



## Updated Data from the BRUIN Phase 1/2 Study of Pirtobrutinib in Chronic Lymphocytic Leukemia and Mantle Cell Lymphoma Presented at the 2023 ASH Annual Meeting

December 12, 2023

INDIANAPOLIS, Dec. 11, 2023 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced updated clinical data from the international Phase 1/2 BRUIN trial of pirtobrutinib, a non-covalent (reversible) Bruton's tyrosine kinase (BTK) inhibitor, in adult patients with a range of B-cell malignancies. These data, which were presented in oral and poster presentations at the 65th American Society of Hematology (ASH) Annual Meeting and Exposition, continue to support the role of pirtobrutinib in the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) and mantle cell lymphoma (MCL).

"With longer follow-up, we continue to observe efficacy and tolerability data that support the potential utility of pirtobrutinib in CLL and B-cell lymphomas in the post-covalent BTK inhibitor setting," said Matthew S. Davids, M.D., M.M.Sc., Dana-Farber Cancer Institute. "These data demonstrate the ability of pirtobrutinib to potentially lengthen the time patients may benefit from inhibiting BTK, a key target in these diseases. It is also encouraging to see the promising initial data for pirtobrutinib combined with venetoclax, which has the possibility to allow for a time-limited regimen for patients with CLL."

"Following the two FDA accelerated approvals for pirtobrutinib in 2023, we are excited to present these data at ASH, further building the body of evidence for this medicine in CLL, SLL, MCL, and other B-cell malignancies," said David Hyman, M.D., chief medical officer, Lilly. "These data support the potential role that pirtobrutinib, the first and only FDA-approved non-covalent BTK inhibitor, can play in extending the time patients may benefit from BTK inhibition therapy and provide additional efficacy data in patients previously treated with a covalent BTK inhibitor. We look forward to expanding our understanding of the broader potential clinical utility of pirtobrutinib as we continue to progress our series of randomized Phase 3 studies in CLL, SLL, and MCL."

The labeling for pirtobrutinib contains warnings and precautions for infections, hemorrhage, cytopenias, cardiac arrhythmias, second primary malignancies, and embryo-fetal toxicity.

### Data from the BRUIN Phase 1/2 Study

The BRUIN Phase 1/2 clinical trial is evaluating pirtobrutinib in patients previously treated for MCL, CLL/SLL, or other non-Hodgkin lymphomas (NHL). The efficacy data presented at ASH for CLL/SLL and MCL are based on independent review committee (IRC) assessment. All presentations of safety and efficacy data from the BRUIN Phase 1/2 trial utilized a cutoff date of May 5, 2023.

#### *Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma*

An oral presentation ([Abstract #325](#)) detailed updated, long-term follow-up data in patients with CLL/SLL. This data set consisted of 282 patients who had received a prior BTK inhibitor. Patients had received a median of four prior lines of therapy (range: 1-11). Efficacy results showed an overall response rate (ORR), including partial response with lymphocytosis (PR-L), of 81.6% (95% CI: 76.5, 85.9) for patients treated with pirtobrutinib. Response rates were consistent across all subgroups analyzed regardless of previous therapies, age, or mutation status. With a median follow-up of 27.5 months, median progression-free survival (PFS) was 19.4 months (95% CI: 16.6, 22.1). With a median follow-up of 29.3 months, median overall survival (OS) was not estimable.

In patients treated with both a prior covalent BTK inhibitor and BCL-2 inhibitor (n=128, median of five prior lines of therapy, range: 1-11), pirtobrutinib demonstrated an ORR, including PR-L, of 79.7% (95% CI: 71.7, 86.3). With a median follow-up of 22.2 months, median PFS was 15.9 months (95% CI: 13.6, 17.5). With a median follow-up of 27.4 months, the median OS was not estimable.

