REVIEW ARTICLE

Narrative Review on Ibrutinib: A New Targeted Therapy for Hematologic Cancers

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Abstract

Ibrutinib is a potent and highly selective irreversible Bruton's tyrosine kinase (BTK) inhibitor. It has transformed the treatment of B-cell lymphomas, particularly mantle cell lymphoma and chronic lymphocytic leukemia (CLL). It is thought that BTK is essential for the survival and activation of healthy and cancerous B-cells. In recent years, an oral BTK inhibitor called ibrutinib has emerged as a ground-breaking treatment for hematological malignancies such as CLL. The viability of ibrutinib, though, could not end there. This drug has been identified to inhibit several additional kinases linked to solid cancers (epidermal growth factor receptor, human epidermal growth factor receptor 2). Recent findings suggest that BTK may be a target for anti-solid tumor treatment. As a result, research has been done on ibrutinib, a BTK-inhibitor, as a potential treatment for solid tumors. This review provides an in-depth analysis of an intriguing medication, emphasizing its mechanism of action, metabolism, safety profile, clinical studies, authorized applications, and prospects in the future.

Key words: Ibrutinib, Hematological cancer, Chronic lymphocytic leukemia, Bruton's tyrosine kinase

INTRODUCTION

Cancer's mortality and incidence rates have increased significantly in recent years, and it is now acknowledged as one of the leading causes of death globally.[1-3] There are several different and intricate factors at play here. Still, they represent the growing and growing of the world's population as well as the increasing prevalence and distribution of several factors associated with cancer risk. Developing a monoclonal population of tiny, mature-appearing CD5+ B cells in the blood, bone marrow, and lymphoid organs is the hallmark of the neoplastic illness known as chronic lymphocytic leukemia (CLL).[4] Genetic variables have been discovered to play a role, even if the reasons remain unclear. Ninety per cent of patients are older than fifty, with a median age of 67 upon diagnosis. The incidence is twice as high in males as in women. Upon diagnosis, about half exhibit splenomegaly, and over 3/4 of those diagnosed have lymphadenopathy.[5] The accepted treatment for CLL is chemotherapy. However, in the modern period, its shortcomings are becoming increasingly obvious. Numerous therapeutic targets have been identified due to the thorough investigation of carcinogenesis and other features of cancer cells. The small-molecule inhibitor ibrutinib is one such tailored medication that has revolutionized the way indolent lymphoma therapy is approached.

Mantle cell lymphoma (MCL) and CLL are two lymphoid cancers that the Food and Drug Administration (FDA) can treat with the recently authorized medication ibrutinib. A Bruton's tyrosine kinase (BTK) inhibitor makes malignant cells more susceptible to apoptosis, resulting in lymphocyte redistribution throughout the tissue. We thoroughly analyze this intriguing medication, emphasizing its safety profile, trials, metabolism, and authorized applications.[6]

DEVELOPMENT OF IBRUTINIB

Celera Genomics initially created ibrutinib to produce tiny compounds that permanently block BTK. Then, Pharmacyclics acquired Celera's miniature molecule BTK inhibitor development program in April 2006 and continued it.

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Based on the identification of anti-lymphoma characteristics *in vivo*, PCI-32765 (ibrutinib) was selected for additional preclinical development.[7]

Dimethyl sulfoxide, methanol, and water are the only solvents in which imatinib cannot dissolve. It has $C_{25}H_{24}N_6O_2$ as its empirical formula. Nov. 13, 2011 – and Feb. 14, 2011 – the US FDA approved ibrutinib for the treatment of MCL.[8]

A RECOGNIZED INDICATION BY THE FDA

The Indian Central Drugs Standard Control Organization (CDSCO) granted ibrutinib authorization in 2015, as did the US FDA in 2013. MCL: Individuals with preferably one prior therapy appointment.

