Pirtobrutinib (JAYPIRCA)
National Drug Monograph
October 2024

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Pirtobrutinib selectively binds Bruton tyrosine kinase (BTK) inhibitor in a non-covalent manner resulting in interruption to signaling supporting proliferation, chemotaxis, and adhesion. Non-covalent binding differentiates pirtobrutinib from other BTK inhibitors and allows preservation of activity despite mutations such as BTK C481.

Indication(s) Under Review in This Document

Adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a BTK inhibitor.

FDA approval via accelerated approval based on response rate; continued approval may be contingent upon verification and description of clinical benefit in a confirmatory trial.

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.

FDA approval via accelerated approval based on response rate; continued approval may be contingent upon verification and description of clinical benefit in a confirmatory trial.

Dosage Form(s) Under Review

- Recommended dosage: 200 mg once daily, with or without food, until disease progression or unacceptable toxicity.
- Tablets: 50 mg, 100 mg
- Dose reduction is recommended for renal dysfunction. Reduce dose 50% for eGFR 15 to 29 ml/min/1.73m^2 to minimum dose of 50 mg daily.

Clinical Evidence Summary

Efficacy Considerations

Table 1.1 Efficacy in Mantle Cell Lymphoma (MCL)

<table>
<tr><th>Design</th><th>Results</th></tr>
<tr><td>BRUIN - Mato et al. Lancet. 2021 Mar 6;397(10277):892-901.:
Phase 1-2 multicentre, open-label trial (27 sites in 6 counties)[2]
Inclusion: Age ≥ 18 years old, ECOG 0-2, Histologically confirmed B-cell malignancy (CLL/SLL, WM, NHL), failed or intolerant to ≥ 2 SoC regimens either in combination or sequentially OR have received past BTK-regimen when approved as first-line therapy

Exclusion: known CNS involvement, clinically significant/uncontrolled cardiovascular disease or MI within 6 months, diagnosis likely to affect GI absorption, active second malignancy unless in remission with life expectancy > 2 years

Primary Endpoint:
II : overall response rate (ORR) by Independent Review Committee</td><td>Demographics:
<table>
<tr><th></th><th>All (n = 323)</th><th>MCL (n=61)</th></tr>
<tr><td>mAge, years (IQR)</td><td>68 (62-74)</td><td>69 (63-75)</td></tr>
<tr><td>Male (n, %)</td><td>214 (66%)</td><td>47 (77%)</td></tr>
<tr><td>ECOG PS 0 n (%)</td><td>161 (50%)</td><td>42 (69%)</td></tr>
<tr><td>All patients
BTK pretreated</td><td>3 (2-5)
3 (2-5)</td><td>3 (2-4)
3 (2-4)</td></tr>
<tr><td>Progressive disease
Toxicity or other</td><td>173 (71%)
70 (29%)</td><td>44 (77%)
13 (23%)</td></tr>
</table>
Phase II: (n=269)
MCL (n=56) after median follow up of 6 months
<u>Primary outcome</u>: ORR 52% (95% CI 38-65)
CR: 14 (25%)
PR: 15 (27%)
<u>Secondary outcome</u>: OS not reported due to immaturity from lack of events</td></tr>
<tr><td>Summary of BRUIN trial</td><td>• In this phase I/II trial, pirtobrutinib had a clear response in patients with B-cell malignancies including relapsed/refractory MCL after two prior treatments.
• Treatment with pirtobrutinib 200mg daily had an ORR of 52% in MCL.
• Survival data was noted immature at the time of publication due to lack of events.</td></tr>
<tr><td>Cohen JB, et al. Blood. 2023. 142 (1): 981. [Abstract]
Phase I/II trial continuing from BRUIN trial
Presenting efficacy results among patients with MCL and previous BTK inhibitor therapy and safety for all patients with MCL.