In BCL-2-naïve patients (n=154, median of three prior lines of therapy, range: 1-9), pirtobrutinib demonstrated an ORR, including PR-L, of 83.1% (95% CI: 76.2, 88.7). With a median follow-up of 27.6 months, median PFS was 23.0 months (95% CI: 19.6, 28.4). With a median follow-up of 31.6 months, the median OS was not estimable.

In the CLL/SLL safety cohort (n=282), the most frequent treatment-emergent adverse events (TEAEs) were fatigue (36.9%), neutropenia (34.4%), diarrhea (28.4%), cough (27.3%), and contusion (26.2%).

A second oral presentation ([Abstract #326](#)) detailed updated analyses of genomic evolution and resistance during pirtobrutinib therapy in patients with relapsed covalent BTK inhibitor pre-treated CLL who subsequently developed disease progression on pirtobrutinib monotherapy (n=88). These data showed that although many patients harbored BTK mutations (C481 and non-C481) prior to initiation of pirtobrutinib therapy, these baseline genomic features did not predict response to pirtobrutinib. Moreover, while many patients acquired mutations at progression (68%), fewer than half were in the BTK gene.

A poster presentation ([Abstract #3269](#)) detailed updated data from the Phase 1b portion of the BRUIN trial, which investigated pirtobrutinib in combination with venetoclax with or without rituximab as a two-year fixed-duration therapy. This data set consisted of 25 patients, 17 of whom had received a prior BTK inhibitor. Patients were enrolled into sequential cohorts, first in the pirtobrutinib plus venetoclax (PV) cohort (n=15) and then the PV plus rituximab (PVR) cohort (n=10). Efficacy results showed an ORR of 96% (95% CI: 79.6, 99.9), with 40% complete responses (PV, n=7; PVR, n=3) and 56% partial responses (PV, n=7; PVR, n=7) across the two arms. Undetectable minimal residual disease (uMRD) was achieved by 87.5% of patients (PV, n=12; PVR, n=9) at some time during the trial. Across the two arms, the PFS rate at 24 months was 79.5% (95% CI: 52.0, 92.3).

The primary endpoint was safety as assessed by TEAEs graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. The safety profiles were generally similar among both combination treatment groups, and no dose limiting toxicities were observed. In the PV cohort, the most frequent treatment-related AEs were neutropenia (46.7%), nausea (46.7%), fatigue (33.3%), diarrhea (26.7%), and decreased platelet count

(26.7%). In the PVR cohort, the most frequent treatment-related AEs were neutropenia (70.0%), diarrhea (60.0%), nausea (40.0%), infusion-related reactions (40.0%), and chills (30.0%). There were no apparent drug interactions between pirtobrutinib and venetoclax.

These efficacy and safety data support the ongoing BRUIN CLL-322 Phase 3 trial evaluating two years of pirtobrutinib plus venetoclax and rituximab versus two years of venetoclax plus rituximab in previously treated CLL/SLL.

#### *Mantle Cell Lymphoma*

An oral presentation ([Abstract #981](#)) detailed updated efficacy results, including in high-risk subgroups. This data set consisted of 152 patients who had received a prior covalent BTK inhibitor. Patients had received a median of three prior lines of therapy (range: 1-9). Efficacy results showed an ORR of 49.3% (95% CI: 41.1, 57.6), including 15.8% complete responses (n=24) and 33.6% partial responses (n=51) for patients treated with pirtobrutinib. At a median follow-up of 14.7 months, the median duration of response (DOR) was 21.6 months (95% CI: 9.2, 27.2). Median PFS and OS were 5.6 months (95% CI: 5.3, 9.2) and 23.5 months (95% CI: 17.1, not estimable), respectively. Response rates were consistent across subgroups regardless of prior treatment or high-risk molecular features.

In the MCL safety cohort (n=166), the most frequent TEAEs were fatigue (31.9%), diarrhea (22.3%), and dyspnea (17.5%).