1. In minor lymphocytic lymphoma or CLL, there is a 17p deletion.
2. Major immunoglobulinemia Waldenström (WM).
3. Patients with MZL have had at least one prior anti-CD20-based therapy.
4. Chronic GVHD after at least one comprehensive therapy attempt that was unsuccessful (*indications approved by the CDSCO).

Adenocarcinoma of the gastroesophageal junction, pancreatic carcinoma, multiple myeloma, follicular lymphoma, and DLBCL are among the FDA-approved orphan designations.[9]

PHARMACOLOGY

The medication is quickly absorbed after oral administration, and the maximal plasma concentration is obtained in 1–2 h. When taken with meals, its oral bioavailability doubles, whereas it is just 2.9% when fasting. For 24 h following oral delivery, the BTK site is fully occupied. The medication has a half-life of 4–13 h and is excreted 80% through feces and <10% through urine.[10]

POSOLOGY OF IBRUTINIB

- WM and CLL: 420 mg once a day, divided into three 140-milligram capsules
- 4 × 140 mg capsules containing 560 mg of MCL, MZL, or GVHD once daily
- It is given once a day when fasting (30 min before or 2 h after a meal)
- Treatment is given continuously until the illness worsens or the patient becomes intolerable.[9,10]

MECHANISM OF ACTION

BTK has a solid biological basis, making it a prime target for treating B-cell malignancies like CLL.[11] Ibrutinib, a recombinant tyrosine kinase inhibitory substance, specifically binds BTK using covalent and irreversible binding. By blocking survival signals from the microenvironment, such as the tumor necrosis factor (TNF)-family B-cell stimulating variable, CD40 L, interleukin-6 [IL-6], IL-4, and TNF-α, it stops CLL cells from thriving and reproducing.

Ibrutinib has anti-proliferative properties, causing tissue-resident CLL cells to be redistributed into the bloodstream and the lymph nodes to atrophy quickly. This hindrance to leukemic cells' ability to homing causes a prolonged buildup of transcriptionally inactive lymphocytes in the peripheral circulation. These lymphocytes mimic quiescence and energy and have a low mitotic index.[12]

DRUG METABOLISM

One can administer ibrutinib orally. The consumption of food doubles the absorption. At a steady state, the distribution's apparent volume is around 10,000 L.[13] Metabolic processes are the primary means of ibrutinib elimination. Cytochrome P450, CYP3A, and, to a lesser degree, CYP2D6 are the main enzymes that metabolize it. Compared to ibrutinib, PCI-45227 is 15 times as powerful as the active metabolite.[14] 4–6 h is ibrutinib's half-life. Once metabolism has occurred, ibrutinib is mainly excreted in feces. Ninety per cent of the radiolabelled excretion product in urine and just 1% in feces comprise metabolites; unchanged ibrutinib makes up the remaining dosage.[13]

ADVERSE EFFECT

The adverse effect profile of ibrutinib differs significantly from that of standard CLL regimens. The research that is now available indicates that adverse consequences are more prevalent among older people.

There are several reasons to stop therapy, such as grade 3 non-hematological toxicity that has just started or is getting worse, grade 3 neutropenia associated with infection or fever, and grade 4 hematological toxicities. Once the toxicity has subsided, therapy is restarted at the initial dose. If toxicity returns, one capsule is removed from the dosage; a second decrease may be required if necessary. Ibrutinib should be stopped entirely if toxicity returns after two dosage decreases.[15]

CLINICAL TRIALS OF IBRUTINIB

In November 2013, the FDA authorized ibrutinib for MCL. According to a study of 111 MCL individuals whose disease had reappeared or whose prior medications were ceaselessly working, permission was given. In the PCYC-1104 phase II

study, the average response rate (ORR) with ibrutinib was 68%, with a satisfactory % response rate of 21%. Moreover, the median reaction period was 17.5 months.[16]

Based on this evidence, ibrutinib was eventually approved by the FDA and given the status of breakthrough treatment. In February 2014, the FDA expanded the use of ibrutinib authorization to include CLL sufferers who had undergone at least one previous treatment based on a single-arm research study demonstrating a persistent enhancement in ORRs.[17] Forty-eight participants in the phase Ib/II PCYC-1102-CA trial who received 420 mg of ibrutinib daily as a single treatment expressly supported the expedited approval.[18]