Please see BRUIN trial above for intervention, criteria, and endpoints.</td><td>Efficacy:
n=152 in efficacy population; n= 166 in safety population;
median 3 prior lines of therapy (range: 1-9)
<table>
<tr><th>Variable</th><th>Previous BTK inhibitor therapy</th></tr>
<tr><td>Overall response - %, (95% CI)</td><td>49.3 (41.1-57.6)</td></tr>
<tr><td>Median duration of response (DOR), months (95% CI)</td><td>21.6 months (9.2-27.2)</td></tr>
<tr><td colspan="2">Best response, n (%)</td></tr>
<tr><td>Complete response (CR)</td><td>24 (15.8)</td></tr>
<tr><td>Partial response (PR)</td><td>51 (33.6)</td></tr>
<tr><td>Median PFS, months (95% CI)</td><td>5.6 (5.3-9.2)</td></tr>
<tr><td>Median OS, months (95% CI)</td><td>23.5 (17.1-NE)</td></tr>
</table></td></tr>
<tr><td>Summary of Cohen JB, et al. Blood. 2023. 142 (1): 981. [Abstract]</td><td>• This abstract falls under the same NCT03740529 as the above BRUIN trial but expanded for follow up though not yet published in full in literature.</td></tr>
</table>

	• Patients with relapsed/refractory MCL with a prior BTK inhibitor therapy saw benefit with progression-free survival 5.6 months and overall survival 23.5 months. • This trial nor any other complete publication is available with a comparator population against pirtobrutinib in the MCL relapsed/refractory setting and may be subject to change.

Abbreviations: SoC – standard of care, Hx – history, SCT – stem cell transplant, CAR T - chimeric antigen receptor-modified T-cell therapy, GI – gastrointestinal, PPIs- proton pump inhibitors

Efficacy Considerations, continued

Table 2.1 in Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL)

<table>
<tr><th>Design</th><th>Results</th></tr>
<tr><td>BRUIN - Mato et al. Lancet. 2021 Mar 6;397(10277):892-901.:
Phase 1-2 multicentre, open-label trial (27 sites in 6 counties)[2]
Inclusion: Age ≥ 18 years old, ECOG 0-2, Histologically confirmed B-cell malignancy (CLL/SLL, WM, NHL), failed or intolerant to ≥ 2 SoC regimens either in combination or sequentially OR have received past BTK-regimen when approved as first-line therapy

Exclusion: known CNS involvement, clinically significant/uncontrolled cardiovascular disease or MI within 6 months, diagnosis likely to affect GI absorption, active second malignancy unless in remission with life expectancy > 2 years

Phase II:
Recommended pirtobrutinib 200 mg daily
Continued until disease progression, unacceptable toxicity, or withdrawal
Primary Endpoint:
II : overall response rate (ORR) by Independent Review Committee</td><td>Demographics:
<table>
<tr><th></th><th>All (n = 323)</th><th>CLL/SLL (n=170)</th></tr>
<tr><td>mAge, years (IQR)</td><td>68 (62-74)</td><td>69 (62-73)</td></tr>
<tr><td>Male, n (%)</td><td>214 (66%)</td><td>109 (64%)</td></tr>
<tr><td>ECOG PS 0, n (%)</td><td>161 (50%)</td><td>87 (51%)</td></tr>
<tr><td>All patients
BTK pretreated</td><td>3 (2-5)
3 (2-5)</td><td>3 (2-5)
4 (2-5)</td></tr>
<tr><td>deletion 17p
TP53 mutation
deletion 11q
unmutated IGHV</td><td></td><td>20 (25%)
27 (30%)
15 (19%)
71 (88%)</td></tr>
<tr><td>Progressive disease
Toxicity or other</td><td>173 (71%)
70 (29%)</td><td>98 (67%)
48 (33%)</td></tr>
</table>
Phase II: (n=269)
CLL/SLL (n=139) after median follow up 6 months
<u>Primary outcome</u>: ORR 63% (95% CI 55–71)
ORR in BTK C481S mutation 71% (95% CI 49-87)
<u>Secondary outcome</u>: OS not reported due to immaturity from lack of events</td></tr>
<tr><td>Summary of BRUIN trial (Mato et al. Lancet. 2021 Mar 6;397(10277):892-901.)</td><td>• In this phase I/II trial, pirtobrutinib had a clear response in patients with B-cell malignancies including relapsed/refractory CLL/SLL after two prior treatments.
• Treatment with pirtobrutinib 200mg daily had an ORR of 63% in CLL/SLL.
• Survival data was noted immature at the time of publication due to lack of events.</td></tr>
<tr><td>Mato et al. N Engl J Med. 2023 Jul 6;389(1):33-44.:
Phase I/II trial continuing from BRUIN trial</td><td>Demographics:
<table>
<tr><th>Characteristic</th><th>Patients (n_{total}=120), n (%)</th></tr>
<tr><td>Median age (range)</td><td>71 years (46 to 88 years)</td></tr>
<tr><td>Sex, n (%)</td><td></td></tr>
</table></td></tr>
</table>

Presenting efficacy results among patients with CLL/SLL and previous BTK inhibitor therapy and safety for all patients with CLL/SLL (49 sites, 10 countries)

Please see BRUIN trial above for intervention, criteria, and endpoints.

