Ibrutinib

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.2. Targeted therapies

ATC codes: L01EL01

Indication	Chronic lymphocytic leukaemia or small lymphocytic lymphoma ICD11 code: 2A82.0
INN	Ibrutinib
Medicine type	Chemical agent
List type	Complementary
Formulations	**Oral > Solid:** 140 mg
EML status history	First added in 2021 (TRS 1035) Changed in 2025 (TRS 1064)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	zanubrutinib (ATC codes: L01EL03) Oral > Solid > capsule: 80 mg
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Tags	Cancer
Wikipedia	Ibrutinib
DrugBank	Ibrutinib

Expert Committee recommendation

The Expert Committee recognized the growing global burden of chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL), with incidence rates rising significantly over the past 30 years, particularly in high-income countries. The Committee also recognized that treatment of CLL/SLL with Bruton tyrosine kinase inhibitors is now considered the standard of care in many countries, replacing chemo-immunotherapy. The Committee recalled that another Bruton tyrosine kinase inhibitor, ibrutinib, was included on the EML in 2021 for use in relapsed/refractory CLL/SLL based on evidence of greater benefit and improved tolerability compared with chemo-immunotherapy. In consideration of the available evidence for zanubrutinib, the Committee considered that the evidence in relapsed/refractory disease demonstrated a survival advantage for zanubrutinib compared with chemo-immunotherapy, and similar survival to that previously observed for ibrutinib. Additionally, zanubrutinib appears to be associated with more favourable safety compared with ibrutinib (e.g. less atrial fibrillation and bleeding adverse events in some trials). The Committee considered that zanubrutinib offered a clinically meaningful alternative to ibrutinib in the relapsed/refractory setting. In the first-line setting, the Committee considered that the available evidence for the benefit of zanubrutinib was promising but not yet as well established as in the relapsed/refractory setting. While no specific price data were provided in the application, the Committee acknowledged the high price of zanubrutinib in different settings. Economic analyses in different settings have reported varying outcomes, with cost–effectiveness often being sensitive to drug acquisition costs. The Committee

also acknowledged that ibrutinib is still highly priced in most countries. The Committee considered that ibrutinib may face competition from newer agents within the class such as zanubrutinib, which is more accessible in some countries, has a better domestic cost–effectiveness profile and could potentially better align with local medicine policy priorities. The Committee noted that not all patients with CLL/SLL require treatment. At diagnosis, many patients have indolent, asymptomatic disease that does not benefit from therapy, and some patients may never require treatment. Criteria that identify clinical and biological states when treatment are indicated (i.e. provides symptom resolution or prolongs life) were well established in the chemo-immunotherapy era and are still applicable for targeted therapies such as Bruton tyrosine kinase inhibitors. To avoid net harm and unnecessary cost, the Committee emphasized that the use of Bruton tyrosine kinase inhibitors, including zanubrutinib, must be restricted to use within guidelines. This is likely to be a main factor in consideration of affordability of this class of medicines in low- and middle-income countries. Based on these considerations, the Expert Committee recommended the inclusion of zanubrutinib on the EML for the treatment of relapsed or refractory CLL/SLL as a therapeutic alternative to ibrutinib (which remains the representative Bruton tyrosine kinase inhibitor) under a square box listing. The Committee did not recommend the inclusion of zanubrutinib for use in the first-line treatment of CLL/SLL but encouraged an application presenting evidence for the class of Bruton tyrosine kinase inhibitors be submitted for consideration in the 2027 update.

Background

Applications for the inclusion of zanubrutinib for the treatment of CLL/SLL have been considered by the Expert Committee on two previous occasions in 2021 and 2023 (1). On each occasion, listing was not recommended. With the 2023 application, the Expert Committee acknowledged the role of targeted therapy with Bruton kinase inhibitors in the treatment of CLL/SLL, especially in high-income countries, The 2023 Committee recalled the recommendation of the 2021 Committee to include ibrutinib on the EML for patients with relapsed/refractory disease as there was compelling evidence of relevant benefit and improved tolerability compared with chemoimmunotherapy. The Committee noted the results of clinical trials comparing zanubrutinib with bendamustine–rituximab in previously untreated patients, and with ibrutinib in patients with relapsed/refractory disease, which showed promising survival gains. However, the Committee considered that the magnitude of these gains may be limited and noted that few long-term data were currently available. The Committee also noted the toxicity concerns highlighted by the Cancer Medicines Working Group and considered longer-term data would be informative to confirm the safety profile of zanubrutinib. The Committee also noted the high price of zanubrutinib and considered that at this price, it was unlikely to be cost-effective or affordable in most low- and middle-income settings. The Committee also considered that the substitution of ibrutinib with zanubrutinib would not necessarily be associated with savings in health budgets as proposed in the application because lower ibrutinib doses than those described in the application could be used in clinical practice (1).

