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Title

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

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

Abstract

Mantle cell lymphoma (MCL) is a subtype of non-Hodgkin lymphoma which is often characterised by a pattern of continued relapse after frontline 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 prioritising clinical trials where available.

1. Introduction

Mantle cell lymphoma (MCL) is an uncommon subtype of non-Hodgkin lymphoma previously considered to have a poor prognosis characterised 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 frontline 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 2 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 paucity of effective approved 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 and bispecific antibodies, and other immune modulators.

2. Mechanisms of cBTKi 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 leukaemia (CLL) and Waldenstrom's macroglobulinaemia (WM). Reported rates of primary resistance (defined as lack any response) in the phase 2 trial setting were 32% for ibrutinib,[4] 19% for acalabrutinib[13] and 16.3% for zanubrutinib.[6] Of those who achieve 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% 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 incompletely 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 have been reported.[16] Instead, cBTKi resistance in MCL is thought to reflect upregulation of alternative B-cell receptor signalling 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-kB 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 signalling 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.[22 17 23] Finally, there is increasing appreciation of the epigenetic influence of the immune-depleted tumour microenvironment in promoting cBTKi resistance in MCL.[18,24] Nodal tissue with transcriptomes characterised by low levels of expression of immune cytokines and stromal cells such as T helper and follicular dendritic was more commonly seen in patients with clinical BTKi resistance.[24]

3. Risk factors for cBTKi failure

Covalant BTK inhibitors are now standard of care for MCL at first relapse following chemo-immunotherapy. 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 alternative 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 2 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 compared to those with wildtype *TP53* had significantly inferior median PFS (4·0 months *vs* 12·0 months) and OS (10·3 months *vs* 33·6 months). Phase 2 data in zanubrutinib-treated patients confirmed inferior outcomes (complete response 67% versus 82%, median progression-free survival was 14·7 months versus 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 overall 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 10 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.[27] The 2L BTKi MIPI[28] is a refinement of this index specific to their anticipated response to cBTKi therapy at first relapse after frontline rituximab-containing chemotherapy derived from multivariate real-world analysis. Variables predictive of progression-free and overall survival were time to progression of disease (POD) on frontline 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 likely because of its strong correlation with Ki-67.

4. Established therapies

4.1 Conventional therapies

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 overall 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 from the pre-CAR T era comes from the SCHOLAR-2 study, a retrospective, European multicentre 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 lines 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 overall survival (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 progression-free survival was however modest at 10.1 months (95% CI 6.9–13.3) and median overall survival 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 hospitalisation event.

4.2 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 favourable outcomes as their wildtype counterparts.[33] This durable disease control is however offset by not insignificant rates 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.

5. Recently approved therapies

5.1 CAR T-cell therapy

CAR 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 costimulatory domain which now has regulatory approval in the US, Europe and Australia for patients with R/R MCL. The phase 2 ZUMA-2 study enrolled 76 heavily pre-treated patients with MCL (median three 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 (TEAEs) 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. Separate analysis of these subgroups showed comparable ORR and CR rates to the all-treated population, albeit with reduced mDOR (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 NE]) compared to those who had received ibrutinib (28.2 months [95% CI 10.4 to 46.7]). It has been hypothesised 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, 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 utilises 4-1BB as a costimulatory molecule and the product features fixed ratios of CD4:CD8 T-cells. The TRANSCEND 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 favourable toxicity profile with overall low incidences of grade ≥3 CRS (1%), neurologic events (9%), and infection (15%). Approval by the US Federal 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 neurological 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), Centre for International Blood and Marrow Transplant Research (CIBMTR), and European Society for Blood and Marrow Transplantation (EBMT) increasingly recommend that CAR T be favoured in appropriate candidates over other potential therapies in patients with cBTKi R/R MCL, however treatment-related toxicity, the need for administration in specialist centres 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 absence of uncontrolled infection.[2,44]

Allogeneic CAR T 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 personalised manufacturing processes associated with autologous CAR T allowing for scalable mass production.[45] Several phase 1 clinical trials (for example, 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 is awaited.