Additionally, Lilly presented posters highlighting pirtobrutinib in relapsed or refractory follicular lymphoma (FL), relapsed or refractory marginal zone lymphoma (MZL), and Richter transformation (RT).

Loxo@Lilly is studying pirtobrutinib in multiple Phase 3 studies. Details on the trials can be found by visiting [clinicaltrials.gov](https://clinicaltrials.gov).

#### **About the BRUIN Phase 1/2 Trial**

The BRUIN Phase 1/2 clinical trial is the ongoing first-in-human, global, multi-center evaluation of pirtobrutinib in patients with hematologic malignancies, including chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), and mantle cell lymphoma (MCL). The BRUIN trial includes one of the largest prospective cohorts of BTK inhibitor pre-treated CLL/SLL patients ever studied.

The trial includes a Phase 1 dose-escalation phase, a Phase 1b combination arm, and a Phase 2 dose-expansion phase. The primary endpoint of the Phase 1 study is maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D). Secondary endpoints include safety, pharmacokinetics (PK), and preliminary efficacy measured by overall response rate (ORR) for monotherapy. The primary endpoint of the Phase 1b study is safety of the drug combinations. The secondary endpoints are PK and preliminary efficacy measured by ORR for the drug combinations. The primary endpoint for the Phase 2 study is ORR as determined by an independent review committee (IRC). Secondary endpoints include ORR as determined by investigator, best overall response (BOR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), safety, and PK.

#### **About Pirtobrutinib**

Pirtobrutinib is a highly selective (300 times more selective for BTK versus 98% of other kinases tested in preclinical studies), non-covalent (reversible) inhibitor of the enzyme BTK.<sup>1</sup> BTK plays a key role in the B-cell antigen receptor signaling pathway, which is required for the development, activation, and survival of normal white blood cells, known as B-cells, and malignant B-cells. BTK is a validated molecular target found across numerous B-cell leukemias and lymphomas, including mantle cell lymphoma (MCL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).<sup>2,3</sup> Pirtobrutinib was developed to reversibly bind BTK, deliver consistently high target coverage regardless of BTK turnover rate, and preserve activity in the presence of the C481 acquired resistance mutations.

Pirtobrutinib was approved under the FDA's Accelerated Approval pathway as Jaypirca<sup>®</sup> (pirtobrutinib) on January 27, 2023, to treat adult patients with relapsed or refractory MCL after at least two lines of systemic therapy, including a BTK inhibitor, and on December 1, 2023, to treat adult patients with CLL/SLL who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor. These indications are approved under accelerated approval based on response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial.

#### **INDICATIONS FOR JAYPIRCA**

Jaypirca is a kinase inhibitor indicated for the treatment of

- Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a BTK inhibitor.
- Adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor.

These indications are approved under accelerated approval based on response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial.

#### **IMPORTANT SAFETY INFORMATION FOR JAYPIRCA<sup>®</sup> (pirtobrutinib)**

**Infections:** Fatal and serious infections (including bacterial, viral, fungal) and opportunistic infections occurred in Jaypirca-treated patients. In a clinical trial, Grade  $\geq 3$  infections occurred in 24% of patients with hematologic malignancies, most commonly pneumonia (14%); fatal infections occurred in 4.4%. Sepsis (6%) and febrile neutropenia (4%) occurred. In patients with CLL/SLL, Grade  $\geq 3$  infections occurred (32%), with fatal infections occurring in 8%. Opportunistic infections included *Pneumocystis jirovecii* pneumonia and fungal infection. Consider prophylaxis, including vaccinations and antimicrobial prophylaxis, in patients at increased risk for infection, including opportunistic infections. Monitor patients for signs and symptoms, evaluate promptly, and treat appropriately. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

**Hemorrhage:** Fatal and serious hemorrhage has occurred with Jaypirca. Major hemorrhage (Grade  $\geq 3$  bleeding or any central nervous system bleeding) occurred in 3% of patients, including gastrointestinal hemorrhage; fatal hemorrhage occurred (0.3%). Bleeding of any grade, excluding bruising and petechiae, occurred in 17%. Major hemorrhage occurred in patients taking Jaypirca with (0.7%) and without (2.3%) antithrombotic agents. Consider risks/benefits of co-administering antithrombotic agents with Jaypirca. Monitor patients for signs of bleeding. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca. Consider benefit/risk of withholding Jaypirca 3-7 days pre- and post-surgery depending on type of surgery and bleeding risk.