According to the FDA, during the average follow-up period of 15.6 months, 58.3% (all partial reactions) of those chosen participants had an ORR. However, the response might extend up to 24.2 months. Three different people receiving a daily dosage of 420 mg of ibrutinib because of insufficient lymphocytic lymphoma (SLL), as well as data from 34 study participants who received the daily dose of 840 mg, were not included in the analysis utilized for the approval. As a second-line therapy, when two drugs were compared head-to-head for the management of recurring CLL or SLL, ibrutinib functioned significantly better than atumumab. In addition, ibrutinib significantly improved the entire group's survival, with a hazard coefficient of 0.43 for mortality and a $P = 0.005$. Following a full year of therapy, the group that received treatment on ibrutinib exhibited an average survival rate of 90%, though the group on atumumab demonstrated an overall longevity rate of just 81%. The ibrutinib group's ORR was considerably more significant than the atumumab group's (42.6% vs. 4.1%, $P < 0.001$).[19]

A SIDE EFFECT OF IBRUTINIB

The most significant and dangerous adverse effects are infections, bleeding, myelosuppression, renal toxicity, and secondary primary cancers, particularly those of the skin.[20] Thrombocytopenia, diarrhea, neutropenia, anemia, tiredness, musculoskeletal discomfort, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, stomach pain, vomiting, and anorexia were the most frequent side events (≥20%) which were reported.[21] Pneumonia, stomach discomfort, atrial fibrillation, diarrhea, exhaustion, and skin infections are the most frequent ≥3-grade non-hematological side effects.[22]

PRECAUTIONS

It is recommended to take ibrutinib orally along with a glass of water. It ought to be consumed as a whole. It is not recommended to open, break, or chew food before swallowing.[23] Ibrutinib should not be taken with grapefruit or Seville orange-containing foods or beverages. It is advised that the patient consumes more fluids. Drugs that interfere with CYP 3A will impact the efficacy of ibrutinib since CYP 3A mostly metabolizes it. Hepatic impairment is exacerbated by its toxicity. In ongoing lymphocytosis, treating physicians should exercise greater caution to avoid abruptly stopping ibrutinib since these cells are transcriptionally inactive.[24] If the patient has an allergy to any of the medication's ingredients, is pregnant or nursing, has liver or kidney issues, high blood pressure, blood difficulties, bleeding issues, or has just had surgery or plans to have surgery, they should not use ibrutinib.[25]

APPLICATIONS OF IBRUTINIB IN VARIOUS CANCER

Lung cancer

Gao *et al*. used naked mice with xenograft tumors as research subjects in their investigation. Researchers employed the non-small cell lung cancer (NSCLC) H1975 cell line, which has a L858R/T790M mutation that made the malignancy resistant to erlotinib. Researchers examined the differences in survival times (ST) between three groups of mice: Those treated with erlotinib, placebo, and ibrutinib (both sold by Selleck Chemicals, Houston, TX, USA). They found that the group receiving ibrutinib had a significantly longer ST than the other two groups combined: In comparison to the placebo or erlotinib-treated categories, which exhibited median ST of 17.8 days (95% confidence interval [CI] = 14.3 to 21.3 days) and 29.8 instances (95% CI = 26.0 to 33.6 days), respectively, for the ibrutinib-treated group.[26]

When researching this topic, Fu *et al*. concentrated on distinct facets, assessing ibrutinib's involvement in tumor cell-platelet crosstalk in lung cancer. Co-culturing thrombocytopenia with A549 cells (American Type Media Collection, Manassas, VA, the United States of America) increased malignant cells' ability to proliferate, migrate, and invade. However, the impacts of ibrutinib therapy swiftly abolished these effects.[27]