5.2 Pirtobrutinib

Pirtobrutinib, formally 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, although in those who had discontinued cBTKi because of disease progression (rather than intolerance), ORR was lower at 43%. The 18- and 24-month DOR rates were 51.9% (95% CI, 37-64.8) and 38.9% (95% CI, 22.7-54.8), respectively. Extended follow-up data[51] has demonstrated a favourable safety profile with fatigue (32%) and diarrhoea (31%) being the most common TEAEs. Dose reduction or 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 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.

6. Emerging therapies

6.1 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. Pre-treatment with step-up doses of glofitamab and obinutuzumab (Gpt) prior to initiation of glofitamab monotherapy is theorised to reduce the risk of CRS by competing for CD20 epitopes and reducing MCL tumour bulk, particularly in those patients with leukaemic phase disease. A phase-1/2 trial[53] examined the efficacy of either 1000 mg or 2000 mg of Gpt followed by 12 cycles of glofitamab monotherapy (approximately 8.3 months) in 61 heavily pretreated 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 grades 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 1000 mg Gpt arm. Although these efficacy and safety outcomes are promising, long-term follow-up is needed and will be assessed in the randomised phase 3 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 1/2 trial[56] of 20 cBTKi exposed patients with R/R MCL for a fixed duration of 17 three-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 AEs, 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 1 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.

6.2 Non-covalent BTK inhibitors and BTK degraders

Although pirtobrutinib is the only approved ncBTKi, 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 1 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 (0.3-38.8 months), primarily due to either clinical (36.4%) or radiologic (20.5%) disease progression. TEAEs were relatively common (80% of patients experienced least one grade ≥3 event), although these were mainly (76%) haematologic in nature. Clinical trials in other ncBTKi's 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]

BTK 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 1a) and cohort-expansion (Phase 1b) 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 TEAEs were neutropenia (38.3%), hypertension (14.9%) and anaemia (12.8%). NX-5948 is a similar molecule with CNS penetrance. In recent phase 1 data, out of 24 disease-evaluable patients with NHL treated with 50–600 mg NX-5948, eight responded. All 4 patients treated at the 450 mg dose achieved response: 3 CRs (MCL, MZL, primary CNS lymphoma); 1 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 1 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 out to 60 weeks. TEAEs 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 is required in order to better understand the efficacy in MCL specifically.

6.3 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 1 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-tumour activity was seen with an ORR of 53% including CR in one patient. Adverse events included neutropenia and peripheral neuropathy consistent with other ADCs containing MMAE. NVG-111 is a first in class, tandem ROR1xCD3 bispecific T cell engager which demonstrated proof of concept in a phase 1 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.

6.4 Bcl-2 inhibitors

The selective targeting of Bcl-2 has a well-established place in the management of MCL with the initial phase 1 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 1 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 two PR seen in a cohort of 28 patients with R/R B-NHL.[71] The BH3 mimetic Bcl-2-selective inhibitor lisaftoclax or APG-2575 (NCT03537482)[72] 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.

7. 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.[73] In the cBTKi R/R population, the favourable 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 (NCT05529069) and the Australasian Leukaemia and Lymphoma Group (ALLG) NHL37 GoldiLox trial of pirtobrutinib in combination with glofitamab (NCT05833763).

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 adverse events, including CRS.[74] The phase 2 TARMAC study[75] included 20 patients of whom nine were cBTKi refractory and examined the combination of tisagenlecleucel (tisa-cel) and fixed-duration ibrutinib commenced before leukapheresis and continued for a minimum of 6 months after CAR T administration. At 13-month median follow-up, 80% of patients demonstrated CR, the estimated 12-month progression-free survival was 75% and overall survival 100%. Fifteen patients (75%) developed CRS (which was grade 3 in 20%), although rates of neurotoxicity were much lower than ZUMA-2 with only two patients experiencing grade 1-2 ICANS and no grade ≥3 events reported. This appears 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.

8. 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 enrolment 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 2 data.[41,76] This is a particular challenge in the post-cBTKi population as abrupt BTKi cessation is often associated with risk of disease flare.[77] 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 tumour volume and rapid disease kinetics as 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 that the use of bendamustine in this setting is generally discouraged due to its T-cell depleting effects.[78]

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 favourable responses and tolerability along with the convenience of oral dosing. T cell engaging bispecific antibody therapies offer the attraction of an off-the-shelf product without need for bridging and time-limited therapy, however an individualised assessment of tolerance of potential CRS and pre-emptive strategies to mitigate risk are particularly important considerations in MCL, where leukaemic phase disease is reasonably common. The BTK degraders may have a role particularly in overcoming refractory disease associated with acquisition of non-canonical *BTK* mutations that would confer resistance to both covalent and non-covalent BTKi.

