phase I/II	31	100	70 (41-84)	74.2	71	CRS (8.3)
Mosunetuzumab -Polatuzuamab	56	Phase I/II	20	100	68.0 (44–82)	75	70	1 patient each with uveitis and pneumonitis (both related to M-Pola) 2 patients with Grade 5 COVID-19 pneumonia (unrelated to M-Pola)
Zilovertamab vedotin	65	Phase I/II	17	100	70 (44-91)	53	1 patient	Neutropenia (32) Thrombocytopenia (11) Peripheral neuropathy (7)
NX-2127	61	Phase Ia/Ib	18	5 (11)	74 (50-92)	27	18	Neutropenia (38.5) Hypertension (14.9) Anemia (12.8)
BGB-16673	63	Phase I	26	4 (15)	70.5 (25-83)	67	1 patient	Neutropenia (15.4) Increased lipase (3.8)

N: number; MCL: mantle cell lymphoma; CI: Confidence Interval; ORR: objective response rate; CR: complete response; CRS: cytokine release syndrome; NE: neurologic event, NR: not reported; M-Pola: polatuzumab vedotin.

discontinuation due to TEAE was rare, occurring in 23 (7%) and 11 (3%) patients, respectively.

Pirtobrutinib is, therefore, an attractive option for cBTKi R/R MCL patients who either cannot tolerate or access CAR T-cell therapy and may also serve as a bridge to help achieve disease control where CAR T-cell therapy is planned. Resistance mechanisms to pirtobrutinib monotherapy in CLL are already being identified,[48] though the resistance mechanisms in MCL are less well understood.

Emerging therapies

T-cell engaging bispecific antibodies

T-cell-activating bispecific antibodies are a novel immunotherapeutic class which bind surface CD20 or CD19 expressed by malignant B cells simultaneously with CD3 on endogenous T cells, triggering *in vivo* T-cell activation and targeted cytotoxicity.[52] Multiple agents are in development and under evaluation in MCL. Glofitamab is a CD20xCD3 bispecific with a 2:1 molecular configuration with bivalency for CD20 and monovalency for CD3. It has been hypothesized that pre-treatment with step-up doses of glofitamab and obinutuzumab (Gpt) prior to initiation of glofitamab monotherapy reduces the risk of CRS by competing for CD20 epitopes and reducing MCL tumor bulk, particularly in those patients with leukemic phase disease. A phase I/II trial[53] examined the efficacy of either 1,000 mg or 2,000 mg of Gpt followed by 12 cycles of glofitamab monotherapy (approx. 8.3 months) in 61 heavily pre-treated patients with R/R MCL. Of the 31 patients (51.7%) who received prior cBTKi therapy, 29 (93.5%) were cBTKi refractory. Recently updated results in the cBTKi-exposed subgroup are shown in Table 2. Median DOCR was 12.6 months and median PFS was 8.6 months. Therapy was generally well-tolerated with grade 1-2 ICANS in 5 patients (13.5%), and while CRS was common, occurring in 75.7% of all patients, it was mild in the majority of cases, with only two grade 4 events occurring in the 1,000 mg Gpt arm. Although these efficacy and safety outcomes are promising, long-term follow-up is needed and will be assessed in the randomized phase III GLOBRYTE trial comparing the same glofitamab regimen with investigator's choice of rituximab plus either bendamustine (BR) or lenalidomide (R^2) in R/R MCL patients who have received ≥1 prior line of therapy including a cBTKi.[54]

Mosunetuzumab is another CD20xCD3 T-cell engaging bispecific with a 1:1 ratio of CD3 to CD20 fragment antigen-binding (Fab) arms. It has demonstrated efficacy in cBTKi R/R MCL both as monotherapy[55] and more recently in combination with the CD79b-targeted antibody-drug conjugate polatuzumab vedotin (Pola) in a phase I/II trial[56] of 20 cBTKi exposed patients with R/R MCL for a fixed duration of 17 3-weekly cycles. Results are presented in Table 2. Median duration of CR was not evaluable (95% CI: 3.8-NE). CRS occurred in half of the patients but all events were grade 1 or 2. Treatment-related neurologic AE, potentially consistent with ICANS, occurred in 3 patients (15%). The combination of CD20 and CD79b targeting with immunotherapeutic approaches clearly holds promise, and longer follow up on this study is required to better assess the durability of responses and incremental benefit over CD20 targeting T-cell engagers alone. Phase I trials of the CD20xCD3 agents epcoritamab[57] and odrononextamab[58] have demonstrated encouraging safety and tolerability in patients with other B-cell malignancies; however, specific data in patients with MCL are awaited at the time of writing.

