VIA ELECTRONIC DELIVERY

March 1, 2025

Stephanie Carlton
Acting Administrator
Centers for Medicare & Medicaid Services
Department of Health and Human Services
Baltimore, MD 21244–1850

RE: Medicare Drug Price Negotiation Program: Selected Oncology Drugs

Dear Acting Administrator Carlton:

The Protecting Innovation in Rare Cancers (PIRC) coalition appreciates the opportunity to submit feedback, including input from our patient communities, on the Centers for Medicare & Medicaid Services' (CMS') selected drugs under the Inflation Reduction Act's (IRA's) Medicare Drug Price Negotiation Program (MDPNP) for iPAY 2027.

PIRC is a collaborative, multi-stakeholder patient advocacy coalition committed to improving access to and affordability of existing treatments for all patients while preserving the incentives required to advance future innovations in rare cancers. Our coalition was created to enable information exchange and collaboration among rare cancer advocates to educate our patient communities and policymakers on the impact the Inflation Reduction Act (IRA) might have on access to existing Part D drugs and development of new therapeutic options.

Medicare beneficiaries with rare cancers face substantial challenges including a limited set of treatment options, high out-of-pocket (OOP) costs, and a relatively small set of specialists with expertise in a particular rare cancer. The IRA's Part D redesign provisions will, for most patients, eliminate the financial struggle of choosing between paying high OOP costs at the pharmacy and maintaining resources for food and housing. The MDPNP, however, is poorly understood by Medicare beneficiaries and the general public. As last year's listening sessions demonstrated, misconceptions included beliefs that the federal government was negotiating prices for all patients, that the "savings" on all negotiated drugs would be passed on directly to patients. The reality for rare cancer patients and others relying on "specialty" drugs is that the negotiated prices will probably not lead to lower OOP costs since they will hit the Part D cap regardless of any negotiated

Medicare price. CMS has also acknowledged that there is a reasonable chance that negotiated prices could lead to increased rather than decreased premiums. This is consistent with Congress' expectation that MDPNP savings would offset the estimated $30 billion increase in Medicare spending due to Part D benefit redesign.[1]

Our feedback focuses primarily on Calquence and its therapeutic alternatives. Many of our concerns, however, are more broadly applicable to rare cancer patients and the treatments they rely on now or may rely on in the future. Our patient communities remain concerned that the MDPNP will reduce the number of new treatments that are brought to market, including initial approvals in rare cancers, follow-on uses in multiple cancers and development of combination therapy regimens that could offer new hope for patients to live longer and enjoy a higher quality of life.

We urge CMS to fully engage stakeholders so that its policy determinations and exercise of discretion achieve Medicare savings without disrupting incentives to scientific advances that have provided hope for cancer patients and their families.

Background: The MDPNP Does Not Fully Account for Research and Development Approaches in Cancer

CMS selected one oncology drug – Imbruvica, indicated for chronic lymphocytic leukemia (CLL) - for the MDPNP's first year. The set of selected drugs for iPAY 2027 includes four oncology drugs (Xtandi, Pomalyst, Ibrance and Calquence), one of which (Calquence) was a therapeutic alternative to Imbruvica. We expect that as Part B drugs become eligible for selection, the proportion of oncology agents subject to negotiated prices will greatly increase, putting pressures on manufacturers and investors to reconsider whether, how, and when to direct funds toward cancer research and development. PIRC believes CMS has more discretion in implementing the MDPNP than it exercised in selecting and negotiating drugs for iPAY 2026.

We ask that CMS avoid aggregating research costs and revenue as it determines whether a manufacturer has recouped its costs and instead calculate return on investment using indication-specific cost and revenue data. In addition, we strongly urge CMS to consider the factors below as it selects and negotiates prices for drugs.

[1] Congressional Budget Office. Estimated budgetary effects of Public Law 117-169, to provide for reconciliation pursuant to Title II of S. Con. Res. 14. Published 2022. https://www.cbo.gov/system/files/2022-09/PL117-169_9-7-22.pdf

- Rare cancers present heightened challenges to drug developers because they tend to have poorly understood natural histories, significant heterogeneity, and diverse clinical manifestations. These factors, together with small patient populations, make it difficult to enroll a sufficient number of participants to conduct clinical trials demonstrating clinical benefit.

- The failure rate for oncology drug candidates is very high. A recent study noted that approximately 97% of oncology drugs studied for an indication never receive FDA approval for that indication due to challenges including:

    - Off-target toxicities in small molecules
    - Misidentification of essential genes in cancer
    - Mischaracterization of target-specific inhibitors[2]

    Although CMS includes specific costs related to study failures within calculated research and development costs for selected drugs, the linkage between the cost of failures and successful drug candidates is complex and extends beyond reportable direct costs.

    - The high failure rate presents a risk that is incorporated into the decision to pursue or abandon a research program.

    - The MDPNP's changes to the long-term upside against which the risk is weighed can and likely will drive the set of new treatment options (and abandoned candidates) over the next decade and beyond.

- Cancer treatments are far less likely to have generic competition than treatments for more common conditions. A recent study compared generic competition for oncologic drugs with that of cardiovascular treatments.

    - A smaller proportion of oncologic products had generics (49% vs. 80%).
    - For off-patent drugs, the median time from approval to the first generic approval was longer for oncologic products compared to cardiovascular products (15.4 years versus 12.3 years).
    - The factors identified as impeding generic development in oncology were product dosage form and FDA recommendations requiring patient enrollment for bioequivalence studies for cancer treatments.

- Availability of generic competition may also be less effective in reducing healthcare costs in cancer than in nonmalignant conditions. This is because newer versions of older cancer drugs generally offer improvements in progression-free survival and/or overall survival and

[2] Ann Lin *et al.*, Off-target toxicity is a common mechanism of action of cancer drugs undergoing clinical trials.*Sci. Transl. Med.**11**,eaaw8412(2019).DOI:10.1126/scitranslmed.aaw8412*

become replacements for, rather than alternatives to, older treatments. Developing generic versions of older medications, therefore, may not be a viable investment given the challenges to developing these drugs identified below combined with the potential that older medications might become obsolete due to superior outcomes from branded competition.

