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PIRTOBRUTINIB: A NOVEL BRUTON'S TYROSINE KINASE INHIBITOR WITH EMERGING POTENTIAL IN MALIGNANCIES

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ABSTRACT

Per year there's an increase in the rate of new cases of lymphocytic leukemia 4.6 percent. Approximately 0.6 percent of women or men in their life at some point in their lifetime will be diagnosed with chronic lymphocytic leukemia. Various tyrosine kinases e.g EGFR, FGFR, are unusually activated in most common tumors, including leukemia, glioblastoma, gastrointestinal stromal tumors, and non-small-cell lung cancer. Nowadays BKT inhibitors are used to treat B-cell malignancies, highly potent second generation BTK inhibitors are Acalabrutinib, Zanubrutinib, Tirabrutinib and Orelabrutinib which can act against on various types of tumors. Pirtobrutinib is non-covalent inhibitor of BTK that inhibits the wild type and C481- mutated BTK both, as the most frequent mutation associated with resistance to covalent BTK inhibitor with side effects are that are manageable for instance tiredness, diarrhea and headache. December 2023 Pirtobrutinib (Jaypirca) got approved by FDA for relapse or refractory mantle cell lymphoma in adults.

Keywords *– Pirtobrutinib, CLL, BTK, Non-covalent, Lymphocytic Leukemia*

1. INTRODUCTION

Hematological malignancies, such as lymphoma, leukemia, and multiple myeloma, have significant challenges in terms of treatment and management. Recent advancements in the field of oncology have catalyzed a substantial proliferation in the development of targeted therapies for hematological malignancies. In this context, Pirtobrutinib, also known as LOXO-305 a novel covalent inhibitor of Bruton's tyrosine kinase (BTK), has garnered significant attention for its potential efficacy and safety profile. As an irreversible BTK inhibitor, Pirtobrutinib has demonstrated promising results in preclinical studies, exhibiting enhanced selectivity and potency compared to other BTK inhibitors [1]. Furthermore, its ability to overcome resistance mechanisms commonly observed with other BTK inhibitors makes Pirtobrutinib a formidable candidate for the treatment of various hematological malignancies, including chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) This review aims to comprehensively evaluate the therapeutic potential of Pirtobrutinib in hematological malignancies, shedding light on its mechanism of action, clinical efficacy, safety profile, and future prospects in the field of oncology. Bruton tyrosine kinase (BTK) is an important signaling molecule in the pathway of cell receptors which is pivotal for B-cell proliferation and survival [2]. The development of BTK inhibitors has resulted in substantial advancements in the management of B-cell malignancies [3]; however, the treatment of such conditions remains challenging in geriatric populations. The ibrutinib (the first-in-class BTK inhibitor), Second-generation agents such as Zanubrutinib, Orelabrutinib, Tirabrutinib, and Acalabrutinib were developed with the primary objective of enhancing drug tolerability. More recently, third-generation agents, including Pirtobrutinib and Nemtabrutinib, have advanced into later-stage clinical development, offering additional

therapeutic options [4]. BTK inhibitors have shown profound activity B cell malignancies. The agents have acceptable tolerability, with adverse effects which generally can be managed with change in dosage form.

Table 1: Key differences between available cBTKis and Pirtobrutinib[1,3]

