Q 26:

Selected Drug - Imbruvica

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Q 27. Questions on Prescribing Information:

What prescribing information has been approved by the FDA for the selected drug and for therapeutic alternative(s) to the selected drug?

A. Selected Drug - IMBRUVICA® is a Bruton's tyrosine kinase (BTK) inhibitor indicated [1] for the treatment of:

Adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

Dose: 420 mg taken orally once daily

Adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) with 17p deletion.

Dose: 420 mg taken orally once daily

Adult patients with Waldenström's macroglobulinemia (WM).

Dose: 420 mg taken orally once daily

Adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

Dose: Patients 12 years and older: 420 mg taken orally once daily; Patients between 1 and 12 years of age: 240 mg/m2 taken orally once daily (up to a dose of 420 mg).

Recommended dosage modifications (CLL/SLL) of IMBRUVICA for Grade 3 or 4 non-hematological toxicities, Grade 3 or 4 neutropenia with infection or fever and Grade 4 hematological toxicities as well as Grade 2 cardiac failure is to restart at 280 mg daily for first occurrence, at 140 mg daily for second occurrence, and discontinue at third occurrence.

Recommended dosage modification for concurrent use of a moderate CYP3A inhibitor is to reduce dose to 280 mg daily. IMBRUVICA should not be co-administered with a strong CYP3A inhibitor.

B. Therapeutic Alternatives

1. Indication: Adult patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

a. **CALQUENCE® (acalabrutinib) [2]**

Dose: 100 mg orally approximately every 12 hours

Recommended dosage modifications of CALQUENCE for Grade 3 or greater non-hematologic toxicities, Grade 3 thrombocytopenia with bleeding, Grade 4 thrombocytopenia or Grade 4 neutropenia lasting longer than 7 days are to interrupt treatment until toxicity has resolved to Grade 1 and then resume at 100 mg every 12 hours for first and second occurrence. For third occurrence, once toxicity has resolved to Grade 1 following interruption, treatment can be resumed at reduced frequency of 100 mg once daily. CALQUENCE should be discontinued if there is a fourth occurrence.

Use of CALQUENCE with strong CYP3A inhibitors should be avoided. CALQUENCE dose should be reduced to 100 mg once daily if used with a moderate CYP3A inhibitor. CALQUENCE should not be used with a strong CYP3A inducer, but if use cannot be avoided, CALQUENCE dose should be increased to 200 mg twice daily.

b. **BRUKINSA® (zanubrutinib)** [3]

Dose: 160 mg taken orally twice daily, or 320 mg taken orally once daily until disease progression or unacceptable toxicity.

Recommended dosage modifications of BRUKINSA for Grade 3 or higher adverse reactions in CLL/SLL are to interrupt treatment until AE has resolved to Grade 1 and then resume at 160 mg twice daily or 320 mg once daily for first occurrence; 80 mg twice daily or 160 mg once daily for second occurrence; 80 mg once daily for third occurrence. Treatment should be discontinued at the fourth occurrence of a Grade 3 or higher AE.

Recommended dosage modifications of BRUKINSA for use with strong or moderate CYP3A inhibitors is 80 mg once daily. Concomitant use with moderate CYP3A inducers should be avoided, but if the inducer cannot be avoided, BRUKINSA dose should be increased to 320 mg twice daily.

2. Indication: Adult patients with Waldenström's macroglobulinemia (WM)

a. BRUKINSA® (zanubrutinib) [3]

Dose and dosage modifications are the same as those for CLL/SLL.

b. CALQUENCE® (acalabrutinib) [2]

CALQUENCE® (acalabrutinib) is used off-label to treat WM.

3. Indication: Adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy.

The selected drug, IMBRUVICA® is the only BTK inhibitor approved for treating cGVHD. It is the only FDA approved treatment for cGVHD in children under 12 years of age.

