Unmet needs in relapsed/refractory mantle cell lymphoma after failure of covalent Bruton's tyrosine kinase inhibitors: An Italian scenario

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Covalent Bruton's tyrosine kinase inhibitors (BTKis) have revolutionized the treatment of mantle cell lymphoma (MCL) and are now the primary option for patients with relapsed or refractory (R/R) MCL after upfront treatment.[1–3]

Despite the significant improvement in survival seen with the use of BTKis, MCL prognosis remains poor—relapse is unavoidable, and options for patients who are intolerant of these agents, or who progress during treatment, are still limited. While there are several new therapies in approval phase, or final stages of clinical development, much remains to be understood about their optimal usage and sequencing based on disease and patient characteristics.

In 2023, in May and July, a panel of six experts on MCL held two virtual meetings to identify the most crucial unmet needs of patients with R/R-MCL in the Italian context. The experts addressed both the logistical and therapeutic challenges that patients may encounter after failure of BTKi therapy. Following identification of the unmet needs, the panel rated their importance using a 5-point Likert scale ranging from 0 ('not important') to 4 ('very important') (Figure 1).

Overall, most unmet needs were related to the scarcity and restricted availability of effective treatments outside of the clinical trial setting, and limited knowledge regarding their optimal sequencing following covalent BTKi treatment failure.

It was generally agreed that Italian haematology service provision is well established. As a result, the distribution of hub/spoke centres across the country, and the procedures for patient referral, do not usually create significant barriers to the management of patients with R/R-MCL; this contrasts with other European contexts.[4] In Italy, although patients with MCL are usually referred to specialized centres more frequently than those with other haematological conditions, they may face organisational barriers that hinder timely access to novel treatments. In this context, the panellists unanimously rated the participation of Italian patients in international clinical studies, especially early-phase trials, as 'important', and currently unsatisfactory. This situation mainly arises from country-specific administrative and regulatory burden, and the suboptimal allocation of administrative resources for study management activity in some centres.

Limited access to anti-CD19 chimeric antigen receptor (CAR) T-cell therapy in peripheral centres was also rated as 'important'.

Regarding diagnostic needs, the experts identified limitation in the lack of standardization of some molecular testing procedures across centres, particularly for the high-throughput assessment of the TP53 mutational profile.

Panellists agreed that while MCL remains unfortunately incurable, the main treatment goal should be to improve overall survival (OS) and highlighted the strong need for novel therapies Historically, patients with R/R-MCL who failed to respond to covalent BTKis displayed a very poor OS, usually not exceeding 10 months.[5] Within this context, the development of CAR T-cell-based strategies was a significant breakthrough, giving rise to a median OS of approximately 47 months in heavily pretreated patients enrolled in the ZUMA-2 study.[6] The panellists highlighted that these impressive results had been confirmed by extensive real-life evidence.[6]

Brexucabtagene autoleucel is available in Europe for adult patients with R/R-MCL after ≥2 lines of systemic therapy, including a BTKi. However, CAR-T cell therapy might result in significant toxicity, limiting its use to younger and clinically fit patients. Consequently, most patients with R/R-MCL cannot receive CAR T-cell therapy due to age, comorbidity, lack of prior exposure to BTKi, or the aggressive nature of their disease, which may prohibit the typical 3–4 weeks turnaround time required by cellular therapies. To optimize the use of CAR T-cell therapy in eligible candidates, panellists emphasized the need for additional data on treatment selection and sequencing prior to therapy. For example, an exploratory analysis of the ZUMA-2 trial indicated that T-cell functionality may be reduced in patients who had previously been treated with bendamustine; this effect was particularly significant when bendamustine was given within 6 months prior to leukapheresis.[7]

Given the impressive outcomes of CAR T-cell therapy, a further need is exploration of the potential benefits of maintenance/consolidation treatment after cellular therapy, including the role, if any, of allogeneic stem cell transplantation in young, high-risk patients.[8]

Experts also emphasized that there is an increasing need to grant access to new treatment options for patients who cannot receive CAR T-cell therapy, for those who display resistance to it, relapse following therapy, or become intolerant of covalent BTKis. Options should include drugs under investigation, such as the first-in-class,

