

# The Emerging Role of Bruton's Tyrosine Kinase Inhibitors in Multiple Myeloma

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Multiple myeloma (MM) remains an essentially incurable plasma cell malignancy despite major advances with proteasome inhibitors, immunomodulatory drugs, anti-CD38 antibodies, and autologous transplantation. Bruton's tyrosine kinase (BTK), a non-receptor kinase central to B-cell receptor signaling, is selectively overexpressed in myeloma stem-like cells and drives both tumor-intrinsic survival pathways and BTK-dependent osteoclast genesis in the bone marrow niche. Ibrutinib, the first covalent BTK inhibitor evaluated in relapsed/refractory MM, showed modest single-agent activity but meaningful responses in combination regimens, though acquired C481S-mediated resistance limited its development. Newer covalent agents improved selectivity without escaping this resistance mechanism, while the non-covalent inhibitor pirtobrutinib and BTK-degrading PROTACs offer mutation-independent strategies. We argue that biomarker selected, combination based, and next generation BTK targeted approaches deserve renewed and focused clinical investigation in multiple myeloma.

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Multiple myeloma (MM) represents the second most frequent hematological malignancy, contributing to about 10% of all blood cancers, which has remained an incurable disease despite the significant advancements in the use of proteasome inhibitors, immunomodulatory agents, CD38-targeting monoclonal antibodies, and autologous stem cell transplantation therapy.<sup>1,2</sup> According to Global Burden of Disease studies, the incidence, prevalence, and disability-adjusted life years of MM are more than doubled over the past three decades and has increased most sharply in environments with a high abundance of resources, where both the effectiveness of diagnostic testing and life expectancy is higher, with males having higher incidence than females.<sup>2</sup> The progress achieved in therapeutic regimens has led to almost a 50% survival rate in multiple myeloma patients during the first five years after diagnosis in well-resourced environments; however, this improvement has not resulted in a cure for the disease.<sup>2</sup> The majority of patients are eventually faced with tumor progression and relapse, and in relapsed/refractory (R/R) multiple myeloma cases, patients demonstrate an increasingly lower effect from each further line of treatment, including shorter periods of remission and ultimately triple and penta-refractory disease. However, in this context, the identification and

manipulation of new targets for therapy become necessary and Bruton's tyrosine kinase (BTK) is a biological target that has been under explored in multiple myeloma (MM). However, targeting BTK in MM has a very sound mechanistic basis.

BTK protein is virtually absent in healthy, terminally differentiated plasma cells, yet it is significantly upregulated in MM cell lines and patient samples, particularly within stem-like CD138<sup>+</sup> MM cells that retain self-renewal capacity and intrinsic resistance to standard therapy.<sup>3</sup> This selective expression pattern is itself attractive from a therapeutic-window standpoint, since it raises the possibility of targeting the clonogenic reservoir of disease while sparing normal, BTK-low plasma cells and thereby limiting on-target toxicity to the humoral immune compartment. Within the tumor cell, BTK signaling feeds into multiple oncogenic pathways, including phosphatidylinositol 3-kinase/AKT and NF- $\kappa$ B, the latter being a well-established driver of bortezomib resistance.<sup>3,4</sup> Constitutive activation of these downstream pathways supports myeloma cell proliferation, anti-apoptotic protein expression, and survival under the metabolic and hypoxic stress typical of the crowded bone marrow niche. Beyond its tumor-intrinsic effects, BTK also shapes the bone marrow microenvironment more broadly. Preclinical work has