**Cytopenias:** Jaypirca can cause cytopenias, including neutropenia, thrombocytopenia, and anemia. In a clinical trial, Grade 3 or 4 cytopenias, including decreased neutrophils (26%), decreased platelets (12%), and decreased hemoglobin (12%), developed in Jaypirca-treated patients. Grade 4 decreased neutrophils (14%) and Grade 4 decreased platelets (6%) developed. Monitor complete blood counts regularly during treatment. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

**Cardiac Arrhythmias:** Cardiac arrhythmias occurred in patients who received Jaypirca. In a clinical trial of patients with hematologic malignancies, atrial fibrillation or flutter were reported in 3.2% of Jaypirca-treated patients, with Grade 3 or 4 atrial fibrillation or flutter in 1.5%. Other serious cardiac arrhythmias such as supraventricular tachycardia and cardiac arrest occurred (0.5%). Patients with cardiac risk factors such as hypertension or previous arrhythmias may be at increased risk. Monitor for signs and symptoms of arrhythmias (e.g., palpitations, dizziness, syncope, dyspnea) and manage appropriately. Based on severity, reduce dose, temporarily withhold, or permanently discontinue Jaypirca.

**Second Primary Malignancies:** Second primary malignancies, including non-skin carcinomas, developed in 9% of Jaypirca-treated patients. The most frequent malignancy was non-melanoma skin cancer (4.6%). Other second primary malignancies included solid tumors (including genitourinary and breast cancers) and melanoma. Advise patients to use sun protection and monitor for development of second primary malignancies.

**Embryo-Fetal Toxicity:** Jaypirca can cause fetal harm in pregnant women. Administration of pirtobrutinib to pregnant rats during organogenesis caused embryo-fetal toxicity, including embryo-fetal mortality and malformations at maternal exposures (AUC) approximately 3-times the recommended 200 mg/day dose. Advise pregnant women of potential fetal risk and females of reproductive potential to use effective contraception during treatment and for one week after last dose.

#### **Adverse Reactions (ARs) in Patients Who Received Jaypirca**

The most common ( $\geq 20\%$ ) ARs in the BRUIN pooled safety population of patients with hematologic malignancies (n=593) were decreased neutrophil count (46%), decreased hemoglobin (39%), fatigue (32%), decreased lymphocyte count (31%), musculoskeletal pain (30%), decreased platelet count (29%), diarrhea (24%), COVID-19 (22%), bruising (21%), cough (20%).

#### **Mantle Cell Lymphoma**

**Serious ARs** occurred in 38% of patients. Serious ARs occurring in  $\geq 2\%$  of patients were pneumonia (14%), COVID-19 (4.7%), musculoskeletal pain (3.9%), hemorrhage (2.3%), pleural effusion (2.3%), and sepsis (2.3%). **Fatal ARs** within 28 days of last Jaypirca dose occurred in 7% of patients, most commonly due to infections (4.7%), including COVID-19 (3.1% of all patients).

**Dose Modifications and Discontinuations:** ARs led to dose reductions in 4.7%, treatment interruption in 32%, and permanent discontinuation of Jaypirca in 9% of patients. ARs resulting in dosage modification in  $>5\%$  of patients included pneumonia and neutropenia. ARs resulting in permanent discontinuation in  $>1\%$  of patients included pneumonia.