I36-42: Patient-Focused Experience

CMS has requested input to improve its understanding of patients' and caregivers' experiences with the selected drug and its therapeutic alternatives. The selected drug Calquence is indicated for adults with Mantle Cell Lymphoma (MCL) (2017), adults with Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) (2019), and in combination with chemoimmunotherapy for previously untreated MCL (2025).

NCCN guidelines provide for off-label use of Calquence:

- In the fixed-duration treatment of CLL/SLL in combination with venetoclax, with or without obinutuzumab
- In treating Marginal Zone Lymphoma (MZL)
    - As a preferred agent in second-line therapy for patients with nodal MZL who have received rituximab-based chemotherapy
    - As third-line therapy for patients with nodal MZL or extranodal MZL (e.g., gastric MALT lymphoma) who have received rituximab-based chemotherapy and another BTK inhibitor (ibrutinib)
- In treating Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma, as a single agent for patients with previously treated disease.

PIRC submits its input on the patient and caregiver experience as a collaborative set of patient advocacy organizations. Unfortunately, the wording of CMS' questions, e.g., "How do the condition(s) you listed in Question 36a1 impact your daily life and well-being or the daily life and well-being of someone you provide care for?" assumes that the responder is a single patient. To avoid misleading and/or incorrect responses, we have provided information on the selected drug, its uses, and its therapeutic alternatives under the condition-specific subheadings below.

CLL/SLL

Diagnosis and disease burden

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. It 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 best understood as a stage of CLL where there are not yet a significant number of cancer cells located in the bloodstream. Throughout this submission, we refer to the disease states collectively as CLL.

It is common for a CLL diagnosis to follow a finding of lymphocytosis from routine blood tests in an asymptomatic indicivual. Others might note painless lymph node swelling and consult a physician. Approximately 5-10% of patient will have the typical symptoms of a "B" lymphoma including one or more of:

- Unintentional weight loss ≥10 percent of body weight within the previous six months
- Fevers of >100.5°F (>38°C) for ≥2 weeks without evidence of infection
- Drenching night sweats without evidence of infection
- Extreme fatigue (ie, unable to work or perform usual activities)

A 2020 analysis of a long-term study assessing how patients with chronic lymphocytic leukemia (CLL) describes quality of life (QoL) compared to other U.S. populations, and the impact CLL has on daily living, finances, and professional and family relationships.[3] The study included 191 patients with CLL who were enrolled in the Cancer Support Community's online cancer experience registry. The mean patient age was 61 years and mean time from CLL diagnosis was 6.6 years. One in 5 patients (19%) reported experiencing a recurrence of CLL. A significant proportion of CLL patients reported significantly worse quality of life (QoL) than the national average of the U.S. population for:

- Anxiety (22%)
- Fatigue (22%)
- Physical functioning (15%)
- Depression (13%)
- Pain interference (12%)
- Social functioning (12%)
- Sleep disturbance (9%)[4]

20% of the CLL patients who responded rated their overall health as poor or fair, 30% said that CLL affects their relationships with friends and family, and 24% were concerned about thinking clearly

[3] https://www.cancersupportcommunity.org/sites/default/files/file/2020-07/CSC_Registry_Report_June_2020.pdf
[4] Id.

("chemo brain" or "brain fog"). 34% reported that CLL affects their ability to work; 42% reported that CLL affects their day-to-day finances.

The most common cancer-related sources of distress reported by respondents were centered around physical and future-focused matters. Respondents reported being moderately to very seriously concerned about:

- Eating and nutrition (52%)
- Exercising and being physically active (42%)
- Worrying about the future/what lies ahead (39%)
- The cancer progressing/recurring (36%)
- Feeling too tired to do the things you need or want to do (35%)
- Health insurance/money worries (33%)
- Sleep problems (32%)
- Changes in work, school or home life (32%)

It is important to note that this study was started before the selected drug, Calquence, was approved as a treatment option for CLL.

A 2020 article examining results from studies published or presented between January 2000 and June 2, 2019[5] confirmed that CLL "imposes a significant HRQoL and economic burden." The authors noted "an unmet need persists in CLL for treatments that delay progression while minimizing AEs. Studies suggest targeted therapies may reduce the economic burden of CLL, but longer follow-up data are needed."

Disease Progression and Treatment Options

CLL is extremely heterogeneous in terms of disease course and progression. Some patients have an aggressive form of the disease, generally identified by genetic expression as higher-risk, 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

[5] Waweru, C., Kaur, S., Sharma, S., & Mishra, N. (2020). Health-related quality of life and economic burden of chronic lymphocytic leukemia in the era of novel targeted agents. *Current Medical Research and Opinion*, *36*(9), 1481–1495. https://doi.org/10.1080/03007995.2020.1784120

survival (OS).[6] Today, the median overall survival (OS) from start of front-line therapy is 5 to 15 years, depending on disease features, individual patient factors, and treatment choices.

Patients with CLL commonly develop complications associated with immune dysfunction resulting in immunodeficiency and autoimmune disorders. The most common CLL- related complications are infection, anemia, and thrombocytopenia. Potentially life-threatening, but less common, complications include tumor lysis syndrome and second cancers.[7]

The addition of BTK inhibitors to the set of CLL treatment options has transformed patient care by introducing a targeted oral small molecule therapy with large, randomized studies showing improved outcomes compared to the previous standard of care (SOC) and demonstrating efficacy in treating CLL subtypes that are refractory to the former SOC. Patients now have more treatment options compared to just years ago when the standard of care was chemoimmunotherapy. Since targeted therapies have replaced chemoimmunotherapy as the preferred option in ***all*** patients with CLL. For most patients front-line treatment options include:

- Continuous therapy with a BTK inhibitor. This may be the preferred choice for patients unable to access a center with venetoclax ramp-up capabilities or other barriers to accessing a fixed-duration treatment course.