After doing research, Zhang *et al*. chose to concentrate on Ibr-7, a derivative of ibrutinib, rather than the drug itself. According to the investigators, the antiproliferative impact of ibrutinib was less than that of Ibr-7. Nevertheless, half-maximal inhibitory concentrations (IC_{50}) for epidermal growth factor receptor (EGFR) could be reached *in vivo* for both ibrutinib and Ibr-7. Interestingly, ibrutinib reduced AKT and ERK phosphorylation, while Ibr-7 significantly inhibited downstream signaling, which includes mTOR, p-S6K, and p-S6. Although mTORC2 is influenced by both medications, only Ibr-7 can dephosphorylate mTORC1. The scientists suggested that mTORC1 inhibition could be this derivative's potential anticancer action when they found that EGFR inhibition was not required for the anti-cancer effect of Ibr-7. Furthermore, the peak serum concentration (C_{max}) of Ibr-7 was less than half that of ibrutinib; as a result, there is

potential for enhancement in Ibr-7's bioavailability. For this reason, biomaterial encapsulation or molecular alteration was suggested as a potential remedy.[28]

A noteworthy disparity between preclinical and clinical research about ibrutinib's viability in NSCLC may be observed. We believe that variations in the ibrutinib pharmacokinetics seen by Wu *et al*.[26] between *in vitro* and *in vivo* are probably the cause, although the exact causes have not yet been determined. Moreover, the patient cohort that Hong *et al*.[34] researched may not completely represent all individuals with NSCLC diagnoses. The patients in this trial have previously experienced a median of three therapeutic failures. One may hypothesize that because this cohort was drug-resistant, the study's findings that looked at a wider population could be different. However, it is believed that ibrutinib, in conjunction with other medicinal products, should be the primary objective of future study. As found by Sagiv-Barfi *et al*., inhibitors of PD-L1 may be a worthwhile alternative to consider.[29]

Ovarian cancer

High levels of BTK expression in cancer cells with metastatic and advanced stages of the illness were observed by Zucha *et al*. (2015), who looked at the function of BTK and BTKi in ovarian cancer. The researchers discovered that cell resistance to platinum-based medications was correlated with increased expression of cancer stem cell (CSC) markers throughout the subsequent phase of this investigation. Since BTK plays a crucial role in controlling ovarian CSC, the authors postulated that BTK contributes to drug resistance to platinum-based therapies. This suggests that ibrutinib could be used as a platinum sensitizer in this setting. Moreover, ibrutinib has been seen to reduce malignant cells' Sox2/Bcl-xL expression and BTK phosphorylation, reducing the fraction of CSCs and the cells' ability to self-renew. Therefore, the authors verified that the overexpression of BTK was responsible for the resistance to the platinum-based medications.[30]

Breast cancer

Eifert *et al*. revealed in 2013 that BTK-C, a new isoform of BTK, prevents breast cancer cells from undergoing apoptosis.[31] After doing further research in 2016, the researchers Wang *et al*. found that ibrutinib (ChemieTek, the city of Indianapolis, IN, the United States of America decreases malignant cell viability and prevents drug resistance in American Type Culture Acquisition, Manassas, VA, USA cancer cells. Human epidermal growth factor receptor 2 (HER2)+ cells are considerably more responsive to this treatment than luminal and triple-negative cells. In line with the findings of the Grabinski and Ewald investigation, ibrutinib was reported by Wang *et al*. to inhibit EGFR, HER2, HER3, and HER4 activation, hence preventing the activation of downstream pathways.[32] The *in vivo* assessment of the xenografted mice later verified these findings.

The impact of ibrutinib (Selleck Chemicals, Houston, TX, USA) on two HER2+ cell lines-BT474 and SKBR3 (American Type Culture Collection, Manassas, VA, USA) was assessed by Prabaharan *et al*. This BTKi-induced modifications in nucleic clear morphology and apoptosis through the extrinsic apoptosis pathway that relies on caspase.[33] In addition, ibrutinib therapy caused p21 to be downregulated and STAT3 to be upregulated. Accordingly, the scientists postulated that the elevation of STAT3 in breast cancer cell lines is a passive response arising from DNA damage and the downregulation of phosphorylated p21, which encourages cell cycle arrest and death. They suggested that STAT3 inhibitors might be a great choice for ibrutinib combo treatment.