Currently, there are three FDA approvals for treatment of chronic GVHD:

- The selected drug, IMBRUVICA® (ibrutinib), was the first drug approved for chronic GVHD in both adults and children under 12 years of age after failure of one or more lines of systemic therapy (August 2, 2017, adults; August 24, 2022, pediatric) [1]
- REZUROCK® (belumosudil), is an oral selective inhibitor of ROCK2 approved for patients 12 years of age and older (July 16, 2021) with chronic GVHD who received at least 2 prior lines of treatment. The recommended dose of REZUROCK is 200 mg given orally once a day until progression of chronic GVHD that requires new systemic therapy. [4]
- JAKAFI® (ruxolitinib) is approved for chronic graft-versus-host disease in adult and pediatric patients 12 years and older after failure of one or two lines of systemic therapy. Ruxolitinib is administered at 5 mg twice daily and can be increased to 10 mg twice daily after 3 days without toxicity (September 22, 2021).
    - Prior to Jakafi treatment, patients should have a complete blood count
    - During treatment with Jakafi, patients should have a complete blood count every 2 to 4 weeks until doses are stabilized and have lipid parameters assessed every 8-12 weeks after Jakafi initiation. [5]

Please provide information about how the selected drug and its therapeutic alternative(s) are used in the course of care for the condition or disease treated by each indication.

CLL/SLL is a chronic blood cancer of the white blood cells known as B-lymphocytes where there is a progressive accumulation of too many mature B-lymphocytes. CLL is the most common type of adult leukemia in the United States, with around 21,000 cases diagnosed annually. It is classified as both a type of leukemia and a type of non-Hodgkin's lymphoma (NHL). SLL is simply a different manifestation of the same disease and is best understood as a stage of CLL where there are not yet a significant number of cancer cells located in the bloodstream. We refer to the disease state collectively as CLL.

CLL is extremely heterogeneous, meaning each person's disease course and progression can vary considerably. Some patients have an aggressive form of the disease, experience rapid deterioration, and survive for as little as two years. Others have a less aggressive form of the disease, may never need treatment, and can expect to have a normal life expectancy. For most patients, CLL is indolent and incurable. Since patients with advanced CLL are not cured with conventional therapy, the goals of therapy are to improve quality of life and prolong overall survival (OS). [6] Today, the median OS from start of front-line therapy is 5 to 15 years, depending on disease features, individual patient factors, and treatment choices. Patients

requiring front-line and even second-line therapy to help control the disease have better treatment options than patients had a decade ago.

Targeted therapies such as BTK inhibitors and the BCL2 inhibitor known as venetoclax offer substantial efficacy against CLL and have transformed care for our patient community. Patients now have more treatment options compared to just years ago when the standard of care was chemoimmunotherapy. They can take continuous daily oral therapy with a BTK inhibitor (with or without the addition of a monoclonal antibody) until their disease progresses. Alternatively, patients can choose a short-term time-limited treatment approach that combines venetoclax and a monoclonal antibody or IMBRUVICA. The latter approach allows for drug discontinuation until active monitoring reveals that another treatment is needed.

The selected drug, IMBRUVICA® (ibrutinib) was heralded as offering a sea change in the treatment of CLL as it was the first targeted oral small molecule therapy with large, randomized studies showing improved outcomes compared to the standard of care (SOC) existing at the time. Like ibrutinib, the more recently approved BTK inhibitors (acalabrutinib and zanubrutinib) are effective in treating CLL subtypes that are refractory to the former SOC.
The NCCN Guidelines for CLL emphasize that the most appropriate treatment plan for a particular patient depends on multiple factors, including the patient's IGHV status, del(17p)/TP53 mutation status, age, and comorbidities. Subsequent therapies are selected based on the prior therapy received, patient comorbidities, resistant mutations, and other factors. In choosing subsequent therapy, prior therapy, comorbidities, and resistance mutations should be considered. [7]

While chemoimmunotherapy had been the SOC for the treatment of CLL, targeted therapies are now the preferred option in ***all*** patients with CLL since chemoimmunotherapy is **not** appropriate for patients with del(17p) and/or TP53 mutation and is less effective in all patients. For most patients, front-line treatment could consist of:

- Continuous therapy with a BTK inhibitor. This is a better option than venetoclax plus obinutuzumab in patients with kidney impairment.
- Fixed-duration venetoclax plus obinutuzumab, administered over one year. This option may be preferred over BTK inhibitors in patients with cardiovascular disorders, uncontrolled hypertension, and/or a high risk for bleeding (e.g., patients receiving anticoagulation medication, especially warfarin).
- Fixed-duration ibrutinib plus venetoclax, administered over 15 months. Although patients with certain cardiovascular disorders may not be able to tolerate a BTK inhibitor, this option is important for patients wishing to avoid continuous therapy.

If the selected drug is used off-label to treat a certain disease or condition, please indicate this and provide evidence from nationally recognized, evidence-based guidelines and recognized by CMS-approved Part D compendia, as applicable.

The manufacturer for the selected drug announced earlier this year that they were withdrawing the accelerated approvals of IMBRUVICA for mantle cell lymphoma (MCL) and marginal zone lymphoma (MZL) based on phase 3 trials. [8]

- Hairy Cell Leukemia (HCL) [9] – HCL is a rare B-cell malignancy with an unmet need in patients failing to benefit from purine nucleoside analogs (PNA). A recent phase 2 study of IMBRUVICA showed promising results. “The durable PFS in this difficult to treat population makes ibrutinib an effective therapy for select patients with HCL who are not expected to benefit from a PNA.” [10]
- Primary CNS lymphoma (PCNSL). PCNSL is a rare form of lymphoma in the central nervous system without evidence of systemic involvement. It comprises approximately 2% of all primary brain tumors. [11] Approximately 80–90% of PCNSL cases are diffuse-large B-cell lymphomas (DLBCL). Several studies have investigated use of ibrutinib alone and in combination with chemotherapy as an option for treating PCNSL. These studies have shown high (and durable) treatment response and tolerability despite a high rate of Aspergillus infections.