Non-covalent Bruton's tyrosine kinase inhibitors and Bruton's tyrosine kinase degraders

Although pirtobrutinib is the only approved non-covalent (nc)BTKi, several other BTK-directed agents have been evaluated or are currently under development.[59] Nemtabrutinib (MK-1026, ARQ-531) is an orally bioavailable, reversible BTK inhibitor. The phase I dose-escalation study in 48 patients with R/R B-non-Hodgkin lymphoma (NHL)[60] reported an ORR of 75%, although, disappointingly, 44 (93.6%) patients discontinued treatment after a median follow-up of only 3.9 months (range: 0.3-38.8 months), primarily due to either clinical (36.4%) or radiologic (20.5%) disease progression. TEAE were relatively common (80% of patients experienced at least one grade ≥3 event), although these were mainly (76%) hematologic in nature. Clinical trials in other ncBTKi, vecabrutinib (SNS-062) and fenebrutinib (GDC-0853), were discontinued due to either toxicity or lack of efficacy, and development has consequentially not progressed further. Several additional agents are in preclinical development; however, *in vivo* human data are awaited.[59]

Bruton's tyrosine kinase degraders are heterobifunctional molecules that induce target protein degradation through the ubiquitin-proteasome system. NX-2127 is an oral, first-in-class, dual-function small molecule degrader for which dose-escalation (phase Ia) and cohort-expansion (phase Ib) data in 47 patients with R/R B-NHL (including 5 with MCL) showed dose-dependent pharmacokinetics and an ORR of 27%.[61] The most common grade ≥3 TEAE were neutropenia (38.3%), hypertension (14.9%), and anemia (12.8%). NX-5948 is a similar molecule with CNS penetrance. In recent phase I data, out of 24 disease-evaluable patients with NHL treated with 50-600 mg NX-5948, 8 responded. All 4 patients treated at the 450 mg dose achieved response: 3 CR (MCL, MZL, primary CNS lymphoma) and one PR (secondary CNS lymphoma).[62] BGB-16673 is a potent, selective, and orally available heterobifunctional small molecule that binds to BTK and E3 ligase, resulting in BTK degradation via ubiquitination. Phase I dose-escalation data[63] in 26 patients with R/R B-NHL (including 4 with MCL) who had been pre-treated with a median of 3.5 prior lines of therapy including cBTKi showed an ORR

of 67% with durability up to 60 weeks. TEAE were mostly limited to mild confusion, pyrexia, neutropenia and transient lipase elevation with no AE-related discontinuations occurring. This class of agent appears well tolerated and promising, although further data are required in order to better understand the efficacy in MCL specifically.

Antibody-drug conjugates

Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is an embryonic-cell surface protein involved in mesenchymal and neural crest proliferation. Physiologic expression is largely absent beyond birth; however, malignant B lymphocytes, including those seen in MCL, can re-express ROR1, which is associated with a high potential for self-renewal and increased survival.[64] Zilovertamab vedotin (previously VLS-101) is an antibody-drug conjugate (ADC) consisting of an ROR1-targeting monoclonal antibody, a cleavable linker, and the anti-microtubule cytotoxin, monomethyl auristatin E (MMAE). A phase I dose escalation study of 32 patients with R/R B-NHL[65] included 17 patients with R/ R MCL all of whom were cBTKi exposed. Proof of anti-tumor activity was seen with an ORR of 53%, including CR in one patient. AE included neutropenia and peripheral neuropathy consistent with other ADC containing MMAE. NVG-111 is a first-in-class, tandem ROR1xCD3 bispecific T-cell engager which demonstrated proof of concept in a phase I study of 12 subjects comprised of patients with both R/R MCL and CLL.[66] Objective clinical responses were observed in 55% (6/11) and, amongst these, one MCL subject achieved complete metabolic response by the Lugano criteria. CRS and ICANS were described but limited to grade 1 or 2. ROR1 holds promise as a therapeutic target in MCL, and may also lend itself to combination strategies using CD20 targeting agents and BTK inhibitors/degraders.