shown that BTK-dependent activation of the RANK pathway triggers osteoclast differentiation, contributing both to the characteristic lytic bone destruction of MM and to the release of osteoclast derived growth factors that in turn, support myeloma cell survival in a feed forward loop that links bone destruction to disease progression rather than treating it as a separate, downstream complication. The combined action of BTK inhibition on malignant plasma cells and on their osteoclast-rich niche is particularly relevant given how central bone pathology is to MM related morbidity, accounting for much of the pain, fracture risk, and reduced quality of life experienced by patients and it distinguishes BTK from many other myeloma directed targets that act on the tumor cell alone without a parallel effect on the supportive microenvironment. Clinical experience with BTK inhibition in MM began with ibrutinib, the first covalent BTK inhibitor developed across several B-cell malignancies and subsequently repurposed for investigation in plasma cell disease. Early phase studies demonstrated only modest single agent antitumor activity in R/R MM, but considerably higher response rates were observed when ibrutinib was combined with dexamethasone, with a response rate of approximately 25% at the highest dose tested (840 mg).<sup>5</sup> Subsequent combinations of ibrutinib with established myeloma backbones-bortezomib-dexamethasone, carfilzomib-dexamethasone and pomalidomide dexamethasone, produced encouraging results in phase I/II testing, suggesting that the drug's principal clinical value in MM, if any, would likely lie in combination rather than monotherapy settings.<sup>5</sup> Mechanistically, ibrutinib's capacity to inhibit NF- $\kappa$ B p65 activity appears to sensitize myeloma cells to the apoptotic effects of proteasome inhibitors, providing a clear biological rationale for these combination strategies and offering one explanation for why response rates rose substantially once a partner agent was added.<sup>4</sup> Despite this encouraging signal, ibrutinib was never advanced to registration for MM, largely because of acquired resistance mediated by the Cys481Ser (C481S) point mutation in BTK, which abolishes covalent drug binding and effectively closes off further dose escalation or prolonged single agent use as a viable strategy.<sup>6</sup> The off-target toxicities associated with ibrutinib including atrial fibrillation, bleeding diathesis, and hypertension together with the problem of C481S mediated resistance, prompted development of second and third generation BTK

inhibitors. Second-generation covalent agents such as acalabrutinib and Zanubrutinib offer improved kinase selectivity and a more favorable safety profile, with substantially less off-target inhibition of EGFR, ITK, and other TEC-family kinases.<sup>6</sup> However, because these agents still depend on covalent binding to the Cys481 residue, they remain susceptible to the same resistance mechanism that limited ibrutinib. The emergence of pirtobrutinib, a third-generation non-covalent (reversible) BTK inhibitor, addresses this limitation directly, since its binding to BTK is independent of Cys481 and is therefore unaffected by the C481S mutation.<sup>6</sup>

The pirtobrutinib efficacy in patients with B-cell malignancies experiencing relapse after prior covalent BTK inhibitor therapy was shown in the phase 1/2 BRUIN study, which proved clinical proof of concept for non-covalent BTK inhibition after covalent resistance.<sup>7</sup> It is a very significant step forward and serves as a good reason to evaluate pirtobrutinib and other inhibitors from this class in specific MM trials. As a complement to the development of small molecule inhibitors, the BTK degraders, which were based on the PROTAC technology, are another line of research, allowing not inhibition but knockdown of the BTK protein, and in principle may be effective against some resistance mutations interfering with inhibitor binding.

Despite more than a decade of preclinical promise, BTK inhibitors have yet to translate into an established role in MM therapy, for several interrelated reasons: the absence of adequately powered randomized trial data in this disease, the lack of validated biomarkers predictive of response, and the absence of well-defined combination regimens optimized specifically for MM rather than extrapolated from lymphoid malignancies. The relatively small number of dedicated MM cohorts within BTK inhibitor trials to date, most of which were designed primarily around CLL, mantle cell lymphoma, or Waldenström macroglobulinemia has further limited the field's ability to draw MM-specific conclusions about optimal dosing, sequencing, and patient selection. We believe several directions merit focused investigation going forward. First, biomarker driven trials are needed to define which MM subpopulations, particularly those with constitutive BCRlike signaling and high BTK expression within the stem-like compartment are most likely to benefit from BTK-targeted therapy, allowing future trials to enrich for biologically appropriate