- Calquence plus obinutuzumab

- 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).

    - Note: Astrazeneca, the manufacturer of Calquence is currently recruiting participants for a global Phase IV, open-label, randomized study evaluating the safety and tolerability of acalabrutinib (monotherapy, 100 mg orally [po], twice daily [bd]) compared to investigator's choice of treatment, in patients with CLL (TN or R/R) and moderate to severe cardiac impairment.

[6] Selection of initial therapy for symptomatic or advanced chronic lymphocytic leukemia/small lymphocytic lymphoma - UpToDate

[7]

- Fixed-duration ibrutinib 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.

- Acalabrutinib–venetoclax with or without obinutuzumab has also demonstrated significantly prolonged progression-free survival compared to chemoimmunotherapy in fit patients with previously untreated CLL. (AMPLIFY ClinicalTrials.govnumber, NCT03836261.)[8]

Since CLL is indolent and generally not "curable," treatment goals focus on improving quality of life and prolonging overall survival. 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.[9] Although most CLL/SLL patients can expect a response to initial therapy, it is common for patients to experience one or more relapses during the course of their disease. Decisions on subsequent treatment courses are based on the prior therapy received, patient comorbidities, resistant mutations, and other factors.[10]

Drug intolerance can disrupt treatment and force CLL patients to either change treatments, take a "drug holiday," or adjust dosing due to drug intolerance. Calquence has demonstrated a lower overall AE burden compared to ibrutinib, particularly with respect to serious AEs that drive treatment plan changes such as atrial fibrillation, hypertension. and hemorrhage [11]

Patient Treatment Preferences

Patients often differ on what attributes of a treatment are most important. A recent study[12] explored patient preferences and CLL patients' willingness to balance treatment related benefits and risks. This study used a web-based survey administered to 229 individuals recruited through

[8] https://www.nejm.org/doi/full/10.1056/NEJMoa2409804
[9] 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)
[10] 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)

[11] Seymour JF, Byrd JC, Ghia P, Kater AP, Chanan-Khan A, Furman RR, O'Brien S, Brown JR, Munir T, Mato A, Stilgenbauer S, Bajwa N, Miranda P, Higgins K, John E, de Borja M, Jurczak W, Woyach JA. Detailed safety profile of acalabrutinib vs ibrutinib in previously treated chronic lymphocytic leukemia in the ELEVATE-RR trial. Blood. 2023 Aug 24;142(8):687-699. doi: 10.1182/blood.2022018818. PMID: 37390310; PMCID: PMC10644206.
[12] Ravelo A, Myers K, Brumble R, Bussberg C, Koffman B, Manzoor BS, Biondo JML, Mansfield C. Patient preferences for chronic lymphocytic leukemia treatments: a discrete-choice experiment. Future Oncol. 2024;20(28):2059-2070. doi: 10.1080/14796694.2024.2348440. Epub 2024 May 22. PMID: 38861284; PMCID: PMC11497998.

the CLL Society in which 12 questions posed a choice between two hypothetical treatment profiles. The profiles were defined by seven attributes associated with targeted therapies for CLL. Respondents preferred treatments:

- Increasing the chance of progression-free survival (PFS) at 2 years from 70 to 90%
- Evaluated to confirm results using measurable residual disease (MRD) testing (this was more important for treatments with a 70% chance of PFS than a 90% PFS probability)
- Administered as a daily oral treatment rather than an intravenous infusion every 4 weeks
- Used for a fixed duration rather than continuously until progression
- Offering a lower risk of side effects

Patients requiring front-line and even second-line therapy to help control CLL have more (and better) treatment options than patients had a decade ago. Unfortunately, a CLL diagnosis means that a patient can expect to live the rest of their life with cancer. It is not surprising that patients prefer treatment options that enable them to live treatment-free for months, years, or longer.

Additional Information on CLL and its Treatment Options

PIRC understands that CMS seeks to ensure that negotiated prices reflect treatment value and capture the benefits and risks of a selected drug compared to those of a therapeutic alternative. The second generation BTK inhibitors (Calquence and Brukinsa) have demonstrated sufficient safety and efficacy profiles to replace Imbruvica monotherapy within NCCN guidelines for first-line CLL treatment. The high variability among CLL patients (age, preferences, aggressiveness of disease, comorbidities, and other factors) not only makes clinical studies in CLL particularly difficult but it injects a great deal of uncertainty into any discussion on comparative effectiveness.

Taken together, the factors outlined above (heterogeneity, indolence, response to previous therapies) make comparative effectiveness analyses difficult in early lines of CLL therapy. Endpoints such as PFS, time to next treatment (TTNT) and duration of response (DoR) may be more meaningful and pragmatic with respect to comparative effectiveness than OS.

We urge CMS to recognize that the relative newness of the BTK inhibitor class targeting rare cancers means that researchers, clinicians and patients are still learning about these treatments. Although clinical guidelines and recommendations recognize that newer BTK inhibitors have greater tolerability that would tend to improve outcomes, clinical studies currently in progress could change how these drugs are used, including the patient population(s) for which one treatment might be a better option than another.

Moreover, Calquence is now being studied in combination with venetoclax with and without obinutuzumab. Data from the AMPLIFY study indicates that Calquence plus venetoclax might reduce the risk of disease progression or death by 35% compared to standard-of-care chemoimmunotherapy, and adding Obinutuzumab yields a 58% reduction in the risk of progression or death. Although a longer follow-up period is needed to evaluate whether the combination is associated with an OS benefit, the manufacturer noted that existing data appears to favor the Calquence combination. The potential that a second generation BTK inhibitor could be used for a fixed duration and deliver a durable response would, from the CLL patient perspective, be a tremendous advance in treating this chronic cancer. The combination would come very close to "checking all the boxes" – oral formulation, fixed duration, reduced side effect profile, improved efficacy – on patient treatment preferences. It allows treatment breaks, reducing the potential for long-term adverse effects and drug resistance, would reduce treatment costs, and would significantly improve quality of life for those living with this chronic cancer.