Hong *et al*. focused on breast tumors treated using the ibrutinib-durvalumab combination, specifically for triple-negative and stage III/IV HER2+ patients. Similar to the results among individuals with NSCLC, overall (n = 45) cancer patients with breast cancer possessed adverse effects (AE) as a result of this treatment; of these, most (n = 35; 78%) experienced AE of category 3 or higher.[34]

Gastric cancer

As far as the authors are aware, Wang *et al*.'s research[35] is the only one that addresses the effectiveness of ibrutinib in treating gastric cancer. The research was divided into two main sections: An *in vitro* assessment of the ibrutinib-treated MGC-803, BGC-823, SGC7901, MKN-45, and MKN-28 gastric cancer cell lines (American Type Culture Collection, Manassas, VA, USA) and an evaluation of the ibrutinib-treated MKN-45 and BGC-823 xenograft tumor growth inhibition. The tumor volume was shown to decrease as a result of BTK, and no notable toxicities were noted. Last but not least, it was shown that ibrutinib and docetaxel had a synergistic impact by acting as a chemosensitizer. Even though we think these data do not support using ibrutinib as an anti-cancer treatment in gastric cancer clinical trials, it appears far more practical to use this BTKi as a chemosensitizer. We suggest that more research should be done on this ibrutinib feature.

Colon cancer

Grassilli *et al*. identified a novel BTK isoform, p65BTK and found it to be highly expressed in tumor tissue samples and several colorectal cancer (CRC) lines.[36] According to the investigators, p65BTK significantly impacts the RAS/ERK pathway. They also found that ERK1/2 engagement is linked to p65BTK upregulation in colon malignancies. The finding that inhibiting this isoform decreased the growth and persistence of cancerous cells in the *in vitro* evaluation lends credence to the possible use of BTK inhibitors for therapy in this particular type of cancer.

Kim *et al*.'s study aimed to assess the effectiveness of pembrolizumab with ibrutinib (IMBRUVICA®) as a therapy alternative.[37] Regretfully, ibrutinib did not work as a treatment option, even though the investigators saw a much-improved safety profile than the Tempero *et al*. investigations, with 16 (42%) patients incurring a grade 3/4 adverse even.[38] The authors noted a mOS of 6.6 months (95% CI: 4.3–12.2) and a mPFS of 1.4 months (95% CI: 1.4–1.5). The study's authors determined that additional investigation into this combination is not warranted because of the low effectiveness of ibrutinib as a therapeutic option for CRC.[37]

Prostate cancer

To the best of the authors' knowledge, Zhu *et al*.'s study is the only one assessing ibrutinib's effectiveness in prostate cancer.[39] The results of this investigation showed that there was a high expression of BTK in the tissues of prostate cancer patients who had bone metastases, particularly in the tumor samples from these individuals. Therefore, it was determined that ibrutinib (Cell Signaling Technology, Danvers, MA, USA) may be a workable treatment for prostate cancer. It was shown that this BTKi effectively inhibits the migration, invasion, and proliferation of prostate cancer cells. In addition, ibrutinib reduced the production of endopeptidases known as matrix metalloproteinases-2 and -9 (MMP-2 and MMP-9), the overexpression of which has been linked to an increase in the severity and invasiveness of prostate cancer. *In vivo*, pre-clinical findings on prostate cancer seem to make ibrutinib an intriguing alternative that merits further research. At present, there is not enough data to draw any clear conclusions.[40]