**ARs (all Grades %; Grade 3-4 %) in  $\geq 10\%$  of Patients:** fatigue (29; 1.6), musculoskeletal pain (27; 3.9), diarrhea (19; -), edema (18; 0.8), dyspnea (17; 2.3), pneumonia (16; 1.4), bruising (16; -), peripheral neuropathy (14; 0.8), cough (14; -), rash (14; -), fever (13; -), constipation (13; -), arthritis/arthralgia (12; 0.8), hemorrhage (11; 3.1), abdominal pain (11; 0.8), nausea (11; -), upper respiratory tract infections (10; 0.8), dizziness (10; -).

**Select Laboratory Abnormalities (all Grades %; Grade 3 or 4 %) that Worsened from Baseline in  $\geq 10\%$  of Patients:** hemoglobin decreased (42; 9), platelet count decreased (39; 14), neutrophil count decreased (36; 16), lymphocyte count decreased (32; 15), creatinine increased (30; 1.6), calcium decreased (19; 1.6), AST increased (17; 1.6), potassium decreased (13; 1.6), sodium decreased (13; -), lipase increased (12; 4.4), alkaline phosphatase increased (11; -), ALT increased (11; 1.6), potassium increased (11; 0.8). Grade 4 laboratory abnormalities in  $>5\%$  of patients included neutrophils decreased (10), platelets decreased (7), lymphocytes decreased (6).

#### **Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma**

**Serious ARs** occurred in 56% of patients. Serious ARs occurring in  $\geq 5\%$  of patients were pneumonia (18%), COVID-19 (9%), sepsis (7%), and febrile neutropenia (7%). **Fatal ARs** within 28 days of last Jaypirca dose occurred in 11% of patients, most commonly due to infections (10%), including sepsis (5%) and COVID-19 (2.7%).

**Dose Modifications and Discontinuations:** ARs led to dose reductions in 3.6%, treatment interruption in 42%, and permanent discontinuation of Jaypirca in 9% of patients. ARs resulting in dose reductions in  $>1\%$  included neutropenia; treatment interruptions in  $>5\%$  of patients included pneumonia, neutropenia, febrile neutropenia, and COVID-19; permanent discontinuation in  $>1\%$  of patients included second primary malignancy, COVID-19, and sepsis.

**ARs (all Grades %; Grade 3-4 %) in  $\geq 10\%$  of Patients:** fatigue (36; 2.7), bruising (36; -), cough (33; -), musculoskeletal pain (32; 0.9), COVID-19 (28; 7), pneumonia (27; 16), diarrhea (26; -), abdominal pain (25; 2.7), dyspnea (22; 2.7), hemorrhage (22; 2.7), edema (21; -), nausea (21; -), pyrexia (20; 2.7), headache (20; 0.9), arthritis/arthralgia (19; 1.8), rash (19; 0.9), peripheral neuropathy (16; 3.6), dizziness (15; -), fall (14; 0.9), constipation (14; -), insomnia (14; -), upper respiratory tract infections (13; 2.7), second primary malignancy (13; 2.7), renal insufficiency (12; 6), hypertension (12; 5), neurological changes (12; 2.7), mucositis (12; 0.9), decreased appetite (12; -), respiratory tract infection (11; 1.8), supraventricular tachycardia (10; 5).

**Select Laboratory Abnormalities (all Grades %; Grade 3 or 4 %) that Worsened from Baseline in  $\geq 20\%$  of Patients:** neutrophil count decreased (63; 45), hemoglobin decreased (48; 19), calcium decreased (40; 2.8), platelet count decreased (30; 15), sodium decreased (30; -), lymphocyte count decreased (23; 8), ALT increased (23; 2.8), AST increased (23; 1.9), creatinine increased (23; -), lipase increased (21; 7), alkaline phosphatase increased (21; -). Grade 4 laboratory abnormalities in  $>5\%$  of patients included neutrophils decreased (23).