PIRC has significant concerns that the MDPNP will not only deter investment in new CLL treatments but will reduce manufacturer interest in the types of post-approval studies that have been conducted or are in progress for Imbruvica, Calquence and Brukinsa. We acknowledge that negotiation in and of itself is not a new concept within the pharmaceutical and biotechnology industries. It has long been an integral part of payer contracting. The statutory price ceilings, however, when applied to small molecules in oncology, create a narrow window of profitability that could reduce the types of research that CLL patients and others with rare cancers rely on to live longer, healthier lives.

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is a rare B cell non-Hodgkin lymphoma that has a variable clinical course and can involve lymph nodes as well as extranodal sites, including the gastrointestinal tract, blood, and bone marrow. MCL comprises about 3-6% of non-Hodgkin lymphomas, with an annual incidence of 0.5 per 100,000 population in Western countries. Approximately 4,000 new MCL patients are diagnosed each year in the U.S. MCL has a median age at diagnosis of 68 years and a patient population that is three-quarters male. White individuals are nearly twice as likely to be diagnosed with MCL as Black individuals.[13] Most cases of MCL have multiple sites of lymph node involvement, with or without extranodal involvement, and an aggressive natural history. Some patients (approximately one-fifth) have a more indolent form of the disease and may not need immediate treatment. A subset of patients have clinical or pathological features associated with a poor response to conventional treatment.

[13] Mantle cell lymphoma: Epidemiology, pathobiology, clinical manifestations, diagnosis, and prognosis - UpToDate

A 2020 article reviewed studies on MCL, healthcare utilization, disease burden, treatment patterns, survival, and costs within the context of the Medicare population.[14] The study revealed that "healthcare costs were substantial and most costs (>80%) were MCL-related. Overall survival was poorer among later lines of treatment (median OS from initiation of 1 L: 53.5 months; 2 L: 22.0 months; 3 L: 11.8 months; 4 L: 7.8 months)." The authors concluded that their "real-world study of U.S. Medicare beneficiaries diagnosed with MCL found short duration of treatment therapies, high rates of hospitalization and hospice care, substantial healthcare costs, and poor overall survival" suggesting an unmet need for "novel agents and treatment modalities with higher efficacy and better tolerability to be used alone or in combination to improve outcomes in elderly patients with MCL."

Imbruvica was granted accelerated approval for use in MCL In November 2013 based on an investigator-assessed overall response rate (ORR) of 65.8% (95% CI, 56.2%-74.5%) reported among 111 treated patients enrolled to an open-label, multicenter, single-arm phase 2 study (NCT01236391). Abbvie, Imbruvica's manufacturer voluntarily withdrew that approval due to treatment toxicity despite confirmatory studies meeting the primary endpoint of PFS in previously untreated MCL patients.[15]

Calquence received accelerated approval in October 2017 for MCL treated with at least one prior treatment. In January 2025, Calquence in combination with bendamustine and rituximab was granted full approval for the treatment of adult patients with previously untreated mantle cell lymphoma (MCL) who are ineligible for autologous hematopoietic stem cell transplantation. Data from the ECHO trial showed Calquence plus bendamustine and rituximab reduced the risk of disease progression or death by 27% compared to standard-of-care chemoimmunotherapy (median PFS was 66.4 months for the Calquence combination versus 49.6 months with chemoimmunotherapy alone). The January 2025 approval also converted the 2017 accelerated approval to full approval.[16]

According to Lymphoma Research Foundation's CEO Meghan Gutierrez, "New treatment options have long been needed in the first-line treatment of mantle cell lymphoma in the US. Patients with this rare and often aggressive cancer can experience severe symptoms by the time they are

---

[14] Squires, P., Puckett, J., Ryland, K. E., Kamal-Bahl, S., Raut, M., Doshi, J. A., & Huntington, S. F. (2023). Assessing unmet need among elderly Medicare Beneficiaries with Mantle cell lymphoma: an analysis of treatment patterns, survival, healthcare resource utilization, and costs. *Leukemia & Lymphoma*, *64*(11), 1752–1770. https://doi.org/10.1080/10428194.2023.2234525

[15] AbbVie Withdraws Ibrutinib MCL and MZL Indications in the United States

[16] FDA approves acalabrutinib with bendamustine and rituximab for previously untreated mantle cell lymphoma | FDA

diagnosed - having an effective therapy that can significantly improve outcomes for patients early in the treatment process is a much-needed advancement."[17]

Results from the randomized, double-blind, placebo-controlled ECHO trial showed Calquence plus bendamustine and rituximab reduced the risk of disease progression or death by 27% compared to standard-of-care chemoimmunotherapy (hazard ratio [HR] 0.73; 95% confidence interval [CI] 0.57-0.94; p=0.016). Median PFS was 66.4 months for patients treated with the Calquence combination versus 49.6 months with chemoimmunotherapy alone. The primary endpoint (PFS) was assessed by an Independent Review Committee. Other efficacy endpoints included OS, overall response rate (ORR), duration of response (DoR) and time to response (TTR).

The safety and tolerability of Calquence was consistent with its known safety profile, and no new safety signals were identified.

Additional Areas of Unmet Need

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. Approximately 80–90% of PCNSL cases are diffuse-large B-cell lymphomas (DLBCL). Several studies have been initiated to investigate the use of Calquence alone and in combination with other agents as an option for treating PCNSL. Although studies investigating Imbruvica in PCNSL have hown high (and durable) treatment response and tolerability, Imbruvica is associated with a high rate of Aspergillus infections.