Parameter	Ibrutinib	Acalabrutinib	Zanubrutinib	Pirtobrutinib
BTK binding	Covalent C481.	Covalent C481.	Covalent C481.	Reversible ATP pocket Distant from C481
Half life	6 hours	1 hour	4 hours	20 hours >90% BTK inhibition
Absorption	From GI	From GI	From GI	From GI
vd	10,000 L	34 L	881 L	32.8L
Metabolism	by CYP3A5 and CYP3A4	By CYP3A ACP-5862 (active metabolite)	by CYP3A4.	By liver enzymes- CYP3A and PHII glucuronidation- UGTI A8 and UGTIA9.
Clearance	Around 8.4 L/h	mean apparent oral clearance observed - 159 L/hr	The mean (%CV) apparent oral clearance (CL/F) - 182 (37%) L/h.	2.02 L/h
Potential interactions	No significant interactions With fatty meal increase the serum concentration with grapefruit	No significant interactions With fatty meal increase the serum concentration with grapefruit	No significant interactions With fatty meal increase the serum concentration with grapefruit	No significant interactions With fatty meal
BTK Y223 autophosphorylation	Inhibited	Inhibited	Inhibited	Inhibited
BTK Y551 phosphorylation	Common	Reported	Reported	Not much effective against C481s
Off-target hits†	BLK BMX BRK EGFR HER2 HER4 ITK JAK3 RLK TEC	HER4	BLK BMX BRK EGFR HER4 RLK	BRK HER4

2. MECHANISM OF ACTION

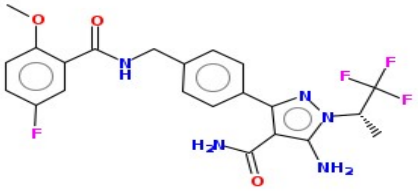

Figure 1. Structure of Pirtobrutinib

The antibody functions as a receptor located on the surface of β cells. It needs some modification, heavy chain of antibodies at C terminal usually undergoes modification such as addition of spacer region ,transmembrane region and addition of short chain amino acid (2-3) at cytoplasmic region . Attachment of antigen on the β cell receptor cannot activate the β cell as the cytoplasmic portion is small therefore downstream signaling will not take place Igα and Igβ help βcell receptor for activation of β cell . The cytoplasmic

portion of Igα and Igβ consist of an immune- receptor Tyrosine activation motif (ITAM) which has amino acid Tyrosine. As the antigen attaches to the β- cells receptor it moves towards the lipid raft region in which there's high cholesterol present in the membrane and abundant amount of tyrosine kinase enzyme present in the membrane. Src families such as Lyn tyrosine kinase are important signaling intermediaries that cause phosphorylation of ITAM. Adaptor protein BLNK gets phosphorylated by activated Syk (kinase enzyme) which causes initiation of downstream signaling PLC-γ2 it also activates the lipid kinase PI3KS which converts PIP2 to PIP3. The BTK phosphorylate phospholipase c(PLCγ2) and AKT activates MTOR pathway. The breakdown of PIP2 into two components IP3 and DAG: the IP3 removes calcium from the endoplasmic reticulum and the 4 calcium ions attaches to calmodulin which thereby attaches to calcineurin (phosphatase enzyme) allows NFAT to enter into the nucleus and DAG causes activation of PKCβ (protein kinase) which in turn stimulate nucleus factor kappa light-chain-enhancer of activated β-cells (NF-Kβ) pathway factor. Unlike other BTK inhibitor that forms covalent bond which is irreversible Pirtobrutinib non covalently binds to BTK at the ATP-binding site and effectively inhibits both wild type BTK and BTK with mutations at the Cys 481 Residue, which offers resistance to other BTK inhibitor. Blockade of BCR signaling leads to apoptosis and inhibition of cancerous β cells [5,6]

While certainly a mechanism of resistance, recent findings have highlighted a spectrum of non-BTK mutants in patients who have shown improvement on Pirtobrutinib(table 1). Surprisingly, a majority of these BTK mutants are kinase-dead, with inactive kinase sites that are unable to auto phosphorylate Y223, yet they still demonstrate active downstream signaling. These kinase-dead mutants are rare in patients who exhibit resistance to Ibrutinib but are generally more prevalent in those treated with Pirtobrutinib or Zanubrutinib. This disparity may be attributed to Ibrutinib's off-target effects on HCK340; the recruitment of HCK could potentially explain how kinase-dead BTK mutants continue to signal. Having after treatment with the drugs like Pirtobrutinib and acalabrutinib the gatekeeper mutation at t474 have reported in patient with slow and steady increase in disease condition [7-9]