Bcl-2 inhibitors

The selective targeting of Bcl-2 has a well-established place in the management of MCL with the initial phase I data from venetoclax demonstrating an ORR of 44% and estimated median PFS of 14 months in BTK-naïve patients.[67] Real-world data from the relapsed and refractory setting were less encouraging with a retrospective analysis of patients treated via a UK-wide compassionate access program reporting a comparable ORR of 53%, but a median PFS of only 3.2 months.[68] However, several emerging BCL2 inhibitors are under early-phase clinical development for patients with R/R MCL. BGB-11417 (sonrotoclax) is a highly selective Bcl-2 inhibitor with 5-fold increased potency in pharmacodynamic studies.[69] Phase I data in patients with R/R MCL showed an ORR of 55% when used in combination with zanubrutinib.[70] The most common grade ≥3 TEAE was neutropenia (12%). Responses when used as monotherapy were not as promising, with only one CR and 2 PR seen in a cohort of 28 patients with R/R B-NHL.[70] The BH3 mimetic Bcl-2-selective inhibitor lisaftoclax or APG-2575 (clinicaltrials.gov 03537482)[71] has a unique pharmacokinetic profile compatible with a potentially more convenient daily (*vs*. weekly) dose ramp-up schedule and induced rapid clinical responses in patients with CLL/SLL, although evaluation in other B-cell malignancies is awaited.

Combination therapies

Despite the relatively limited durability of venetoclax monotherapy in R/R MCL, the combination of BTKi and Bcl-2 inhibition has been trialled based on pre-clinical synergy and non-overlapping toxicities with durable long-term responses.[72] In the cBTKi R/R population, the favorable toxicity profile of pirtobrutinib makes it appealing in combination strategies. This is currently being explored in several investigator-initiated studies including an MD Anderson study evaluating pirtobrutinib and venetoclax (clinicaltrials.gov 05529069) and the Australasian Leukaemia and Lymphoma Group (ALLG) NHL37 GoldiLox trial of pirtobrutinib in combination with glofitamab (clinicaltrials.gov 05833763).

A combined CAR T and cBTKi approach has also been described in cBTKi-exposed patients, based on a purported synergistic effect on CAR T-cell sustenance, *in vivo* expansion and lower severity of AE, including CRS.[73] The phase II TARMAC study[74] included 20 patients, of whom 9 were cBTKi refractory, and examined the combination of tisagenlecleucel (tisa-cel) with fixed-duration ibrutinib commenced before leukapheresis and continued for a minimum of six months after CAR T administration. At 13-month median follow-up, 80% of patients demonstrated CR, the estimated 12-month PFS was 75% and OS 100%. Fifteen patients (75%) developed CRS (which was grade 3 in 20%), although rates of neurotoxicity were much lower than ZUMA-2, with only 2 patients experiencing grade 1-2 ICANS and no grade ≥3 events reported. This appears to be in keeping with the lower rates of ICANS following tisa-cel compared with brexu-cel in MCL, although the TARMAC authors suggested a mitigating role from ibrutinib was also possible.[74]

Suggested treatment strategy

The management of cBTKi R/R MCL increasingly requires an approach tailored to the individual patient, their disease kinetics and performance status. alloSCT has historically been standard of care for young, fit patients based on long-term follow-up data showing clear evidence of graft-*versus*-lymphoma effect. In recent years, the advent of CAR T-cell therapy has demonstrated durable responses in cBTKi R/R MCL, however the associated toxicities mandate careful patient selection. A suggested treatment

approach based on the available data is set out in Figure 2, noting that clinical trial enrollment should be strongly considered in all patients, particularly those who either cannot access or would be inappropriate for CAR T-cell therapy.