Male	168 (68.0)
Rai stage 0-II	131 (53.0)
Bulky disease ≥ 5 cm, n (%)	78 (31.6)
ECOG performance status, 0	
BTK C481 mutated, n (%)	84 of 222 (37.8)
17p deletion, n (%)	51 of 176 (29.0)
TP53 mutation, n (%)	87 of 222 (39.2)
17p deletion and TP53 mutation, n (%)	90 of 193 (46.6)
Unmutated IGHV, n (%)	48 of 170 (28.2)
Complex karyotype, n (%)	168 of 198 (84.8)

Efficacy:

Variable	**Previous BTK inhibitor therapy (n=247)**	**Previous BTK inhibitor and BCL2 inhibitor therapy (n=100)**
Overall response - %, (95% CI)		
CR, nodular PR, PR, or PR with lymphocytosis	82.2 (76.8 – 86.7)	79.0 (69.7 – 86.5)
Progression free survival		
Median, mo (95% CI)	19.6 (16.9 – 22.1)	16.8 (13.2-18.7)
Median follow up, mo	19.4	18.2
12-month Overall survival	86.0% (95% CI: 81.0- 89.8)	
18-month Overall survival	80.5% (95% CI: 74.8 - 85.0)	

Summary of Mato et al. N Engl J Med. 2023 Jul 6;389(1):33-44.

- This trial falls under the same NCT03740529 as the above BRUIN trial but expanded from the original 27 sites in 6 countries to 49 sites in 10 countries with data cutoff in 2022 rather than the original 2020 deadline and limited to results from patients with CLL/SLL.
- Patients with relapsed/refractory CLL/SLL with a prior BTK inhibitor therapy saw a progression free survival benefit of 19.6 months and benefit was retained to 13.8 months in patients additionally treated with BCL2 inhibitor, PI3k inhibitor, chemotherapy and an anti-CD20 antibody in the past. Additionally the total efficacy population had an 18 month overall survival of 80.5%.
- This trial nor any other complete publication is available with a comparator population against pirtobrutinib in the CLL/SLL relapsed/refractory setting.

Table 1.2 Safety in Mantle Cell Lymphoma (MCL)

	Regardless of Attribution, n (%)		Treatment-Related, n (%)	
Adverse Event	**All Grades ≥ 10%**	**Grade 3-4**	**All Grades**	**Grade 3-4**
BRUIN (Mato et al. Lancet. 2021 Mar 6;397(10277):892-901.)				
Fatigue	65 (20)	3 (1)	27 (8)	2 (1)
Diarrhea	55 (17)	0	28 (9)	0
Bruising	53 (16)	0	37 (12)	0
Contusion	42 (13)	0	29 (9)	0
Neutropenia	41 (13)	32 (10)	20 (6)	17 (5)
Rash	35 (11)	0	18 (6)	0
Adverse Event	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Cohen JB, et al. Blood. 2023. 142 (1): 981. [Abstract]				
Fatigue	31.9%			
Diarrhea	22.3%			
Dyspnea	17.5%			
Neutropenia	--	13.3%		
Infections	--	19.9%		

Safety in Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL)