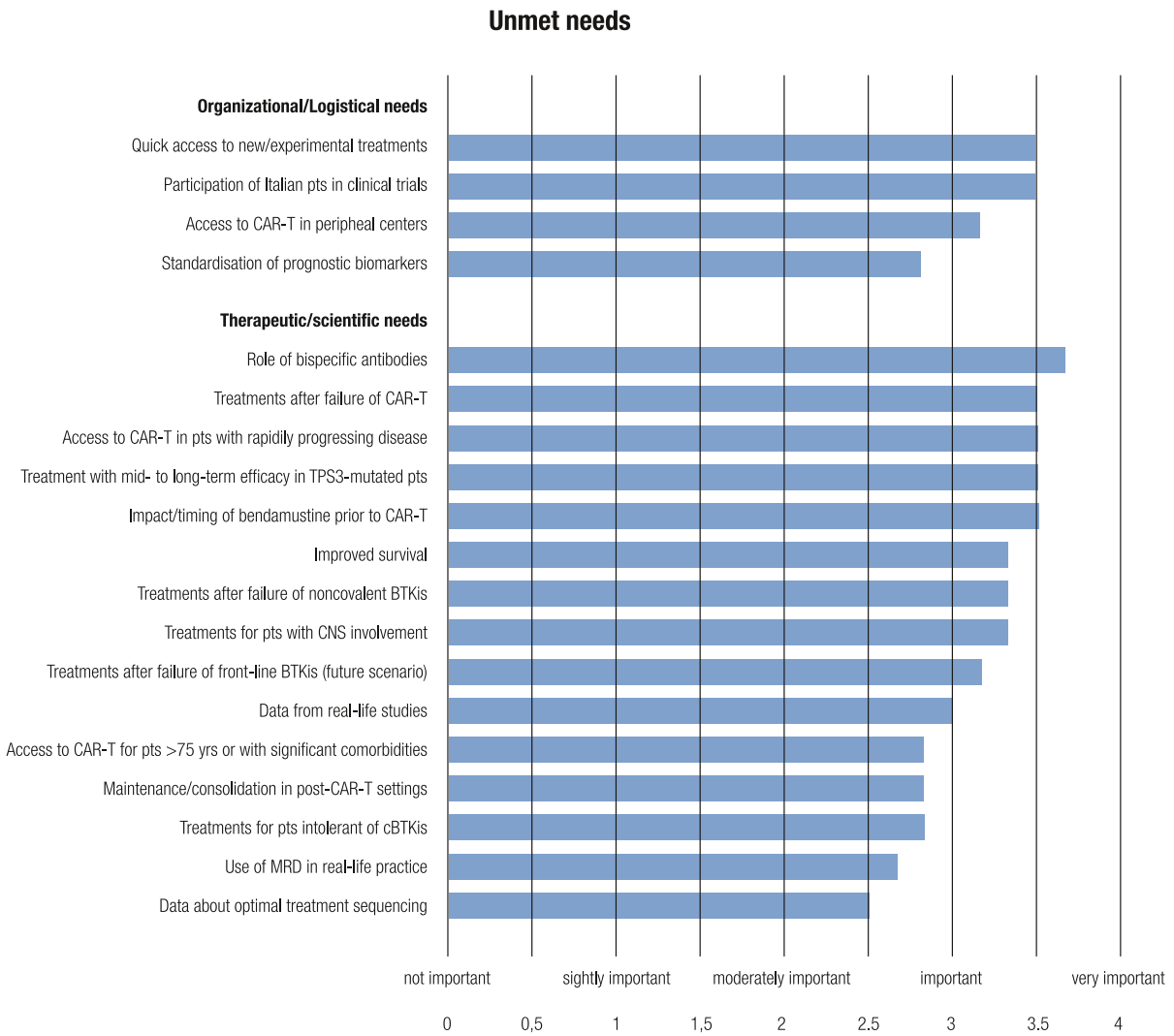

FIGURE 1 Unmet needs in patients with relapsed/refractory mantle cell lymphoma after failure of Bruton's tyrosine kinase inhibitors. Relevance was evaluated on a 5-point Likert scale from 0 ('not important') to 4 ('very important').

non-covalent BTKi, pirtobrutinib, and anti-CD20/CD3 bispecific antibodies.[1]

The results of the phase I/II BRUIN trial indicate that pirtobrutinib is effective and well tolerated in heavily treated patients with R/R-MCL who have failed to respond to covalent BTKis. The median duration of response was nearly 22 months, indicating the potential of pirtobrutinib to restore BTK inhibition.[7] Similarly, bispecific antibodies, including glofitamab and epcoritamab, demonstrated encouraging results, and their role in the management of R/R-MCL needs to be actively investigated.[1] Glofitamab, a 2:1 anti-CD20/anti-CD3 antibody, resulted in a durable, complete response in approximately 68% of patients previously treated with a BTKi.[1,9]

Treatment of patients with central nervous system involvement at relapse, although rare (~4%), was considered an unmet need that could benefit from further evidence-based guidance.[8] Comprehensive characterization of R/R-MCL at the patient level, including TP53 status, Ki67 levels, blastoid morphology, and minimal residual disease (MRD) assessment, was regarded as essential for risk stratification and selection of treatment. The panel highlighted an urgent need for therapies with long-term effectiveness, especially for patients with TP53 mutation. This mutation is associated with an aggressive clinical course and treatment resistance, making it necessary to conduct dedicated research, including prospective trials and real-life studies.[1] MRD status was also identified as a crucial predictive factor, highlighting the need for more specific data to guide its incorporation into clinical practice.[8]

In summary, experts underlined the necessity of further improving the diagnostic approach, and to rethink and clarify the role of conventional and novel treatments in patients with R/R-MCL. The introduction of BTKis in frontline therapy in the near future may potentially result in additional challenges with sequencing and accessing subsequent treatment. More real-life data from risk-stratified populations will be necessary to guide optimal treatment selection and sequencing.

Despite recent improvements, overall patient outcomes with R/R-MCL remain unsatisfactory. Therefore, there is an urgent need to investigate novel agents and treatment options.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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