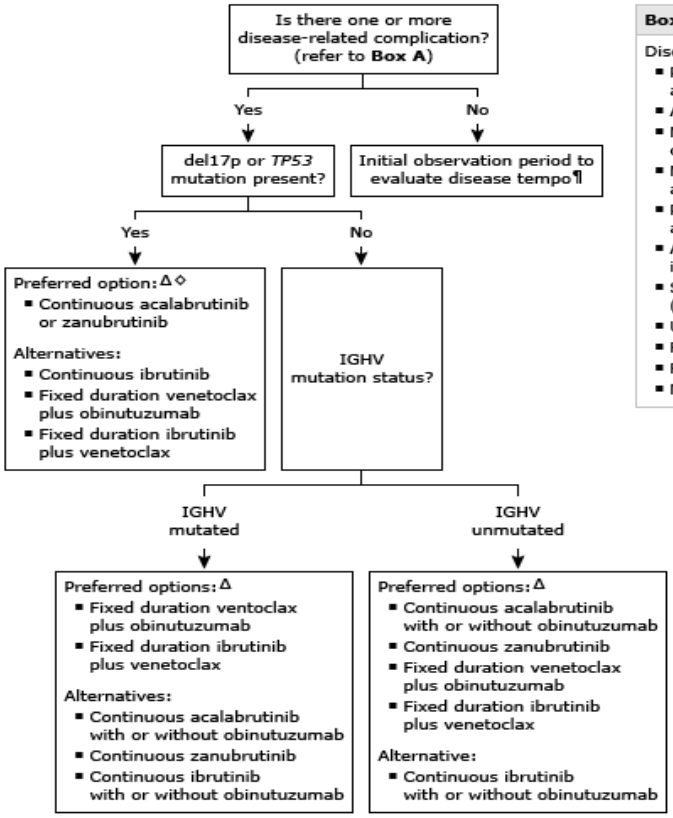
References

1. Dosing & Administration - CLL/SLL | IMBRUVICA® (ibrutinib) HCP (imbruvicahcp.com)
2. Calquence Full Prescribing Information (den8dhaj6zs0e.cloudfront.net)
3. prescribing-information.pdf (brukinsa.com)
4. (REZUROCK) label (fda.gov)
5. prescribing-information.pdf (jakafi.com)
6. Selection of initial therapy for symptomatic or advanced chronic lymphocytic leukemia/small lymphocytic lymphoma - UpToDate
7. NCCN Guidelines Update: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma in: Journal of the National Comprehensive Cancer Network Volume 21 Issue 5.5 (2023) (jnccn.org)
8. Update on IMBRUVICA® (ibrutinib) U.S. Accelerated Approvals for Mantle Cell Lymphoma and Marginal Zone Lymphoma Indications | AbbVie News Center
9. Update on IMBRUVICA® (ibrutinib) U.S. Accelerated Approvals for Mantle Cell Lymphoma and Marginal Zone Lymphoma Indications | AbbVie News Center
10. Kerry A. Rogers, Eric McLaughlin, Lai Wei, Mirela Iulia Anghelina, Mir Khader Ali, Leslie A. Andritsos, Evgeny Arons, James S. Blachly, Timothy G. Call, S. Percy Ivy, Lacey James-Echenique, Jeffrey A. Jones, Robert J. Kreitman, Gerard Lozanski, Farhad Ravandi, Charles A. Schiffer, William E. Carson, Michael R. Grever; Extended Follow up of a Phase 2 Study of Ibrutinib in Hairy Cell Leukemia. *Blood* 2022; 140 (Supplement 1): 6494–6495. doi: https://doi.org/10.1182/blood-2022-165795

11. T Low J, B Peters K. Ibrutinib in primary central nervous system diffuse large B-cell lymphoma. CNS Oncol. 2020 Mar 1;9(1):CNS51. doi: 10.2217/cns-2019-0022. Epub 2020 Mar 6. PMID: 32141313; PMCID: PMC7163401.
12. Ostrom QT, Gittleman H, De Blank PM. et al. American Brain Tumor Association adolescent and young adult primary brain and central nervous system tumors diagnosed in the United States in 2008–2012. *Neuro Oncol.* 18(Suppl. 1), i1–i50 (2016).
13. T Low J, B Peters K. Ibrutinib in primary central nervous system diffuse large B-cell lymphoma. CNS Oncol. 2020 Mar 1;9(1):CNS51. doi: 10.2217/cns-2019-0022. Epub 2020 Mar 6. PMID: 32141313; PMCID: PMC7163401.

CHART 1 QUESTION 27

Initial management of chronic lymphocytic leukemia



Box A

Disease-related complications include:*

- Progressive marrow failure (developing or worsening anemia/thrombocytopenia)
- Advanced stage (Binet C, Rai 3 or 4)
- Massive (ie, >6 cm below left costal margin), enlarging, or symptomatic splenomegaly
- Massive (ie, >10 cm in longest diameter), enlarging, and/or symptomatic lymphadenopathy
- Progressive lymphocytosis with an increase of >50% over a 2 month period or lymphocyte doubling time <6 months
- Autoimmune hemolytic anemia and/or thrombocytopenia inadequately responsive to glucocorticoids
- Symptomatic or functional extranodal involvement (eg, skin, kidney, lung, spine)
- Unintentional weight loss of 10% or more over 6 months
- Fatigue that impairs ability to work or perform usual activities
- Fevers for at least 2 weeks without evidence of infection
- Night sweats for at least 1 month without evidence of infection

IGHV: immunoglobulin heavy chain variable region; BTK: Bruton tyrosine kinase.

* Lymphocytosis itself, even if extreme, is not a strict indication for treatment. Likewise, treatment is not indicated solely on the basis of hypogammaglobulinemia or the presence of a monoclonal or oligoclonal paraproteinemia.

¶ Treatment is indicated if the patient develops significant disease-related complications at any time. During observation, we perform blood counts at 3-month intervals along with a clinical examination. At the end of 12 months, these evaluations can determine disease aggressiveness. The interval of examination may be lengthened for those with clinically stable disease.