patients rather than testing BTK inhibition in unselected populations; minimally invasive approaches such as flow cytometric quantification of BTK expression on circulating or marrow resident plasma cells could plausibly serve this enrichment role without requiring extensive additional tissue sampling. Second, combination regimens pairing BTK inhibitors with newer immunotherapeutic modalities, such as bispecific T-cell engaging antibodies or CAR-T cell therapy, warrant systematic evaluation; BTK inhibition's immunomodulatory effects on T-cell activation and proliferation could plausibly potentiate these approaches, analogous to combination strategies already being explored in chronic lymphocytic leukemia, where BTK inhibitor immunotherapy pairings have shown encouraging early signals. Third, the bone-protective potential of BTK inhibition deserves dedicated study in patients with MM-associated osteopathy, an area where existing antiresorptive agents (bisphosphonates, denosumab) address symptoms without targeting the underlying BTK-RANK signaling axis; a BTK-targeted approach could in principle complement rather than replace these standard bone-modifying agents.

Finally, the incorporation of non-covalent BTK inhibitors and BTK-targeted PROTACs in early phase trials of MM is both scientifically sound and logistically plausible owing to their safety track record in other types of B-cell malignancies, which will help elucidate whether circumventing C481S based resistance can reestablish the activity signal found with the initial ibrutinib regimens. From a practical standpoint, considering the comparatively lower costs involved in conducting small phase II trials compared to large phase III trials, we feel that academic institutions, even in low resource countries, are well-equipped to provide early proof of concept data to conduct large phase III trials.

Overall, BTK inhibition stands out as a mechanistically sound but clinically understudied approach in multiple myeloma. The shift from irreversible to reversible BTK inhibitors and even protein degraders, which directly counteract the mechanisms of resistance, provides

promising paths in the clinical development of this drug class which were inaccessible to ibrutinib during its early clinical trials in multiple myeloma. The convergence of an increasingly precise understanding of BTK's dual role in myeloma cell biology and bone marrow microenvironment remodeling, together with a maturing pipeline of mutation independent BTK targeting agents, creates a timely opportunity to revisit this target with better tools than were available a decade ago. I would therefore propose that BTK targeted therapy merits renewed attention as a candidate modality in MM, particularly through biomarker driven patient selection and evaluation of next generation inhibitors and degraders, with the potential to contribute meaningfully to the long-term goal of durable disease control and ultimately cure in this still largely incurable malignancy.

## References

1. Tai YT, Chang BY, Kong SY, Fulciniti M, Yang G, Calle Y, et al. Bruton tyrosine kinase inhibition is a novel therapeutic strategy targeting tumor in the bone marrow microenvironment in multiple myeloma. *Blood*. 2012;120(9):1877-1887.
2. Miao X, Wang Z, Wang H, Zeng X, Wang J, Luo B, Yang Y, et al. Global, regional, and national burden of multiple myeloma, 1990 to 2021 and predictions to 2035: an analysis of the Global Burden of Disease Study 2021. *Front Med (Lausanne)*. 2025;12:1609692.
3. Yang YH, Dowell AC, Pan B, et al. BTK is enriched in myeloma stem cell-like cells and is associated with clonogenic growth and resistance. *Leukemia*. 2015;29(11):2268-2271.
4. Elbezanti WO, Al-Odat OS, Chitren R, et al. Development of a novel BTK inhibitor that exerts anti-cancer activities and potentiates response of chemotherapeutic agents in multiple myeloma stem cell-like cells. *Front Pharmacol*. 2022;13:894535. <https://doi.org/10.3389/fphar.2022.894535>
5. El Khatib H, Abdulla K, Nassar L, et al. Advancements in multiple myeloma therapies: a comprehensive review by disease stage. *Lymphatics*. 2025;3(1):2. <https://doi.org/10.3390/lymphatics3010002>
6. Roeker LE. A fresh look at covalent BTK inhibitor resistance. *Blood*. 2024;144(10):1029-1031. <https://doi.org/10.1182/blood.2024025237>
7. Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. *Lancet*. 2021;397(10277):892-901. [https://doi.org/10.1016/S0140-6736\(21\)00224-5](https://doi.org/10.1016/S0140-6736(21)00224-5)