Patients with CNS disease at relapse post-BTKi represent a particularly poor prognostic group for whom there is no consensus on management. CAR T therapy merits some consideration in this setting as a real-world series[79,80] 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 centres (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 median follow-up of 15.4 months. Seven patients developed ICANS, of which 5/10 (50%) G3 but no G4–G5 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 frontline management of newly diagnosed MCL.[81] 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 treatment-related toxicity from prior therapies on patient fitness, particularly in respect to eligibility for CAR T therapy. The results of the current phase 3 head-to-head

trial comparing pirtobrutinib versus investigator's choice of cBTKi (NCT04662255) 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 R/R setting.

9. Conclusion

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

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Therapy	Ref	Design	N	Median age, yrs (range)	Median prior lines of therapy (range)	cBTKi exposed (%)	Response (95% CI)		Outcomes (95% CI)		Follow-up (median)	Major (grade ≥3) treatment-emergent toxicities
							ORR	CR	OS	PFS		
Brexucabtagene autoleucel	[38]	Phase 2	68	65 (38–79)	3 (1-5)	100	91% (81.8- 96.7)	68% (55.2-78.5)	46.6 months (24.9-NE)	25.8 months (9.6 to 47.6),	35.6 months (range, 25.9-56.3)	Neutropenia (85%) Thrombocytopenia (51%), Anaemia (50%) CRS (15%) NEs (31%)
Lisocabtagene maraleucel	[43]	Phase 1	83	*68.5* (36-86)	3 *(1-11)*	94	83%	72%	18.2 (12.9–36.3)	15.3 months (6.6–24.9)	16.1 months (range, 0.4–60.5)	Neutropenia (33–58%) Infection (15%) CRS 1% NE 9%
Pirtobrutinib	[36]	Phase 1/2	152	70 (46-88)	3 (1-9)	100	49.3% (41.1-57.6)	15.8%	23.5 months (17.1-NE),	5.6 months (5.3-9.2),	24 months	Neutropenia (13.3%) Infections (19.9%) Bleeding (2.4%) AFib (3.6%)

Table 1: Recently FDA approved therapies for patients with cBTKi relapsed/refractory MCL
(CI = confidence interval; ORR = objective response rate; CR = complete response; OS = overall survival; PFS = progression-free survival; CRS = cytokine release syndrome; NE = neurologic event)