	Regardless of Attribution, n (%)		Treatment-Related, n (%)	
Adverse Event	**All Grades ≥ 10%**	**Grade 3-4**	**All Grades**	**Grade 3-4**
BRUIN (Mato et al. Lancet. 2021 Mar 6;397(10277):892-901.)				
Fatigue	65 (20)	3 (1)	27 (8)	2 (1)
Diarrhea	55 (17)	0	28 (9)	0
Bruising	53 (16)	0	37 (12)	0
Contusion	42 (13)	0	29 (9)	0
Neutropenia	41 (13)	32 (10)	20 (6)	17 (5)
Rash	35 (11)	0	18 (6)	0
Adverse Event	**All Grades ≥ 20%**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Mato et al. N Engl J Med. 2023 Jul 6;389(1):33-44.				
Infections	225 (71.0)	89 (28.1)	39 (12.3)	12 (3.8)
Bleeding	135 (42.6)	7 (2.2)	75 (23.7)	3 (0.9)
Neutropenia	103 (32.5)	85 (26.8)	62 (19.6)	47 (14.8)
Fatigue	100 (31.5)	6 (1.9)	11 (3.5)	1 (0.3)
Bruising	96 (30.3)	0	62 (19.6)	0
Diarrhea	84 (26.5)	2 (0.6)	28 (8.8)	1 (0.3)
Contusion	77 (24.3)	0	52 (16.4)	0
Cough	77 (24.3)	0	5 (1.6)	0
Coronavirus disease	76 (24.0)	16 (5.0)	5 (1.6)	0
Hemorrhage	67 (21.1)	7 (2.2)	22 (6.9)	3 (0.9)

Overall Safety Concerns

- **Boxed warnings:** None.
- **Contraindications:** None.
- **Other warnings / precautions**:
    - Infections: Serious infections of grade ≥ 3 occurred in 24% of patients. Pneumonia was most common (14%). Sepsis occurred in 6% and febrile neutropenia in 4% with fatal infections occurred in 4.4%. Grade ≥ 3 infection was higher in patients with CLL/SLL at 32% and fatal infections increased to 8%. Consider prophylaxis for patients at increased risk for infection, including opportunistic pathogens. Monitor for signs and symptoms for prompt treatment and pirtobrutinib adjustment.
    - Hemorrhage: Bleeding of any grade occurred in 17% of patients treated with pirtobrutinib with major hemorrhage (grade ≥ 3 bleeding or any CNS bleeding) occurring in 3% of patients. Of patients with major hemorrhage, 2.3% occurred in those without antithrombotic agents. Consider risk versus benefit of concurrent antithrombotic agents and monitor for signs of bleeding for potential therapy adjustment.
    - Cytopenias: Notably include neutropenia, thrombocytopenia, and anemia. Grade 3 or 4 cytopenias included neutropenia (26%), thrombocytopenia (12%), and anemia (12%). Of these, grade 4 neutropenia developed in 14% and grade 4 thrombocytopenia in 6%.
    - Cardiac Arrhythmias: Atrial fibrillation or flutter was reported in 3.2% of all patients and, of those, 1.5% were Grade 3 or 4. Other serious arrhthmias included supraventricular tachycardia and cardiac arrest in 0.5% of patients. Concurrent cardiac risk factors including hypertension or history of arrhythmias may increase risk. Monitor for signs and symptoms to manage appropriately.
    - Second Primary Malignancy: Second primary malignancies have been observed, including skin cancers (4.6%) and nonskin carcinomas (9%), with pirtobrutinib monotherapy. Advise patients to wear sunscreen and monitor patients for development of a second primary malignancy.
    - Hepatotoxicity: There is minimal metabolism of pirtobrutinib through the liver though increases in liver function tests (ALT) were observed in animal toxicity studies. Potentially fatal cases of drug-induced liver injury have been reported. Pirtobrutinib should be permanently discontinued for hepatotoxicity during treatment and held if suspected. Evaluate LFTs at baseline as well as throughout treatment.
    - Embryo-fetal toxicity: Based on animal reproduction trials in rats, embryo-fetal toxicity including mortality and malformations at exposures approximately 3-times recommended dose of pirtobrutinib 200 mg daily. Recommend effective contraception during treatment and for one week after last dose to female patients of reproductive potential.