Glioblastoma

The authors of Wei *et al*. found that ibrutinib (Selleck Chemicals, Taiwan) inhibited glioblastoma cell tumorigenesis *in vitro*.[41] Notably, temozolomide (Selleck Chemicals, Taiwan), an alkylating agent, combined with ibrutinib more effectively inhibited the capacity of GBM to form spheres and, as a result, the stemness and metastatic potential than did either medication by itself. Moreover, the xenograft animal study provided additional confirmation of these results. The researchers discovered that temozolomide alone was not as effective as ibrutinib/temozolomide or ibrutinib alone in its anti-tumorigenic properties.[41]

Wang *et al.* attempted to look into a related topic.[42] However, they concentrated on evaluating LN229, U87, T98, and U251 cell lines (American Type Culture Collection, Shanghai, China) *in vitro* and U87 in an animal xenograft investigation. It was shown that ibrutinib (Selleck Chemicals, Houston, TX, USA) boosted the LN229 and U87 cell lines' apoptosis and autophagy while decreasing the glioblastoma cells' cellular proliferation and migration. The process is inhibited by overexpressing Akt protein, while the aforementioned LN229 and U87 cell lines showed enhanced autophagy and apoptosis when Akt protein was inhibited by LY294002, a PI3K inhibitor. In the final analysis, ibrutinib's anti-cancer effects have been further improved both *in vitro* and *in vivo* by reducing autophagy prompted by 3-methyladenine through Atg to the diet7, addressing using small disrupting RNA.[42]

CONCLUSION AND FUTURE PROSPECTIVES

The readily accessible nature of ibrutinib and other BCR-targeted drugs, along with the encouraging results of the above investigations, will likely dramatically change the therapy landscape for CLL in the many years to come. Because of its exceptional toxicity profile, ibrutinib may be a suitable option for CLL patients for whom chemotherapy is medically contraindicated. Their elderly age and/or concurrent comorbidities usually cause this. This medication may also be offered for individuals with high-risk diseases for whom chemotherapeutic techniques are not working.

Moreover, ibrutinib may be considered a maintenance treatment option for high-risk individuals who have responded to traditional forms of care. Ultimately, further research is required to determine the role of ibrutinib in stem + cell transplantation, either as a preventative measure or as a component of induction therapy before the operation.

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REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.
2. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, *et al*. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: A systematic analysis for the global burden of disease study 2017. Lancet 2018;392:1736-88.
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, *et al*. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-49.
4. Chiorazzi N, Rai KR, Ferrarini M. Chronic lymphocytic