Δ The choice among targeted agents is strongly dependent upon patient comorbidities and preferences. Fixed duration therapy is more intensive and logistically complicated but offers a treatment-free interval. Continuous therapy is given until progression or unacceptable toxicity. When selecting among the BTK inhibitors, we prefer acalabrutinib or zanubrutinib rather than ibrutinib as acalabrutinib and zanubrutinib appear to be at least as effective and better tolerated than ibrutinib. If the goal is best efficacy with acceptable tolerability, we offer zanubrutinib. If the goal is best tolerability with good efficacy, we offer acalabrutinib. The addition of obinutuzumab to acalabrutinib or ibrutinib increases efficacy and increases toxicity with higher rates of cytopenias and infections. Further details on the impact of comorbidities and drug interactions is provided in related UpToDate content.

◇ In patients with del17p or *TP53* mutation, continuous acalabrutinib or zanubrutinib may be preferred over fixed duration venetoclax plus obinutuzumab based on cross-trial comparisons that suggest decreased efficacy of the latter in this population.

Question 28: Therapeutic Impact and Comparative Effectiveness

CLL Society wishes to emphasize that the high variability among CLL patients (age, preferences, aggressiveness of disease, comorbidities, and other factors) not only makes clinical studies particularly difficult but inject a great deal of uncertainty into any discussion on comparative effectiveness. Taken together, the factors outlined above (heterogeneity, indolence, response to previous therapies) make overall survival a poor endpoint in clinical trials and comparative effectiveness analyses for CLL, particularly in early lines of therapy.

As noted above, BTK inhibitors offer considerable improvements in care for our patients but can result in drug intolerance requiring interruption, dose reduction, and even treatment discontinuation. The relatively recent approval of second generation BTK inhibitors makes it difficult to undertake a comparative effectiveness analysis with any degree of precision. To date, we have an extremely limited set of head-to-head studies and are unaware of any studies directly comparing acalabrutinib to zanubrutinib or ibrutinib. Zanubrutinib has demonstrated fewer cases of atrial fibrillation than ibrutinib and no cardiac-related deaths. CLL patients taking zanubrutinib also appear to have a higher response rate and a longer time to disease progression. The reduced side effect profile for both acalabrutinib and zanubrutinib will likely enable more patients to remain on treatment longer. But once their disease progresses, they cannot simply switch to one of the other irreversibly binding BTK inhibitors that are approved for CLL and expect a response. This is because once a drug within that same BTK inhibitor drug class has failed the patient, all drugs within that same class will also likely fail.

In addition, it is important to recognize that BTK inhibitors are a relatively new class of drugs targeting rare cancers and, as expected, new market entrants focus on improved response, greater tolerability, or both. Although the selected drug does not have ***generic*** competition, the emergence of next generation BTK inhibitors have created a highly competitive landscape in a relatively small disease population. Although clinical guidelines and recommendations recognize that newer BTK inhibitors have greater tolerability that would tend to improve outcomes, there is still much to learn about the various BTK inhibitors through real world data generated over time. For patients, it is vital that payers, including Part D plans, include all available treatment options in their formularies so that clinicians and patients are able to make treatment decisions based on what will enable the patient to achieve a durable treatment response while maintaining their quality of life.

For now, patients with a CLL diagnosis can expect to live the rest of their lives with cancer. This means that endpoints demonstrating the potential for patients to live treatment-free for months, years, or longer can be particularly meaningful. Endpoints such as progression-free survival (PFS), time to next treatment (TTNT), duration of response (DoR), and measurable residual disease (MRD) may be more meaningful and pragmatic with respect to comparative effectiveness. Although MRD has not yet been included as an endpoint toward gaining approval of a CLL treatment, data suggests that it is predictive of overall survival.