Disease kinetics are an important consideration in therapy sequencing in MCL, with recently published real-world intention-to-treat analyses highlighting that failure to ultimately receive CAR T cells due to progressive disease was the main difference in outcome when compared to phase II data.[41,75] This is a particular challenge in the post-cBTKi population as abrupt BTKi cessation is often associated with risk of disease flare.[76] It is, therefore, strongly advised that potential CAR T candidates should be risk-assessed at the time of their first relapse prior to initiation of cBTKi, including reassessment of *TP53* mutational status, and then monitored closely with early referral of those deemed at high risk of early progression.[2] Additional bridging therapies may be required in those patients with high tumor volume and rapid disease kinetics, as these factors are known to be predictive of reduced CAR T response and early relapse. The optimum strategy for bridging in MCL is yet to be determined; however, potential options include radiation therapy to localized disease bulk, corticosteroids and non-cross-reactive immunochemotherapy regimens, noting that the use of bendamustine in this setting is generally discouraged due to its T-cell depleting effects.[77] Emerging therapeutic options in patients who would otherwise be CAR T ineligible include non-covalent BTK inhibitors and BTK degraders, T-cell engaging antibodies and novel antibody-drug conjugates. Of these, we would currently advocate selection of pirtobrutinib where access is available due to its combination of relatively favorable tolerability, along with the convenience of oral dosing. T-cell engaging bispecific antibody therapies offer the attraction of an off-the-shelf product without the need