leukemia. N Engl J Med 2005;352:804-15.
5. Ries L, Melbert D, Krapcho M, Stinchcomb DG, Howlader N, Horner MJ, *et al*. SEER Cancer Statistics Review, 1975-2005. Bethesda, MD: National Cancer Institute; 2008.
6. García-Muñoz R, Galiacho VR, Llorente L. Immunological aspects in chronic lymphocytic leukemia (CLL) development. Ann Hematol 2012;91:981-96.
7. O'Brien S, Furman RR, Coutre SE, Sharman JP, Burger JA, Blum KA, *et al*. Ibrutinib as initial therapy for elderly patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: An open-label, multicentre, phase 1b/2 trial. Lancet Oncol 2014;15:48-58.
8. Wang ML, Rule S, Martin P, Goy A, Auer R, Kahl BS, *et al*. Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma. N Engl J Med 2013;369:507-16.
9. US Food and Drug Administration. Imbruvica (Ibrutinib). Capsules: US Prescribing Information; 2016. Available from: https://www.com/fda.gov [Last accessed on 2025 Jan 20].
10. European Medicines Agency. Imbruvica (Ibrutinib) Hard Capsules: EU Summary of Product Characteristics; 2016. Available from: https://www.com/ema.europa.eu [Last accessed on 2025 Jan 20].
11. Niemann CU, Wiestner A. B-cell receptor signaling as a driver of lymphoma development and evolution. Semin Cancer Biol 2013;23:410-21.
12. Darzentas N, Stamatopoulos K. The significance of stereotyped B-cell receptors in chronic lymphocytic leukemia. Hematol Oncol Clin North Am 2013;27:237-50.
13. Cheson BD, Byrd JC, Rai KR, Kay NE, O'Brien SM, Flinn IW, *et al*. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. J Clin Oncol 2012;30:2820-2.
14. Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, *et al*. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013;369:32-42.
15. Molica S, Matutes E, Tam C, Polliack A. Ibrutinib in the treatment of chronic lymphocytic leukemia: 5 years on. Hematol Oncol 2020;38:129-36.
16. Winer ES, Ingham RR, Castillo JJ. PCI-32765: A novel Bruton's tyrosine kinase inhibitor for the treatment of lymphoid malignancies. Expert Opin Investig Drugs 2012;21:355-61.
17. Byrd J, Blum K, Burger J, Sharman JP, Furman RR, Flinn IW, *et al*. Activity and tolerability of the Bruton's tyrosine kinase inhibitor PCI-32765 in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma: Interim results of a phase Ib/II study. J ClinOncol 2011;29 Suppl 15:6508.
18. Ponader S, Chen SS, Buggy JJ, Balakrishnan K, Gandhi V, Wierda WG, *et al*. The Bruton tyrosine kinase inhibitor PCI-32765 thwarts chronic lymphocytic leukemia cell survival and tissue homing *in vitro* and *in vivo*. Blood 2012;119:1182-9.
19. Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, *et al*. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 2014;371:213-23.
20. Burger JA, Keating MJ, Wierda WG, Hartmann E, Hoellenriegel J, Rosin NY, *et al*. The BTK inhibitor ibrutinib (PCI-32765) in combination with rituximab is well tolerated and displays profound activity in high-risk chronic lymphocytic leukemia patients. Blood 2012;120 Suppl 21:187.
21. Jaglowski SM, Jones JA, Flynn JM, Andritsos LA, Maddocks KJ, Blum KA, *et al*. A phase Ib/II study evaluating activity and tolerability of BTK inhibitor PCI-32765 and ofatumumab in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma and related diseases. J Clin Oncol 2012;30 Suppl 15:6508.
22. Honigberg LA, Smith AM, Sirisawad M, Verner E, Loury D, Chang B, *et al*. The Bruton tyrosine kinase inhibitor PCI-32765 blocks B-cell activation and is efficacious in models of autoimmune disease and B-cell malignancy. Proc Natl AcadSci U S A 2010;107:13075-80.
23. De Rooij MF, Kuil A, Geest CR, Eldering E, Chang BY, Buggy JJ, *et al*. The clinically active BTK inhibitor PCI-32765 targets B-cell receptor- and chemokine-controlled adhesion and migration in chronic lymphocytic leukemia. Blood 2012;119:2590-4.
24. Woyach JA, Smucker K, Smith LL, Lozanski A, Zhong Y, Ruppert AS, *et al*. Prolonged lymphocytosis during ibrutinib therapy is associated with distinct molecular characteristics and does not indicate a suboptimal response to therapy. Blood 2014;123:1810-7.
25. Rossi D, Rasi S, Spina V, Bruscaggin A, Monti S, Ciardullo C, *et al*. Integrated mutational and cytogenetic analysis identifies new prognostic subgroups in chronic lymphocytic leukemia. Blood 2013;121:1403-12.
26. Gao W, Wang M, Wang L, Lu H, Wu S, Dai B, *et al*. Selective antitumor activity of ibrutinib in EGFR-mutant non-small cell lung cancer cells. J Natl Cancer Inst 2014;106:dju204.
27. Fu Z, Wang H, Zhou Y, Zhou Q. Inhibition of platelet-tumour cell interaction with ibrutinib reduces proliferation, migration and invasion of lung cancer cells. Trop J Pharm Res 2018;17:589-96.
28. Zhang B, Wang L, Zhang Q, Yan Y, Jiang H, Hu R, *et al*. The Ibr-7 derivative of ibrutinib exhibits enhanced cytotoxicity against non-small cell lung cancer cells via targeting of MTORC1/S6 signaling. Mol Oncol 2019;13:946-58.
29. Sagiv-Barfi I, Kohrt HEK, Czerwinski DK, Ng PP, Chang BY, Levy R. Therapeutic antitumor immunity by checkpoint blockade is enhanced by ibrutinib, an inhibitor of both BTK and ITK. Proc Natl Acad Sci U S A 2015;112:E966-72.
30. Zucha MA, Wu AT, Lee WH, Wang LS, Lin WW, Yuan CC, *et al*. Bruton's tyrosine kinase inhibitor