- **Adverse reactions**
    - **Common ≥ 20% ADE, %):** Infections (71.0), bleeding (42.6), neutropenia (32.5), fatigue (31.5), bruising (30.3), diarrhea (26.5), contusion (24.3), cough (24.3) coronavirus (24.0), hemorrhage (21.1).
    - **Serious Adverse events / Deaths / Discontinuation:**
        - The most common grade 3 or higher treatment-related adverse events in Mato et al. (N Engl J Med. 2023 Jul 6;389(1):33-44) were neutropenia and infection. The most common grade 3 or higher treatment-related adverse events in the BRUIN trial were anemia and neutropenia.
        - One grade 5 fatal event was reported in the BRUIN trial in a patient with CLL whose death from septic shock with *Enterococcus faecium* infection was attributed to treatment.
        - Sixteen grade 5 fatal events were reported in Mato et al. (N Engl J Med. 2023 Jul 6;389(1):33-44) including: Covid-19 pneumonia, Covid-19, pneumonia, fungal pneumonia, septic shock, shock, respiratory failure, splenic rupture, *Legionella* infection, *Eschirchia sepsis.*
        - Drug-drug interactions: Pirtobrutinib is a major substrate of CYP3A4, a minor substrate for P-glycoprotein, and for BCRP/ABCG2, UGT1A8, UGT1A9. Weak for Substrate of BCRP/ABCG2, CYP3A4 (major), P-glycoprotein/ABCB1 (minor), UGT1A8, UGT1A. Also is a weak inhibitor of CYP2C19 and CYP3A4, a moderate inhibitor of CYP2C8, and additionally inhibits BCRP/ABCG2 and P-glycoprotein/ABCB1.

Other Considerations

- **Appropriate use:**
    - Patients with relapsed or refractory mantle cell lymphoma (MCL) who have received two lines of systemic therapy including a BTK inhibitor.
    - 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.
- **Pregnancy considerations:** In an animal embryo-fetal development study, pregnant rats administered doses of at least 375 mg/kg BID experienced decreased fetal body weight,, increased malformation incidence, changes in urinary tract, changes in reproductive tract, and altered bone formation. This dose in rats approximately equates 3 times the human exposure of 200 mg daily. No human data is available, and females of reproductive potential should verify pregnancy status and use effective contraception while on pirtobrutinib through 1 week after last dose taken.
- **Breastfeeding considerations:** No data is available on clinical use of pirtobrutinib during breastfeeding. The highly protein bound nature of pirtobrutinib reduces likelihood of elevated concentration in breastmilk. The prescribing information recommends patients avoid breastfeeding while taking pirtobrutinib through 1 week after taking the last dose.

- **Older adults:** In the pooled safety population of patients with hematologic malignancies, patients age ≥ 65 years old had higher rates of grade 3 or above adverse effects compared to those < 65 years old.

Other Therapeutic Options

Alternative treatments for MCL after at least two lines of systemic therapy, including a BTK inhibitor, are listed in table 3 below and alternative treatments for relapsed/refractory CLL/SLL after at least two prior lines of therapy, including a BTK inhibitor and a BCL-2 inhibitor, are listed in table 4 below.

Table 3 Treatment Alternatives in Mantle Cell Lymphoma (MCL)

Drug	Formulary status	Clinical Guidance	Other Considerations
Bortezomib, Rituximab (VR) **Bortezomib 1.3-1.5 mg/m^2 on days 1,4,8,11 and rituximab 375 mg/m^2 day 1,8 q21 days x 1-5 cycles**	PA-F, PA-F	NCCN: 2L and subsequent, useful in certain circumstances regimen, cat 2A VA clinical pathway: patients who are not candidates for aggressive therapy and refractory to cBTKi UptoDate: high rates of toxicity when combined with rituximab	3L: P2 bortezomib and rituximab; n=25 with relapsed follicular or MCL, n=13 with MCL **ORR:** 29% (n=4/13), all CR by cycle 3 **Median follow-up of 21.5 mos** **mPFS in MCL:** 1.9 mos (95% CI 1.6-NA) Twice weekly bortezomib schedule resulted with 54% grade 3 neurotoxicity
Lenalidomide, Rituximab (R^2) **Lenalidomide 20 mg days 1-21 q28 days Rituximab 375 mg/m^2 IV day 1,8,15,22 of cycle 1 only**	PA-F, PA-F	NCCN: 2L and subsequent, Preferred regimen, cat 2A VA clinical pathway: patients who are not candidates for aggressive therapy and refractory to cBTKi UptoDate: recommends lenalidomide for its efficacy and modest toxicity	2L->3L:P2 lenalidomide and rituximab In relapsed/refractory MCL patients who received 1-4 prior lines of therapy; n = 44 **ORR**: 57% **mPFS**: 11.1 mos, 95% CI 8.3-24.9 mos **mOS**: 24.3 mos, 95% CI 19.8-NR mos
CAR T-cell therapy: Brexucabtagene autoleucel suspension of 2 × 10^6 CAR-positive viable T cells kg of body weight, with a maximum of 2 × 10^8 CAR-positive viable T cells in approximately 68 mL	NF	**FDA approval** is for 3L of therapy with past use of BTKi and chemoimmunotherapy NCCN: 2L and subsequent, useful in certain circumstances: progressive disease after cBTKi, cat 2A VA clinical pathway: relapsed/refractory MCL, in candidates for aggressive therapy UptoDate: suggests use in fit patients with second relapse of MCL and fit patients who did not achieve a complete response (CR) with initial salvage therapy	2->3L: P2 brexcabtagene autoleucel in relapsed/refractory MCL after 1-5 prior treatments **Efficacy in Evaluable Patients (not ITT, n=68):** **ORR** 91%, 95% CI: 81.8 - 96.7 **CRR** 68%, 95% CI: 55.2 - 78.5 **Median DOR**: 28.2 mos (95% CI: 13.5 - 47.1) **mPFS**: 25.8 mos (95% CI: 9.6 - 47.6) **mOS:** 46.6 mos (95% CI:24.9 -NE) **Black Box Warnings:** Cytokine release syndrome, neurologic toxicities, secondary hematological malignancies, REMS program **Considerations**: poorly tolerated and requires good performance status, caretaker requirement, accessibility