Richter's syndrome (RS) is a very rare and aggressive histologic transformation of CLL that results in a very poor prognosis. Further studies on combinations of BTK inhibitors with other treatments could confirm what small studies have found – that BTK inhibitors plus a PD-1 inhibitor can significantly improve outcomes for these patients.

Attached, please see our table outlining rare cancer studies of Calquence that are currently underway. We strongly urge CMS to actively monitor the drug negotiation program's impact on industry-sponsored studies of existing treatments. The cost/benefit balance for rare cancers is particularly fragile. For patients, competition is both meaningful and beneficial when it results in improved treatments and/or expands the base of knowledge on how existing treatments can be used – alone and with other therapies. The BTK inhibitor class is an example where we expect that, without pricing intervention, the set of available products and our understanding of their value would continue to evolve over time to the benefit of patients.

[17] Calquence plus chemoimmunotherapy approved in the US for patients with previously untreated mantle cell lymphoma

Additional Information

PIRC appreciates that the Administration has committed to increase transparency in the negotiation process, facilitate savings for beneficiaries and the Medicare program, and avoid adverse impacts on innovation. PIRC continues to believe that CMS' decison to identify a qualifying single-source drug based on common active moiety (drugs) or common active ingredient (biologics) will have repercussions that fall disproportionately on rare and ultra-rare disease patients with high unmet needs. We urge CMS to adopt an approach that treats products as the same qualifying single-source drug onily when they share an NDA or BLA. This is within the plain language of the statute and it would reduce the burden on manufacturers and increase the utility of the collected information in identifying an MFP based on the statutory factors and considerations.

All patients, but especially those with rare cancers, pin their hopes for new treatment options on the value and efficiencies inherent in repurposing and pursuing follow-on indications. The IRA's timeline from NDA/BLA approval to negotiation eligibility combined with CMS implementation of the MDPNP needlessly reduce the value of new indications to manufacturers, their investors and shareholders, and potential licensing partners.

We are also concerned that CMS' implementation approach, rather than the statute, necessitated creation of the Primary/Secondary Manufacturer construct. Manufacturers, particularly the smaller clinical stage compaies innovating in rare cancers, often develop drug candidates and license one or more indications to a partner. Research and development costs may be split across multiple entities and a manufacturer with data on costs may not have access to data on sales volume, revenue, and other data elements required within the ICR. PIRC expects that implementation of the MFP will present similar problems, particularly if one entity is fully responsible for ensuring access to the MFP through rebates on sales revenue that accrues to another, unrelated entity.

In addition, PIRC urges CMS to:

- Solicit and consider patient information that reflects the whole patient, including quality of life impacts not quantified in clinical studies, and other information that is important to patients.

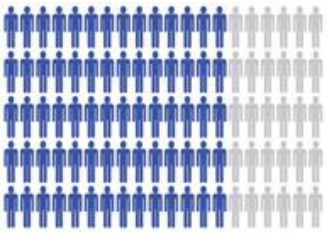
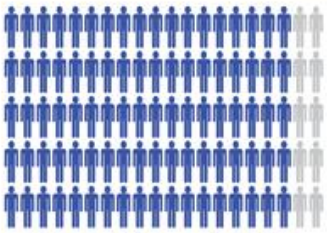
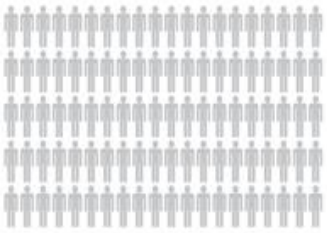
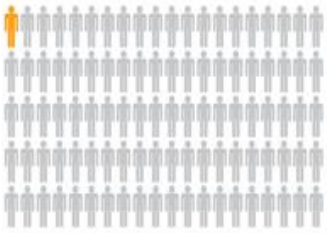
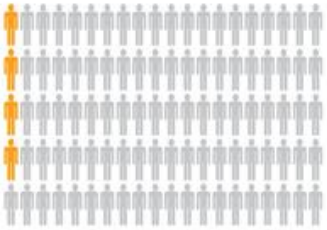
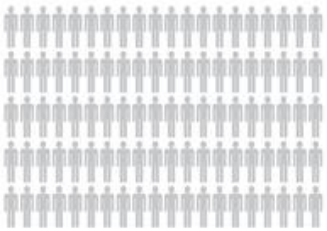
- Include factors such as drug toxicity and side effect profiles in assessing unmet need.