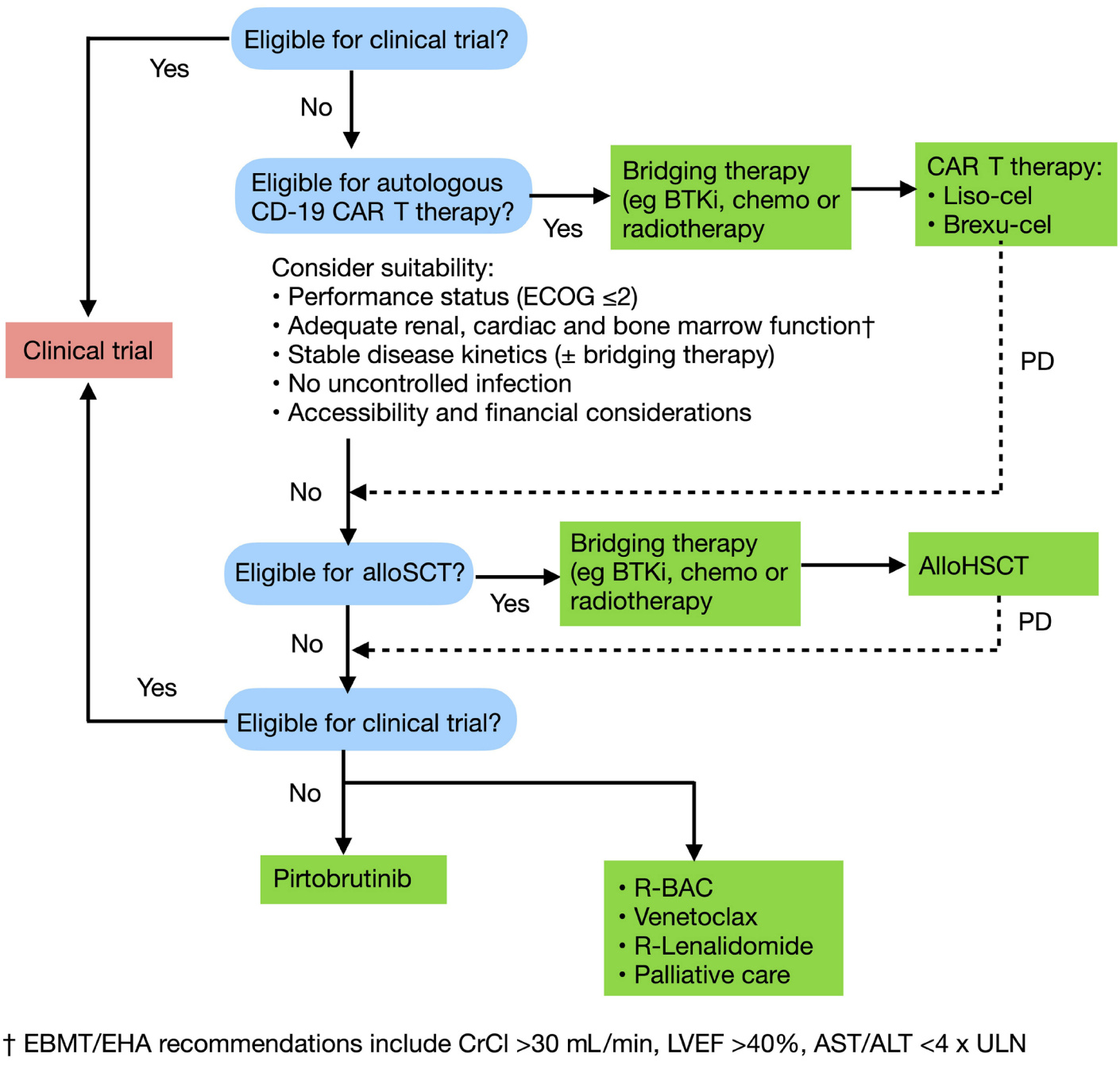

Figure 2. Suggested treatment algorithm for covalent Bruton's tyrosine kinase inhibitors relapsed refractory mantle cell lymphoma. CAR T: chimeric antigen receptor T cell; BTKi: Bruton's tyrosine kinase inhibitors; ECOG: Eastern Cooperative Oncology Group; PD: progressive disease; alloSCT: allogeneic stem cell transplantation; R-BAC: rituximab, bendamustine and cytarabine.

for bridging and time-limited therapy; however, an individualized assessment of tolerance of potential CRS and pre-emptive strategies to mitigate risk are particularly important considerations in MCL, where leukemic phase disease is reasonably common. The BTK degraders may have a role, particularly in overcoming refractory disease associated with the acquisition of non-canonical *BTK* mutations that would confer resistance to both covalent and non-covalent BTKi.

Patients with CNS disease at post-cBTKi relapse represent a particularly poor prognostic group for whom there is no consensus on management. CAR T-cell therapy merits some consideration in this setting as a real-world series[78,79] of 10 patients with BTKi-exposed R/R MCL with a history of secondary CNS involvement treated with anti-CD19 CAR T at three US academic centers (7 of whom had active CNS disease at the time of infusion) reported an ORR of 86% (CR 28.6%), with median PFS of 11.7 months. Median OS was not reached after a median follow-up of 15.4 months. Seven patients developed ICANS, of which 5/10 (50%) were Grade 3, but there were no Grade 4-5 events. Leptomeningeal involvement and advanced age correlated with ICANS occurrence. As CNS disease was an exclusion criterion for prospective studies using pirtobrutinib and bispecific antibodies, their efficacy in CNS MCL is unknown.

Recently published data suggest a potential role for BTKi as part of the front-line management of newly diagnosed MCL.[80] This could mean that the therapeutic options discussed here will increasingly need to be considered in the setting of first relapse; however, this may also mitigate some of the impact of treatment-related toxicity toxicity from prior therapies on patient fitness, particularly with respect to eligibility for CAR T therapy. The results of the current phase III head-to-head trial comparing pirtobrutinib *versus* investigator's choice of cBTKi (clinicaltrials.gov 04662255) in the R/R setting are also awaited as this could result in use of pirtobrutinib in the setting of first relapse as well, supporting an ongoing need for therapies with a broad range of mechanisms of action in the management of R/R disease.

Conclusion

While covalent BTKi have achieved robust disease responses in patients with MCL in the setting of first relapse, the management of patients experiencing treatment failure remains a challenge. Selection of the appropriate treatment at the time of relapse requires a carefully individualised approach taking into account patient fitness and preferences, local medication reimbursement status, and clinical trial availability.

Disclosures

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Contributions

BTG drafted the manuscript and CYC provided critical review. Both authors approved the final version of the manuscript for publication.

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