#### **Drug Interactions**

**Strong CYP3A Inhibitors:** Concomitant use with Jaypirca increased pirtobrutinib systemic exposure, which may increase risk of Jaypirca ARs. Avoid use of strong CYP3A inhibitors with Jaypirca. If concomitant use is unavoidable, reduce Jaypirca dosage according to approved labeling.

**Strong or Moderate CYP3A Inducers:** Concomitant use with Jaypirca decreased pirtobrutinib systemic exposure, which may reduce Jaypirca efficacy. Avoid concomitant use of Jaypirca with strong or moderate CYP3A inducers. If concomitant use with moderate CYP3A inducers is unavoidable, increase Jaypirca dosage according to approved labeling.

**Sensitive CYP2C8, CYP2C19, CYP3A, P-gp, or BCRP Substrates:** Concomitant use with Jaypirca increased their plasma concentrations, which may increase risk of adverse reactions related to these substrates for drugs that are sensitive to minimal concentration changes. Follow

recommendations for these sensitive substrates in their approved labeling.

### Use in Special Populations

**Pregnancy and Lactation:** Due to potential for Jaypirca to cause fetal harm, verify pregnancy status in females of reproductive potential prior to starting Jaypirca and advise use of effective contraception during treatment and for one week after last dose. Presence of pirtobrutinib in human milk is unknown. Advise women not to breastfeed while taking Jaypirca and for one week after last dose.

**Geriatric Use:** In the pooled safety population of patients with hematologic malignancies, patients aged  $\geq 65$  years experienced higher rates of Grade  $\geq 3$  ARs and serious ARs compared to patients  $< 65$  years of age.

**Renal Impairment:** Severe renal impairment increases pirtobrutinib exposure. Reduce Jaypirca dosage in patients with severe renal impairment according to approved labeling.

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Please see [Prescribing Information](#) and [Patient Information](#) for Jaypirca.

### About Lilly

Lilly unites caring with discovery to create medicines that make life better for people around the world. We've been pioneering life-changing discoveries for nearly 150 years, and today our medicines help more than 51 million people across the globe. Harnessing the power of biotechnology, chemistry and genetic medicine, our scientists are urgently advancing new discoveries to solve some of the world's most significant health challenges, redefining diabetes care, treating obesity and curtailing its most devastating long-term effects, advancing the fight against Alzheimer's disease, providing solutions to some of the most debilitating immune system disorders, and transforming the most difficult-to-treat cancers into manageable diseases. With each step toward a healthier world, we're motivated by one thing: making life better for millions more people. That includes delivering innovative clinical trials that reflect the diversity of our world and working to ensure our medicines are accessible and affordable. To learn more, visit [Lilly.com](#) and [Lilly.com/newsroom](#) or follow us on [Facebook](#), [Instagram](#), and [LinkedIn](#). P-LLY

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### Lilly Cautionary Statement Regarding Forward-Looking Statements

This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about pirtobrutinib as a treatment for adult patients with mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a BTK inhibitor, as a treatment for adult patients with chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL) who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor, and a potential treatment for follicular lymphoma (FL), relapsed or refractory marginal zone lymphoma (MZL), and Richter transformation (RT) and reflects Lilly's current beliefs and expectations. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of drug research, development, and commercialization. Among other things, there is no guarantee that planned or ongoing studies will be completed as planned, that future study results will be consistent with study results to date, or that pirtobrutinib will receive additional regulatory approvals. For further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, see Lilly's Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

1. 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. doi:10.1016/S0140-6736(21)00224-5
2. Hanel W, Epperla N. Emerging therapies in mantle cell lymphoma. *J Hematol Oncol*. 2020;13(1):79. Published 2020 Jun 17. doi:10.1186/s13045-020-00914-1
3. Gu D, Tang H, Wu J, Li J, Miao Y. Targeting Bruton tyrosine kinase using non-covalent inhibitors in B cell malignancies. *J Hematol Oncol*. 2021;14(1):40. Published 2021 Mar 6. doi:10.1186/s13045-021-01049-7

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