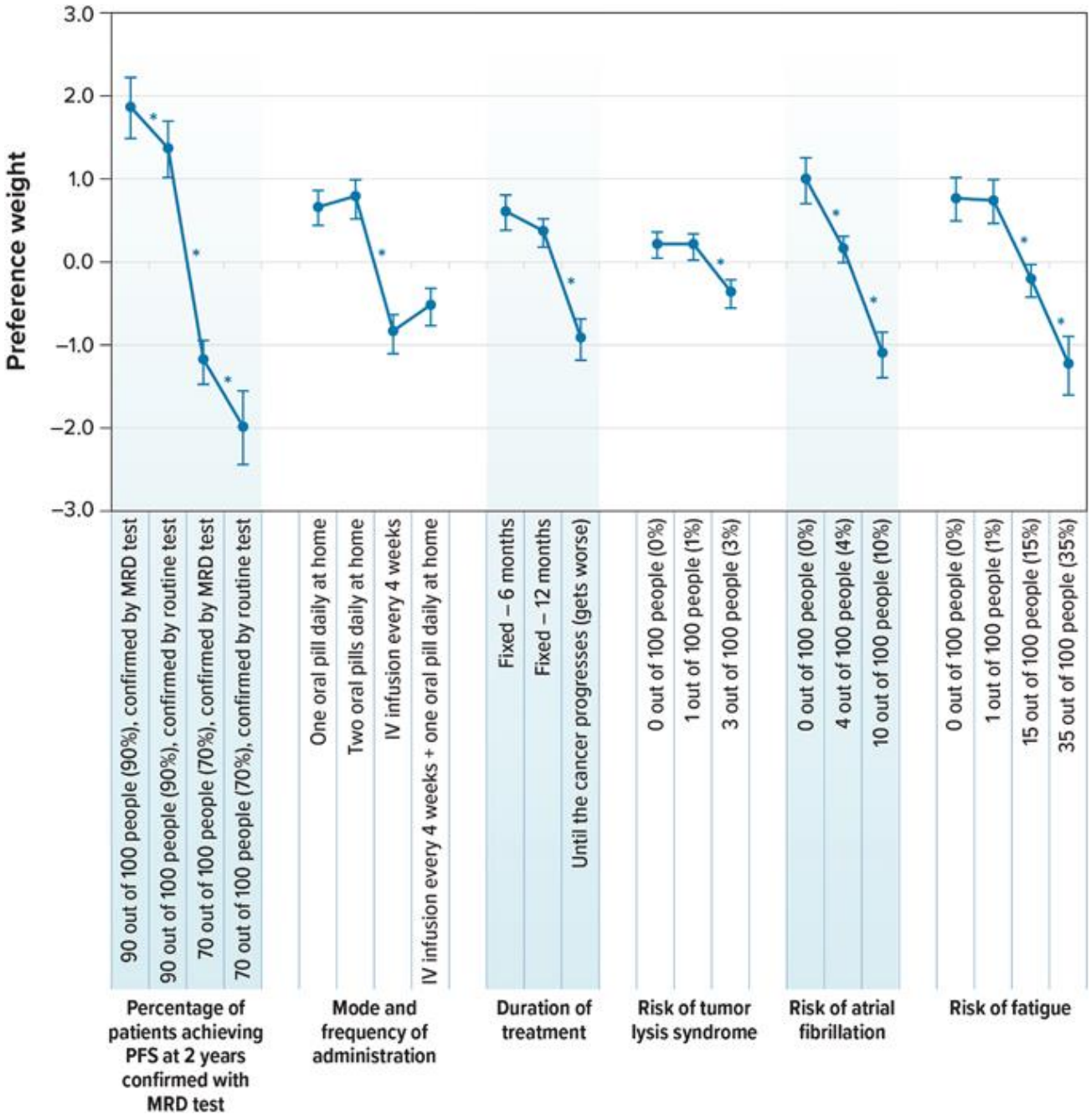
- Consider the fact that rare cancer patients can have multiple treatments available and still have unmet need as they progress through lines of treatment.