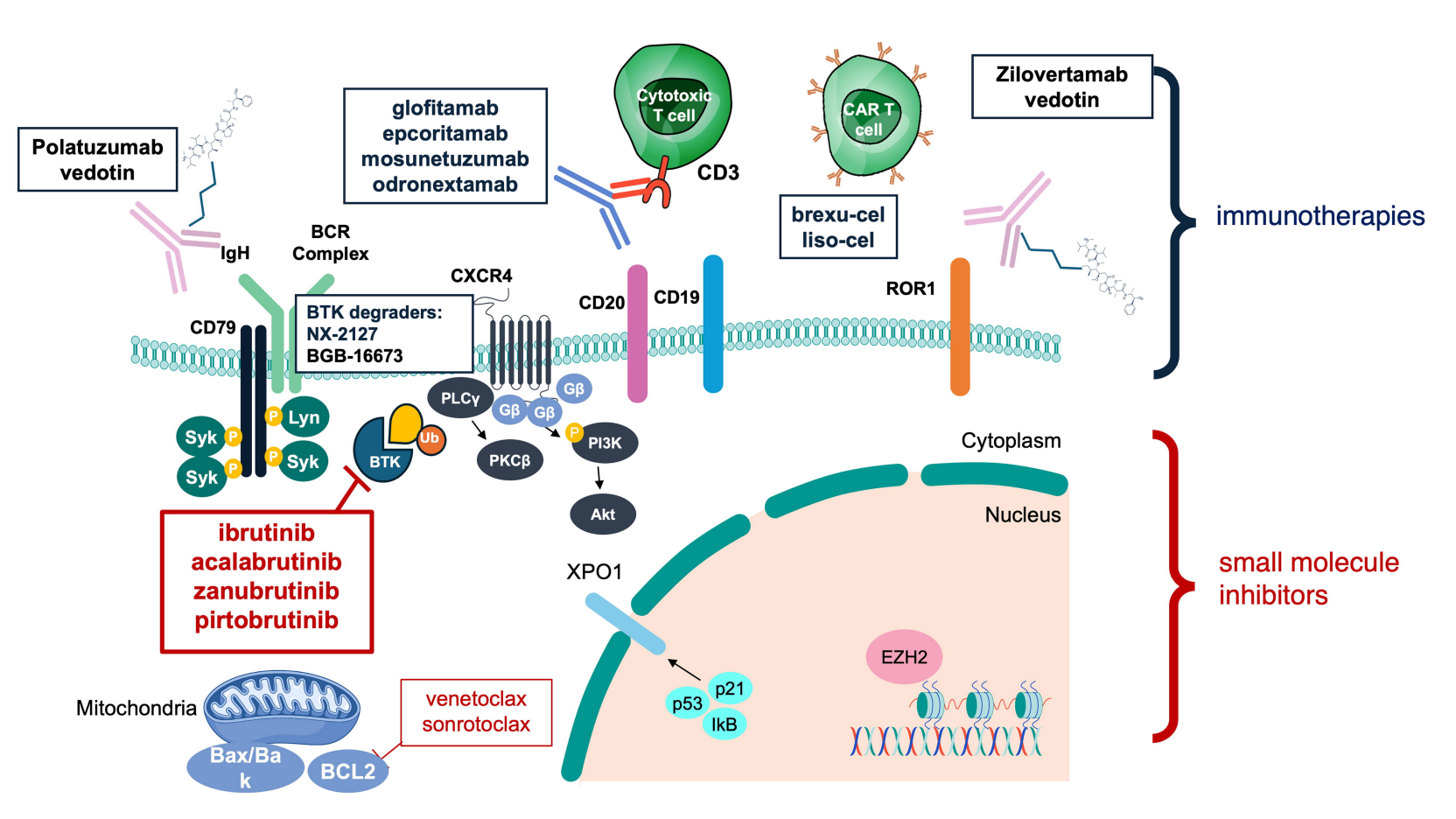
Therapy	Ref	Design	N	Patients with MCL N (%)	Median age, yrs (range)	Response (95% CI)		Major (grade ≥3) treatment-emergent toxicities
						ORR	CR	
Glofitamab	[53]	Phase 1/2	31	100	70 (41-84)	74.2%	71%	CRS (8.3%)
Mosunetuzumab - Polatuzuamab	[56]	Phase 1/2	20	100	68.0 (44–82)	75%	70%	1 patient each 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 1/2	17	100	70 (44-91)	53%	1 patient	Neutropenia 32%, Thrombocytopenia 11% Peripheral neuropathy 7%
NX-2127	[61]	Phase 1a/1b	18	5 (11%)	74 (50-92)	27%	18%	Neutropenia 38.5% Hypertension 14.9% Anaemia 12.8%
BGB-16673	[63]	Phase 1	26	4 (15%)	70.5 (25-83)	67%	1 patient	Neutropenia 15.4%, Lipase increased 3.8%

Table 2: Emerging therapies for patients with relapsed-refractory B-cell non-Hodgkin lymphoma, which have included patients with mantle cell lymphoma
(CI = confidence interval; ORR = objective response rate; CR = complete response; OS = overall survival; PFS = progression-free survival; CRS = cytokine release syndrome; NE = neurologic event, NR = not reported)

Figure legends

Figure 1: Mechanisms of action of selected targeted therapies (adapted from Cheah CY *et al* Ann Oncol 2016;27(5):778-787).