CAR T-cell therapy: Lisocabtagene maraleucel 1:1 CAR-positive viable T cells of the CD8 and CD4 components	NF	**FDA approval** is for 3L of therapy with past use of BTKi NCCN: 2L and subsequent, useful in certain circumstances: progressive disease after cBTKi, cat 2A VA clinical pathway: relapsed/refractory MCL, in candidates for aggressive therapy UptoDate: suggests use in fit patients with second relapse of MCL and fit patients who did not achieve a complete response (CR) with initial salvage therapy	L: P1-2 Lisocabtagene in R/R MCL after ≥ 2 previous therapies including a BTK inhibitor, an alkylating agent, and a CD20 antibody; n=83 **ORR:** 83.1%, 95% CI 73.3 - 90.5 **CRR:** 72.3%, 95% CI 61.4 - 81.6 **mPFS:** 15.3 mos, 95% CI 6.6 - 24.9 **mOS:** 24.0 mos, 95% CI 23.7 - 24.2 **Median DOR:** 15.7 months, 95% CI 6.2 - 24.0 **Black Box Warnings:** Cytokine release syndrome, neurologic toxicities, secondary hematological malignancies, REMS program **Considerations:** poorly tolerated and requires good performance status, caretaker requirement, accessibility

Other Considerations

Risk-Benefit Assessment in Mantle Cell Lymphoma (MCL)

- **Outcome in clinically significant area:** ORR published, PFS and OS released in ASH abstract
- **Effect & Effect Size:**
    - ORR 52%, 95% CI: 38-65
    - mPFS 5.6 months, 95% CI 5.3-9.2
    - mOS 23.5 months, 95% CI 17.1- NE
- **Potential Harms (n ≥10%):** fatigue, diarrhea, bruising, contusion, neutropenia, rash; Grade ≥3 neutropenia & infection
- **Net Clinical Benefit:** unable to determine due to accelerated approval endpoints

Table 4 Treatment Alternatives in Chronic Lymphocytic Leukemia (CLL)/ Small Lymphocytic Lymphoma (SLL)