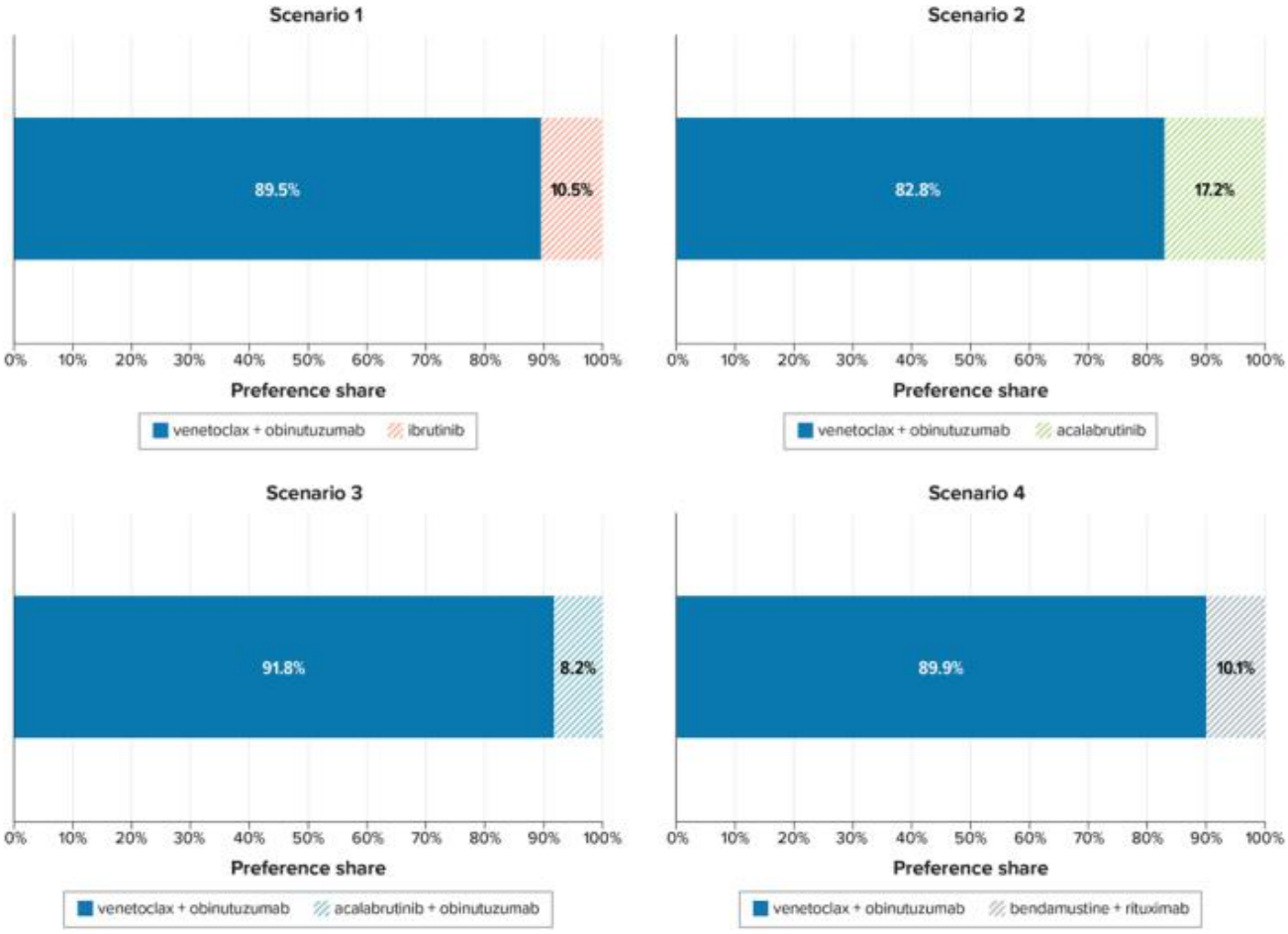
Conclusion

PIRC appreciates the opportunity to contribute the perspectives of those within the rare cancer patient and caregiver community as CMS starts the negotiation process for iPAY 2027. We look forward to a continuing dialogue throughout the IRA implementation process and welcome the opportunity to discuss our comments or the experience of rare cancer patients generally.

Biomarker Collaborative
Cancer*Care*
Cancer Support Community
Chondrosarcoma Foundation
CLL Society
Cutaneous Lymphoma Foundation
Exon 20 Group
Life Raft Group
Haystack Project
ICAN, International Cancer Advocacy Network
Life Raft Group
MET Crusaders
No Stomach for Cancer
PDL1 Amplifieds

Treatment Feature	Treatment A	Treatment B
Chance that the cancer does not progress (remains stable) for at least 2 years	 70 out of 100 people (70%)	 90 out of 100 people (90%)
Treatment results confirmed with measurable residual disease (MRD) test	**Yes** Confirmed by MRD test	**No** Confirmed by routine test
How you take the treatment	 IV infusion every 4 weeks	 One oral pill daily at home
How long you have to take the treatment	Fixed – 6 months	Until the cancer progresses (gets worse)
Increased risk of tumor lysis syndrome (TLS) in the first few weeks of taking the treatment	 0 out of 100 people (0%)	 1 out of 100 people (1%)
Increased risk of having an irregular heartbeat (atrial fibrillation) each year while you are taking the treatment	 4 out of 100 people (4%)	 10 out of 100 people (10%)
Increased risk of fatigue for several days each month while you are taking the treatment	 0 out of 100 people (0%)	 35 out of 100 people (35%)
Which would you choose?	☐	☐


Preference weight
3.0
2.0
1.0
0.0
−1.0
−2.0
−3.0
90 out of 100 people (90%), confirmed by MRD test
90 out of 100 people (90%), confirmed by routine test
70 out of 100 people (70%), confirmed by MRD test
70 out of 100 people (70%), confirmed by routine test
One oral pill daily at home
Two oral pills daily at home
IV infusion every 4 weeks
IV infusion every 4 weeks + one oral pill daily at home
Fixed – 6 months
Fixed – 12 months
Until the cancer progresses (gets worse)
0 out of 100 people (0%)
1 out of 100 people (1%)
3 out of 100 people (3%)
0 out of 100 people (0%)
4 out of 100 people (4%)
10 out of 100 people (10%)
0 out of 100 people (0%)
1 out of 100 people (1%)
15 out of 100 people (15%)
35 out of 100 people (35%)
Percentage of patients achieving PFS at 2 years confirmed with MRD test
Mode and frequency of administration
Duration of treatment
Risk of tumor lysis syndrome
Risk of atrial fibrillation
Risk of fatigue


Scenario 1
89.5%
10.5%
0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%
Preference share
venetoclax + obinutuzumab
ibrutinib
Scenario 2
82.8%
17.2%
Preference share
venetoclax + obinutuzumab
acalabrutinib
Scenario 3
91.8%
8.2%
Preference share
venetoclax + obinutuzumab
acalabrutinib + obinutuzumab
Scenario 4
89.9%
10.1%
Preference share
venetoclax + obinutuzumab
bendamustine + rituximab