Figure 2: Suggested treatment algorithm for cBTKi relapsed refractory mantle cell lymphoma.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Cytotoxic T cell
CD3
CAR T cell
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liso-cel
Zilovertamab vedotin
immunotherapies
IgH
BCR Complex
CXCR4
CD20
CD19
ROR1
CD79
BTK degraders:
NX-2127
BGB-16673
Lyn
Syk
Syk
Syk
Syk
BTK
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PLCγ
Gβ
Gβ
Gβ
PKCβ
PI3K
Akt
ibrutinib
acalabrutinib
zanubrutinib
pirtobrutinib
Cytoplasm
Nucleus
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small molecule inhibitors
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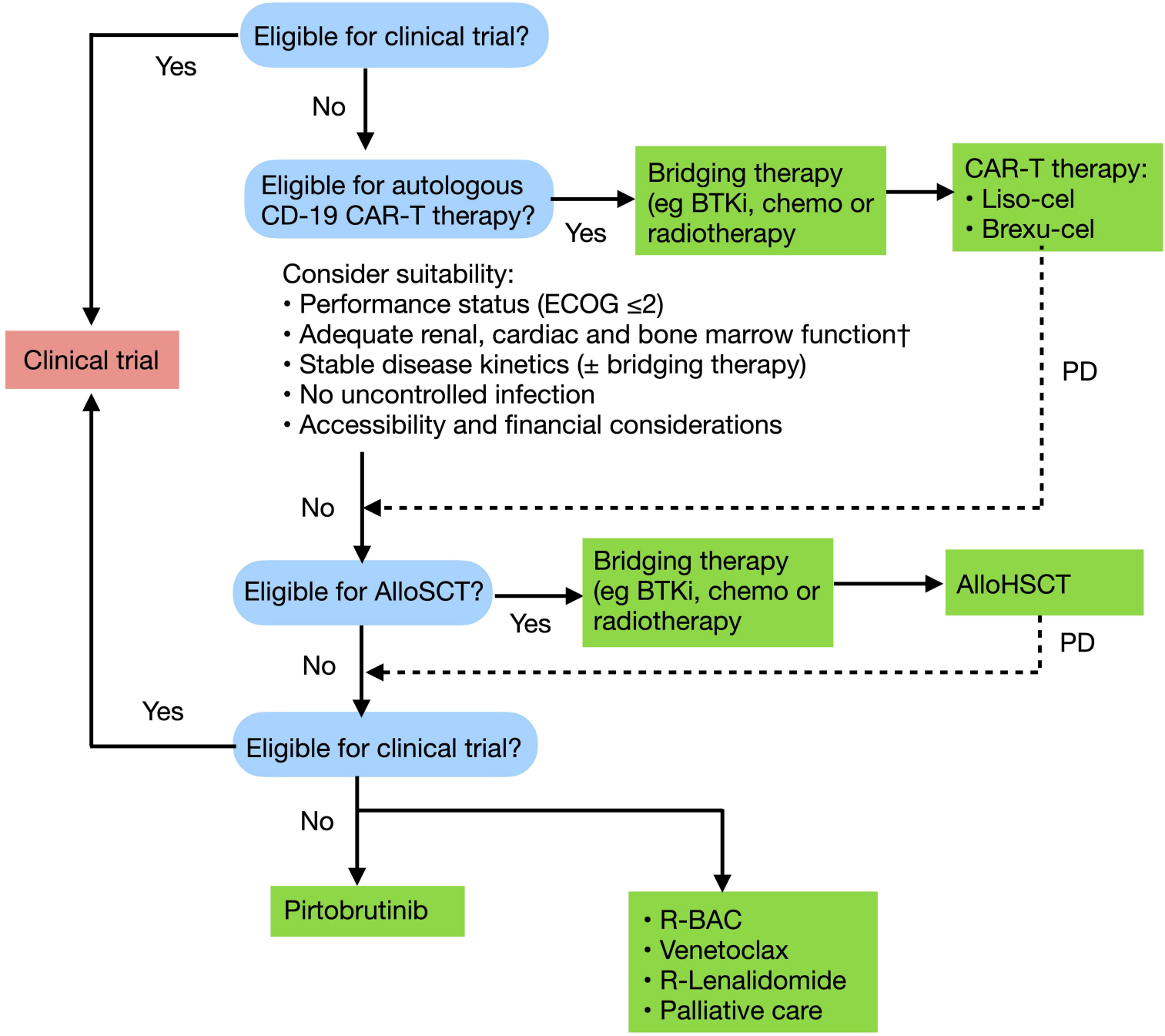

† EBMT/EHA recommendations include CrCl >30 ml/min, LVEF >40%, AST/ALT <4 x ULN