A recent review on the use of MRD in CLL[1] concluded that, "[m]easurable residual disease (MRD) status in chronic lymphocytic leukemia (CLL), assessed on and after treatment, correlates with increased progression-free and overall survival benefit." Use of MRD as an endpoint would not only improve the breadth of data available to FDA and CMS but could significantly improve patient and clinician understanding of the treatment effects of emerging CLL product candidates.

Question 29: Comparative Effectiveness on Specific Populations

Patient comorbidities, combined with expected toxicities, can impact patient outcomes with specific treatment options.

A recent article focused on selecting the appropriate BTK inhibitor emphasized that patient-specific factors should guide treatment choice. "Now that ibrutinib is no longer the sole BTK inhibitor on the market for the treatment of CLL, clinicians are faced with the challenge of selecting the most appropriate BTK inhibitor and weighing the advantages and disadvantages of each. Selection of the appropriate BTK inhibitor is multifactorial and depends on side effect profile, comorbidities of the patient, concomitant medications, and potential drug–drug interactions, cost, ease of administration, and desired outcomes of therapy."

Ibrutinib is the least selective of the BTK inhibitors, with off-target effects leading to increased incidence of adverse events, particular cardiovascular adverse events.

Certain disease-related factors may influence the choice of a BTK inhibitor. In the ELEVATE-TN and ELEVATE-RR studies, patients with significant cardiovascular disease and those taking vitamin K antagonists were excluded. [13] The SEQUOIA trial included patients with cardiovascular disease and those receiving anticoagulation. [14] Zanubrutinib could be considered for those at risk for major bleeds, such as patients on concomitant anticoagulation or antiplatelet therapy, as the SEQUOIA trial demonstrated safety in this population, but it has not been studied head-to-head against acalabrutinib.

All three available BTK inhibitors are associated with drug-to-drug interactions that can complicate treatment. The selected drug, ibrutinib, however, has the most tablet or capsule strengths available and its label includes manufacturer-recommended dose modifications for those taking moderate or strong CYP3A inhibitors. Clinicians and patients may be more comfortable with the dose adjustments associated with ibrutinib in some patient populations despite clinical guidelines that increasingly prefer the second generation BTK inhibitors.

[1] Fisher A, Goradia H, Martinez-Calle N, Patten P, Munir T. The evolving use of measurable residual disease in chronic lymphocytic leukemia clinical trials. Front Oncol. 2023 Feb 22;13:1130617. doi: 10.3389/fonc.2023.1130617. PMID: 36910619; PMCID: PMC9992794.

Disease-related factors may also impact BTK inhibitor selection as well. [15-17] An analysis of 89 newly diagnosed patients with TP53 aberrations treated with ibrutinib or the combination of ibrutinib with an anti-CD20 monoclonal antibody showed a 4-year PFS rate of 79%. In comparison, a trial evaluating venetoclax combined with obinutuzumab revealed a 4-year PFS rate of 53% in patients with TP53 mutations. [18] Zanubrutinib has demonstrated robust responses in patients with del17p. [19]

REFERENCES

14. Lovell AR, Jammal N, Bose P. Selecting the optimal BTK inhibitor therapy in CLL: rationale and practical considerations. Therapeutic Advances in Hematology. 2022;13. doi:10.1177/20406207221116577
15. Byrd JC, Hillmen P, O'Brien S, et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. *Blood* 2019; 133: 2031–2042.
16. Allan JN, Shanafelt T, Wiestner A, et al. Long-term efficacy of first-line ibrutinib treatment for chronic lymphocytic leukaemia in patients with TP53 aberrations: a pooled analysis from four clinical trials. *Br J Haematol* 2022; 196: 947–953.
17. Visentin A, Mauro FR, Cibien F, et al. Continuous treatment with Ibrutinib in 100 untreated patients with TP53 disrupted chronic lymphocytic leukemia: a real-life campus CLL study. *Am J Hematol* 2022; 97: E95–E99.
18. Sivina M, Kim E, Wierda WG, et al. Ibrutinib induces durable remissions in treatment-naïve patients with CLL and 17p deletion and/or TP53 mutations. *Blood* 2021; 138: 2589–2592.
19. Al-Sawaf O, Zhang C, Robrecht S, et al. Venetoclax-obinutuzumab for previously untreated chronic lymphocytic leukemia: 4-year follow-up analysis of the randomized CLL14 study. *Hematol Oncol* 2021; 39: S146.
20. Tam CS, Robak T, Ghia P, et al. Zanubrutinib monotherapy for patients with treatment naïve chronic lymphocytic leukemia and 17p deletion. *Haematologica* 2020; 106: 2354–2363.