ibrutinib suppresses stem-like traits in ovarian cancer. Oncotarget 2015;6:13255-68.
31. Eifert C, Wang X, Kokabee L, Kourtidis A, Jain R, Gerdes MJ, *et al*. A novel isoform of the B cell tyrosine kinase BTK protects breast cancer cells from apoptosis. Genes Chromosomes Cancer 2013;52:961-75.
32. Wang X, Wong J, Sevinsky CJ, Kokabee L, Khan F, Sun Y, *et al*. Bruton's tyrosine kinase inhibitors prevent therapeutic escape in breast cancer cells. Mol Cancer Ther 2016;15:2198-208.
33. Prabaharan CB, Yang AB, Chidambaram D, Rajamanickam K, Napper S, Sakharkar MK. Ibrutinib as a potential therapeutic option for HER2 overexpressing breast cancer-the role of STAT3 and P21. Invest New Drugs 2020;38:909-21.
34. Hong D, Rasco D, Veeder M, Luke JJ, Chandler J, Balmanoukian A, *et al*. A phase 1b/2 study of the Bruton tyrosine kinase inhibitor ibrutinib and the PD-L1 inhibitor durvalumab in patients with pretreated solid tumors. Oncology 2019;97:102-11.
35. Wang JD, Chen XY, Ji KW, Tao F. Targeting Btk with ibrutinib inhibit gastric carcinoma cells growth. Am J Transl Res 2016;8:3003-12.
36. Grassilli E, Pisano F, Cialdella A, Bonomo S, Missaglia C, Cerrito MG, *et al*. A novel oncogenic BTK isoform is overexpressed in colon cancers and required for RAS-mediated transformation. Oncogene 2016;35:4368-78.
37. Kim DW, Tan E, Zhou JM, Schell MJ, Martinez M, Yu J, *et al*. A phase 1/2 trial of ibrutinib in combination with pembrolizumab in patients with mismatch repair proficient metastatic colorectal cancer. Br J Cancer 2021;124:1803-8.
38. Tempero M, Oh DY, Tabernero J, Reni M, Van Cutsem E, Hendifar A, *et al*. Ibrutinib in combination with nab-paclitaxel and gemcitabine for first-line treatment of patients with metastatic pancreatic adenocarcinoma: Phase III RESOLVE study. Ann Oncol 2021;32:600-8.
39. Zhu Z, Ling L, Qi L, Chong Y, Xue L. Bruton's tyrosine kinase inhibitor (ibrutinib)-suppressed migration and invasion of prostate cancer. Onco Targets Ther 2020;13:4113-22.
40. Aalinkeel R, Nair BB, Reynolds JL, Sykes DE, Mahajan SD, Chadha KC, *et al*. Overexpression of MMP-9 contributes to invasiveness of prostate cancer cell line LNCaP. Immunol Invest 2011;40:447-64.
41. Wei L, Su YK, Lin CM, Chao TY, Huang SP, Huynh TT, *et al*. Preclinical investigation of ibrutinib, a Bruton's kinase tyrosine (Btk) inhibitor, in suppressing glioma tumorigenesis and stem cell phenotypes. Oncotarget 2016;7:69961-75.
42. Wang J, Liu X, Hong Y, Wang S, Chen P, Gu A, *et al*. Ibrutinib, a Bruton's tyrosine kinase inhibitor, exhibits antitumoral activity and induces autophagy in glioblastoma. J Exp Clin Cancer Res 2017;36:96.

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