2.1 Efficacy in Mantle Cell Lymphoma (MCL)

Several reports have observed the effectiveness of ibrutinib, and Zanubrutinib as monotherapy in adults having relapsed MCL after one or more prior therapies has been demonstrated in single-arm phase II clinical trials [5]. Differences in trial design and patient populations limit the ability to compare data across trials, but drugs have clear efficacy in the treatment of MCL with progression free survival generally around 1–2 years [5]. Further, the open-label randomized controlled phase III Ray trial has demonstrated that, relative to the mTOR inhibitor temsirolimus, ibrutinib prolongs PFS and is associated with a significantly higher all-inclusive response rate in t/o MCL. Present available data from phase I and phase I/II trials also support the efficacy of Pirtobrutinib as monotherapy in t/o MCL [11,14]. the trials of Pirtobrutinib involved heavily pretreated patients with good activity observed, including in patients with resistance or intolerance to prior BTK inhibitor therapy Ibrutinib has also been evaluated in clinical trials in combination with various agents, including the anti-CD20 monoclonal antibody rituximab [13-15]and the BCL2 inhibitor venetoclax. Pirtobrutinib has demonstrated good overall response rates and progression-free survival, suggesting its potential as a valuable therapeutic option for relapsed or refractory MCL. The safety profile of Pirtobrutinib in these trials has also been favorable, with manageable side effects that make it suitable for long-term use. This positions Pirtobrutinib as a critical addition to the treatment arsenal for MCL, particularly for patients who have limited options due to resistance or intolerance to other therapies. [16-20]

2.2 Efficacy in Chronic Lymphocytic Leukemia (Cll)

Chronic Lymphocytic Leukemia (CLL) is a common type of B-cell malignancy characterized by the accumulation of functionally incompetent lymphocytes. While first-generation Bruton's tyrosine kinase (BTK) inhibitors like Ibrutinib have revolutionized the treatment landscape for CLL, resistance and intolerance have emerged as significant challenges. Pirtobrutinib, a next-generation, non-covalent BTK inhibitor, has shown promising efficacy in overcoming these hurdles, particularly in patients who have relapsed or are refractory to other BTK inhibitors [17].

Pirtobrutinib's non-covalent binding to the BTK enzyme distinguishes it from earlier inhibitors that covalently bind to the cysteine 481 (C481) residue. This difference is crucial because mutations at this site, particularly the C481S mutation, are a common

mechanism of resistance to covalent BTK inhibitors like Ibrutinib. Pirtobrutinib's ability to effectively inhibit both wild-type and C481-mutated BTK allows it to retain efficacy where other BTK inhibitors fail, offering a valuable option for patients with resistant CLL [3].

Clinical trials have highlighted Pirtobrutinib's efficacy in CLL, particularly in heavily pretreated patients. The Phase I/II BRUIN trial, which included patients with relapsed or refractory CLL, demonstrated notable results [3,11]. In this study, Pirtobrutinib showed an overall response rate (ORR) of approximately 68% in patients who had previously been treated with covalent BTK inhibitors [11]. This response rate is particularly significant given the challenging nature of treating CLL after failure of previous BTK inhibitor therapy.

In addition to its efficacy in overcoming resistance, Pirtobrutinib has been well-tolerated in CLL patients, with a safety profile that supports its use in this population. The adverse events observed in clinical trials have generally been manageable, with the most common side effects being mild to moderate, such as fatigue, diarrhea, and headache. Importantly, the incidence of cardiovascular events, a notable concern with first-generation BTK inhibitors, appears to be lower with Pirtobrutinib, potentially making it a safer option for long-term treatment [18].

Furthermore, Pirtobrutinib has shown promise in combination with other therapeutic agents. Early studies suggest that combining Pirtobrutinib with agents such as venetoclax, a BCL-2 inhibitor [5], or anti-CD20 monoclonal antibodies could further enhance treatment outcomes, particularly in high-risk CLL patients. This potential for combination therapy expands the therapeutic options for patients and may lead to more durable responses.[19]

In summary, Pirtobrutinib represents a significant advancement in the treatment of CLL, particularly for patients with resistant or refractory disease. Its ability to overcome common resistance mechanisms, coupled with its favorable safety profile, positions it as a vital tool in the ongoing effort to improve outcomes for CLL patients.