Question 30: Addressing Unmet Medical Needs

- BTK inhibitors have changed the landscape of CLL treatment in a way that not only improves survival but improves quality of life. Introduction of an oral treatment is extremely important as patients have expressed a preference for long term oral medications over infused chemoimmunotherapy. [20]
    - As one CLL patient reported, "After failing a bone marrow transplant for aggressive CLL, I was out of options that offered any probability of success based on the genetics of my CLL. I entered a phase 1 trial of PCI-32765, that later was known as ibrutinib and enjoyed a 7-year remission."
    - "My health was severely compromised with problems with massive internal bleeding due to low platelets, massive splenomegaly, massively enlarged and

painful lymph nodes in the neck, axillae, and groin, overwhelming fatigue, and general malaise. All of those improved dramatically soon after starting therapy."
- "I did have significant side effects that limited my ability to work, sleep, and enjoy life. They included GI issues and severe muscle pains, rashes, and other symptoms. I still have hypertension induced by the therapy. Fortunately, I did not develop any of the serious cardiac arrythmias and obviously I was not part of the 1-2% that suffered sudden death."

- CLL Society has significant concerns, however, that innovation to address unmet needs could be substantially deterred if manufacturers find that increasing competition within a small disease population is riskier now than it was before enactment of the Inflation Reduction Act's drug negotiation program. There is, therefore, a significant unmet need for new treatments and treatment combinations that improve the depth and duration of response, and/or are better tolerated, so that fewer of our patients experiencing serial relapses are without an approved therapeutic option.

- Richter's syndrome (RS) is an aggressive histologic transformation of CLL, most often into diffuse large B-cell lymphoma (DLBCL). These patients have poor outcomes, with CR rates of approximately 20% and long-term survival below 20% with chemoimmunotherapy. Several studies have demonstrated activity for PD-1 inhibitors, especially in combination with ibrutinib, with ibrutinib-naïve patients having high response rates. [21] Further studies on combination therapy regimens including ibrutinib and other BTK inhibitors are needed. But their feasibility may depend on whether sponsors can make a case for investing in this patient population.

REFERENCES

21. *Factors That Influence Treatment Decision-Making: Perspectives of 1147 Chronic Lymphocytic Leukemia (CLL) Patients in the United States*): "82% were willing to take a life-long tx for long-term control without potential for cure." https://doi.org/10.1182/blood-2018-99-112971
22. Treatment of Richter's syndrome | Hematology, ASH Education Program | American Society of Hematology (ashpublications.org)

EXECUTIVE SUMMARY

While the drug price negotiation program may have a marginal impact on healthcare costs for patients with relatively common conditions, as well as CLL patients who are not currently receiving active treatment, it will likely have no impact on out-of-pocket costs for patients requiring active therapy. There is little doubt that the decisions CMS makes now on the price negotiation program will become part of the complex calculations researchers, investors, and drug manufacturers make when determining whether to pursue a particular drug candidate for

a specific indication. We fear that without a proactive intent to preserve the fragile cost/benefit balance in small population diseases, CMS will inadvertently tip the scales away from innovation in CLL and other related blood cancers.

We are concerned that if ibrutinib is priced in a way that encourages health plans to insist on it as a first step, more patients will be forced to experience potentially dangerous serious adverse events and discontinue treatment. At the same time, we want to see all medications be accessible, as some patients may tolerate ibrutinib and be unable to take an alternative BTK inhibitor.

[continue this section based on finalized response]