Drug	Formulary status	Clinical Guidance	Other Considerations
Venetoclax-Rituximab Venetoclax, cycle 1: 20 mg once d1-7 50 mg once d8-14 100mg once d15-21 200mg once d22-28 then cycle 2-26 400 mg daily d1-28 Rituximab Cycle 2: **375 mg/m^2 IV day 8** Cycles 3-7: 500 mg/m^2 IV day 8	PA-F, PA-F	NCCN: Other recommendation in 2L or subsequent therapy, cat 1 VHA clinical pathways: 2L after BTKi or venetoclax-obinutuzumab with >2-3 year duration off therapy UptoDate: "cross-trial comparisons that suggest deeper responses with combination therapy and the ability to administer a time-limited course"	2->3L: P3 venetoclax-rituximab vs bendamustine-rituximab; n=389 **mPFS:** 84.9% vs 36.3%, p<0.0001 HR 0.17, 95% CI 0.11-0.25 *2L specific HR 0.14, 95%CI 0/.08-0.24 *3L specific HT 0.24, 95%CI 0.11-0.50 *>3L specific HR 0.24, 95%CI 0.10-0.57 **5-year mOS:** 82.1% vs 62.2%, p<0.0001 HR 0.40, 95% CI 0.26, 0.62
CAR T-cell Therapy: Lisocabtagene maraleucel 1:1 CAR-positive viable T cells of the CD8 and CD4 components	NF	NCCN: R/R disease following BTKi- and venetoclax- based regimens VHA clinical pathway: Multiply relapsed with IGHV unmutated, del17p, del11q, and/or TP53 mutation in patients <65 years old with good PS and low burden of comorbidities UptoDate: Modestly effective with substantial toxicity; expensive	3L: P1-2 lisocabtagene 50x106 or 100x106; n=117 In patients with at least 2 prior lines of treatment including BTKi ORR: 21 (43%), 95% CI 29-58, p = 0.39 CR: 9(18%), 95% CI 9-32, p=0.0006 mPFS: 11.9 months (95% CI 5.7–26.2) mOS: 30.3 months (95% CI 11.2–NR) Median DOR: 35.3 months (95% CI 11.0-NR) **Black Box Warnings:** Cytokine release syndrome, neurologic toxicities, secondary hematological malignancies, REMS program **Considerations:** poorly tolerated and requires good performance status, caretaker requirement, accessibility

Other Considerations

Risk-Benefit Assessment in Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

- **Outcome in clinically significant area:** PFS
- **Effect & Effect Size:**
    - **ORR** 82%, 95% CI: 77-87
    - **mPFS, 2L to BTKi:** 19.6 months, 95% CI: 16.9-22.1
    - **mPFS, 3L:** 16.8 months, 95% CI: 13.2-18.7
    - **12-month OS :** 86.0%, 95% CI: 81.0- 89.8
    - **18-month OS:** 80.5%, 95% CI: 74.8 - 85.0
- **Potential Harms (n ≥ 20%):** Infection, bleeding, neutropenia, fatigue, bruising, diarrhea, contusion, cough, hemorrhage; grade ≥ 3: infection, neutropenia
- **Net Clinical Benefit:** unable to determine due to accelerated approval endpoints

Projected Place in Therapy

- Veterans exposed to agent orange are at increased risk for developing Mantle Cell Lymphoma (MCL).
- High-risk MCL has an estimated OS of 29 months versus 56 months in intermediate-risk MCL. Five year survival in low-risk MCL was 60%.
- NCCN guidelines recommends pirtobrutinib as a second-line of therapy or subsequent therapy after covalent BTK inhibitor or covalent BTK inhibitor intolerance.
- The MCL VA clinical pathway recommends considering pirtobrutinib for third line MCL following prior covalent BTK inhibitor therapy.
- The Phase I/II BRUIN trial found high ORR in patients with MCL treated with pirtobrutinib in the 2L, however a published abstract available of the expanded follow up in this population showed modest mPFS. Longer follow up is needed to fully assess OS.

- Chronic Lymphocytic Leukemia (CLL)/Small lymphocytic lymphoma (SLL) is a disease associated with agent orange exposure. Older age and predominantly male demographic of the veteran population also aligns with the CLL/SLL patient population in trials.
- A retrospective study of veterans diagnosed with CLL over 20 years from 1999 found median OS from initiation of treatment was 5.0 years.
- The CLL/SLL VA clinical pathway recommends pirtobrutinib in the setting of multiple relapses following Acalabrutinib and Venetoclax-Obinutuzumab treatment.
- NCCN guidelines provide category 2A recommendations for pirtobrutinib as a 2L or subsequent therapy and as 3L after covalent BTK inhibitor and Venetoclax based regimen or covalent BTK inhibitor intolerance.
    - Would reserve to the 3L setting, though may consider in the setting of BTK C481S mutation given greater response rate compared to that of the total population in the BRUIN trial.
- The Phase I/II BRUIN trial found high ORR in patients with CLL/SLL 2L to BTKi or 3L, which increased in setting of BTK C481S mutation. Expanded follow up demonstrated improved mPFS and high levels of 12-month and 18-month OS. Longer follow up will be needed to fully assess long-term OS.
    - Data is limited for this medication and recommendations may change as the available literature expands.

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