3. FUTURE DIRECTIONS FOR PIRTOBRUTINIB

Pirtobrutinib is approved by FDA for patients with conditions such as Mantle Cell Lymphoma, also those previously received cBTK is Phase III studies investigating Pirtobrutinib in earlier treatment lines and directly comparing it to covalent BTK inhibitors are currently in progress (see supplemental Table 1). A first-line approval strategy is being sought exclusively for CLL. In R/R MCL, the sole phase 3 trial compares Pirtobrutinib to the investigator's choice of cBTKi. The phase 3 development program in CLL comprises 4 studies: 2 evaluate Pirtobrutinib compared with standard-of-care.

1L (BR) and R/R regimens (BR or idelalisib + rituximab); 1 compares Pirtobrutinib with ibrutinib in both 1L and R/R CLL; the fourth compares a triplet of Pirtobrutinib + venetoclax and rituximab versus venetoclax + rituximab (VR) in R/R CLL. The VR vs Pirtobrutinib + venetoclax and rituximab study represents the first major trial of time-limited venetoclax in patients with progression after covalent BTKi therapy; 80% of the patients enrolled will be BTKi pretreated. On the other hand, in the trial of MURANO, which contributed to approval of venetoclax + rituximab, the number of patients received the previous the inhibitors of B-cell receptor–signaling were about 2.5% to 2.7%. Several investigator-initiated Phase II studies are exploring new combination strategies in first-line and relapsed/refractory CLL, Richter's transformation (RT), and relapsed/refractory MCL with venetoclax.

Several clinical trials, summarized in Table 2, are ongoing to establish the role for Pirtobrutinib in the treatment of B-cell malignancies. Notably, prior venetoclax therapy is not required for enrollment on this trial. If successful, this trial could result in the approval of Pirtobrutinib in the post-covalent BTKi setting, providing an additional therapeutic option for patients who have contraindications to Venetoclax therapy [3], including significant renal disease or the inability to complete the necessary dose ramp for tumor lysis syndrome monitoring, poses challenges.

Table 2. Ongoing phase 3 clinical trials with Pirtobrutinib [3].

Trial	Population	Experimental Arm	Control Arm
NCT05023980, phase 3	Untreated CLL/SLL	Pirtobrutinib	Bendamustine + Rituximab
NCT04965493, phase 3	Previously treated CLL/SLL	Pirtobrutinib + Venetoclax + Rituximab	Venetoclax + Rituximab
NCT04666038, phase 3	BTK inhibitor pre-treated CLL/SLL	Pirtobrutinib	Investigator's choice of Idelalisib + Rituximab or Bendamustine + Rituximab
NCT04662255, phase 3	Previously treated, BTK inhibitor naïve MCL	Pirtobrutinib	Investigator choice of covalent BTK Inhibitor

Additionally, the availability of Pirtobrutinib could address a significant unmet need in CLL by providing an effective treatment option for patients who have previously received covalent BTKi and venetoclax therapies. Real-world data cited previously already suggests that in 'double-exposed' patients, treatment [20-27]with a non-covalent BTK[28]. Table 2. Ongoing phase 3 clinical trials with Pirtobrutinib. Trial Population Experimental Arm Control Arm NCT05023980, phase 3 Untreated CLL/SLL Pirtobrutinib Bendamustine + Rituximab NCT04965493, phase 3 Previously treated CLL/SLL Pirtobrutinib + Venetoclax + Rituximab Venetoclax + Rituximab NCT04666038, phase 3 BTK inhibitor pre-treated CLL/SLL Pirtobrutinib Investigator's choice of Idelalisib + Rituximab or Bendamustine + Rituximab NCT04662255, phase 3 Previously treated, BTK inhibitor naïve MCL Pirtobrutinib Investigator choice of covalent BTK Inhibitor BTK, Bruton's tyrosine kinase; CLL/SLL, In chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and mantle cell lymphoma (MCL), BTK inhibition has been shown to result in longer progression-free survival (PFS) compared to PI3K inhibitors or chemoimmunotherapy[29-32].