NCT Number	Study Status	Conditions	Interventions
NCT04630756	ACTIVE_NOT_RECRUITING	Advanced Haematological Malignancies	AZD4573, Acalabrutinib
NCT04008706	ACTIVE_NOT_RECRUITING	Chronic Lymphocytic Leukemia	Acalabrutinib
NCT03836261	ACTIVE_NOT_RECRUITING	Chronic Lymphocytic Leukemia	Acalabrutinib, Venetoclax, Chemoimmunotherapy, Obinutuzumab
NCT03580928	ACTIVE_NOT_RECRUITING	Chronic Lymphocytic Leukemia (CLL)	Venetoclax, Obinutuzumab, Acalabrutinib
NCT05057494	ACTIVE_NOT_RECRUITING	Chronic Lymphocytic Leukemia or Small Lymphocytic Lymphoma	Acalabrutinib, Venetoclax, Obinutuzumab
NCT04722172	ACTIVE_NOT_RECRUITING	Chronic Lymphocytic Leukemia|Small Lymphocytic Lymphoma	Acalabrutinib, Obinutuzumab
NCT04529772	ACTIVE_NOT_RECRUITING	Diffuse Large B-Cell Lymphoma	acalabrutinib, Rituximab, Cyclophosphamide, Vincristine,Doxorubicin
NCT02972840	ACTIVE_NOT_RECRUITING	Lymphoma, Mantle Cell	Acalabrutinib, Bendamustine, Rituximab
NCT03863184	ACTIVE_NOT_RECRUITING	Mantle Cell Lymphoma	Acalabrutinib,Lenalidomide, Rituximab
NCT05951959	ACTIVE_NOT_RECRUITING	Mantle Cell Lymphoma (MCL)	Acalabrutinib, Venetoclax, Rituximab
NCT02717624	ACTIVE_NOT_RECRUITING	Mantle Cell Lymphoma (MCL)	Acalabrutinib in combination with BR or VR
NCT05214183	ACTIVE_NOT_RECRUITING	MCL|Mantle Cell Lymphoma	Acalabrutinib-rituximab
NCT02180711	ACTIVE_NOT_RECRUITING	Non Hodgkin Lymphoma	acalabrutinib, rituximab, Lenalidomide
NCT02328014	ACTIVE_NOT_RECRUITING	Non-Hodgkins Lymphoma|Multiple Myeloma|B-All	Acalabrutinib, ACP-319
NCT03198650	ACTIVE_NOT_RECRUITING	Part1: Advanced B-cell Malignancies|Part2: r/rCLL and r/rMCL|Part3: Untreated CLL	Acalabrutinib, Obinutuzumab
NCT03932331	ACTIVE_NOT_RECRUITING	Phase I: Relapsed or Refractory B-cell Malignancies|Phase II Cohort A: Relapsed or Refractory Mantle Cell Lymphoma|Phase II Cohort B: Relapsed or Refractory Chronic Lymphocytic Leukemia	Acalabrutinib
NCT04075292	ACTIVE_NOT_RECRUITING	Untreated Chronic Lymphocytic Leukemia	Acalabrutinib, Rituximab, Chlorambucil
NCT04624906	ACTIVE_NOT_RECRUITING	Waldenstrom Macroglobulinemia	AcalabrutiniB, Bendamustine, Rituximab
NCT06757647	NOT_YET_RECRUITING	Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma	Acalabrutinib
NCT06839872	NOT_YET_RECRUITING	Chronic Lymphocytic Leukemia|Small Lymphocytic Lymphoma	Pirtobrutinib| : Acalabrutinib
NCT05004064	NOT_YET_RECRUITING	Mantle Cell Lymphoma	Acalabrutinib| : Rituximab
NCT04257578	RECRUITING	B-Cell Non-Hodgkin Lymphoma|Diffuse Large B-Cell Lymphoma, Not Otherwise Specified|High Grade B-Cell Lymphoma|Primary Mediastinal (Thymic) Large B-Cell Lymphoma|Transformed Follicular Lymphoma to Diffuse Large B-Cell Lymphoma|Grade 1 Follicular Lymphoma|Grade 2 Follicular Lymphoma|Grade 3a Follicular Lymphoma	Acalabrutinib|BIOLOGICAL: Axicabtagene Ciloleucel

NCT04548648	RECRUITING	Central Nervous System Lymphoma	Acalabrutinib
NCT06651970	RECRUITING	Chronic Lymphocytic Leukaemia|Heart Failure	Acalabrutinib
NCT06564038	RECRUITING	Chronic Lymphocytic Leukaemia|Small Lymphocytic Leukaemia|Mantle-cell Lymphoma|Large B-cell Lymphoma|B-cell Non-Hodgkin Lymphoma	: AZD0486, Acalabrutinib
NCT05950997	RECRUITING	Chronic Lymphocytic Leukemia	Acalabrutinib, Obinutuzumab
NCT05197192	RECRUITING	Chronic Lymphocytic Leukemia	Obinutuzumab, Venetoclax, Acalabrutinib
NCT04546620	RECRUITING	Diffuse Large B Cell Lymphoma	R-CHOP, R-CHOP + acalabrutinib
NCT05952024	RECRUITING	Diffuse Large B-Cell Lymphoma	Acalabrutinib, Rituximab
NCT05256641	RECRUITING	Diffuse Large B-Cell Lymphoma|High-grade B-cell Lymphoma|Transformed Lymphoma|Secondary Central Nervous System Lymphoma	Acalabrutinib
NCT04883437	RECRUITING	Grade 1 Follicular Lymphoma|Grade 2 Follicular Lymphoma|Grade 3a Follicular Lymphoma|Indolent Non-Hodgkin Lymphoma|Lymphoplasmacytic Lymphoma|Lymphoproliferative Disorder|Mantle Cell Lymphoma|Marginal Zone Lymphoma	Acalabrutinib, Obinutuzumab
NCT05065554	RECRUITING	IgM MGUS|Waldenstrom Macroglobulinemia|Neuropathy;Peripheral	Acalabrutinib, Rituximab
NCT05820841	RECRUITING	Large B-cell Lymphoma|Diffuse Large B Cell Lymphoma	R-miniCHOP + Acalabrutinib| : R-miniCHOP
NCT04855695	RECRUITING	Mantle Cell Lymphoma|Refractory Lymphoma	Acalabrutinib, Venetoclax, Obinutuzumab
NCT04462328	RECRUITING	Primary Central Nervous System Lymphoma	Durvalumab, Acalabrutinib
NCT04941716	RECRUITING	Recurrent Chronic Lymphocytic Leukemia|Recurrent Small Lymphocytic Lymphoma|Refractory Chronic Lymphocytic Leukemia|Refractory Small Lymphocytic Lymphoma	Acalabrutinib, Venetoclax
NCT04198922	RECRUITING	Recurrent Moderate-Severe Chronic Graft Versus Host Disease|Hematopoietic and Lymphoid Cell Neoplasm	Acalabrutinib
NCT05583149	RECRUITING	Refractory Aggressive B-cell Lymphomas|Refractory B-Cell Non-Hodgkin Lymphoma|Aggressive B-cell NHL|Diffuse Large B-cell Lymphoma (DLBCL)|De Novo or Transformed Indolent B-cell Lymphoma|DLBCL, Nos Genetic Subtypes|T Cell/Histiocyte-rich Large B-cell Lymphoma|EBV-Positive DLBCL, Nos|Primary Mediastinal [Thymic] Large B-cell Lymphoma (PMBCL)|High-Grade B-Cell Lymphoma, Nos|C-MYC/BCL6 Double-Hit High-Grade B-Cell Lymphoma|Grade 3b Follicular Lymphoma|C-MYC/BCL2 Double-Hit High-Grade B-Cell Lymphoma	ACALABRUTINIB