The NCT04662255 in MCL trial is currently recruiting those who are BTK inhibitor-naïve and also have been treated previously. Participants will be randomized to receive either Pirtobrutinib or one of the three FDA-approved covalent BTK inhibitors, with PFS as the primary endpoint. Should Pirtobrutinib lead to superior PFS, this may lead to improved out- comes among MCL patients needing BTK inhib-itor therapy. This information will give an understanding of information regarding Pitrobrutinibs toxicity profile with other cBTK inhibitors

Studies on cell lines have shown that kinase domain mutations may lead to resistance against both non-covalent and covalent BTK inhibitors, which raises concerns that patients who become refractory to Pirtobrutinib might also exhibit resistance to covalent BTK inhibitors, even if they have not been previously treated with them. It is still uncertain whether patients who receive Pirtobrutinib earlier in their treatment will develop similar genetic escape mechanisms. Furthermore, it is important to investigate whether patients with Waldenström's Macroglobulinemia (WM), Mantle Cell Lymphoma (MCL), or Richter's Transformation (RT) might develop these same mutations.

4. CONCLUSION

Targeting BTK has led to significant advancements for patients with B-cell malignancies, and the development of Pirtobrutinib builds on these successes by offering a new therapeutic option for those with CLL/SLL, MCL, and other lymphomas. Pirtobrutinib effectively bypasses C481 mutations, which are a common genetic resistance mechanism to covalent BTK inhibitors, thereby enhancing the role of BTK inhibition in treating these diseases and providing an additional therapeutic option for patients who are refractory to covalent BTK inhibitors.

Pirtobrutinib exhibits high selectivity for BTK, contributing to its favorable tolerability profile, which results in a low rate of treatment discontinuations due to adverse events. Notably, Pirtobrutinib has shown a lower incidence of atrial fibrillation compared to covalent

BTK inhibitors. While the majority of ongoing clinical trials focus on CLL/SLL, upcoming data on MCL may establish Pirtobrutinib's role in the relapsed/refractory disease setting, where significant progress is needed. Additionally, Pirtobrutinib may prove beneficial in other aggressive B-cell malignancies, such as Richter's Transformation (RT), where current therapies yield poor outcomes. Pirtobrutinib builds on the success of covalent BTK inhibitors by demonstrating efficacy in patients with BTK inhibitor-refractory disease and maintaining a strong safety profile. Numerous trials are underway to further define the optimal use of Pirtobrutinib. However, the best approach to treating patients who develop resistance to Pirtobrutinib remains unknown.

understanding of molecular mechanisms of relapse expand, personalizing therapy by selecting subsequent treatments based on molecularly predicted sensitivity becomes critical. Preliminary findings from studies on BTK degrader molecules indicate that these compounds may be effective against diseases with mutated BTK, including those with kinase-dead mutations that lead to pan-resistance to BTK inhibitors. Emerging immunotherapies, including bispecific antibodies and chimeri

antigen receptor (CAR) T-cell therapies, offer a mutation-agnostic approach to treating patients with multi-refractory disease. These therapies may also be synergistically combined with Pirtobrutinib, similar to the combination of Ibrutinib with lisocabtagene maraleucel in CLL. The incidence of BTK mutations during covalent BTK inhibitor therapy is most prevalent in patients with high-risk genomic features, such as del(17p) and complex karyotypes. The BRUIN trial specifically enrolled multi-refractory patients with a predisposition to resistance mutations. Evaluating Pirtobrutinib in earlier treatment stages and in populations with lower-risk profiles will be crucial for understanding its potential to induce long-term remissions, as seen in first-line studies with covalent BTK inhibitors. Therefore, we await data from studies investigating Pirtobrutinib in combination with other therapeutic agents in the treatment of Richter's Transformation (RT).

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