Public health relevance

The global incidence of CLL/SLL increased from 40 537 in 1990 to 103 467 in 2019, with age-standardized incidence rates rising from 0.76 per 100 000 people in 1990 to 1.34 per 100 000 people in 2019. In 2019, the highest age-standardized incidence rates were reported in western Europe, North America and central Europe. Globally, almost 45 000 deaths due to the disease occurred in 2019 (2).

Benefits

Systematic reviews A 2024 systematic review and meta-analysis of 15 prospective studies (10 single-arm studies and five randomized controlled trials; 2066 participants) evaluated the efficacy and safety of acalabrutinib, zanubrutinib and tirabrutinib, alone or in combination with other regimens for treatment-naïve and relapsed/refractory CLL/SLL (3). Some studies included more than one disease state or intervention, resulting in 20 studies being evaluated – 12 involving acalabrutinib, seven involving zanubrutinib and one involving tirabrutinib. Efficacy endpoints assessed were overall response rate, complete response rate, 24-month overall survival and progression-free survival rates. The pooled 24-month overall survival rate for CLL patients treated with Bruton tyrosine kinase inhibitors was 94% (95% confidence interval (CI) 92% to 97%; $P = 0.06$). Subgroup

analyses for acalabrutinib monotherapy and zanubrutinib monotherapy showed pooled 24-month overall survival rates of 92% (95% CI 89% to 96%) and 95% (95% CI 92% to 96%; P = 0.72), respectively. The 24-month progression-free survival rates were 86% (95% CI 82% to 90%) for Bruton tyrosine kinase inhibitors, 83% (95% CI 75% to 90%) for acalabrutinib and 86% (95% CI 80% to 91%) for zanubrutinib. Pooled overall response rate and complete response rate for Bruton tyrosine kinase inhibitors were 92% (95% CI 89% to 95%) and 10% (95% CI 6% to 14%), respectively. Subgroup analyses by disease status in treatment-naïve patients showed pooled overall response rate and complete response rate of 96% (95% CI 92% to 98%) and 16% (95% CI 7% to 28%), respectively. In patients with relapsed/refractory disease, pooled overall response rate and complete response rate were 90% (95% CI 85% to 95%) and 7% (95% CI 4% to 10%), respectively. The overall response rate and complete response rate were 87% (95% CI 81% to 93%) and 3% (95% CI 1% to 6%), respectively, for acalabrutinib monotherapy and 93% (95% CI 89% to 97%) and 13% (95% CI 6% to 22%), respectively, for zanubrutinib monotherapy. Clinical studies The SEQUOIA trial was an open-label, multicentre, phase III trial comparing zanubrutinib and bendamustine–rituximab in patients with previously untreated CLL/SLL (4). Patients without 17p deletion (del(17p13·1)) were randomly assigned to receive zanubrutinib (group A) or bendamustine–rituximab (group B). Patients with del(17p13.1) were enrolled in group C and received zanubrutinib. Administered doses were: zanubrutinib 160 mg orally twice daily (28-day cycles); bendamustine 90 mg/m2 intravenous on days 1 and 2 for six cycles plus rituximab 375 mg/m2 intravenous the day before or on day 1 of cycle 1, and 500 mg/m2 intravenous on day 1 of cycles 2–6. The primary endpoint was progression-free survival assessed by an independent review committee in the intention-to-treat population in groups A and B. With median follow-up of 26.2 months, zanubrutinib showed a statistically significantly reduced risk of disease progression (hazard ratio (HR) 0.42, 95% CI 0.28 to 0.63). Zanubrutinib had a longer progression-free survival compared with bendamustine–rituximab in most patient subgroups. After 42 months of median follow-up, the progression-free survival benefit of zanubrutinib over bendamustine-rituximab was sustained (HR 0.30, 95% CI 0.21 to 0.43). Estimated 42-month progression-free survival rates were 82.4% and 50.0%, respectively. Median overall survival was not reached in either treatment arm (5). In group C, with median follow-up of 30.5 months, median progression-free survival was not reached. Estimated 24-month progression-free survival and overall survival for zanubrutinib was 88.9% and 93.6%, respectively (4). After 42 months of median follow-up, median progression-free survival and overall survival were not reached. The 42-month event-free rates were 79.4% for progression-free survival and 89.5% for overall survival (5). An interim analysis of health-related quality of life outcomes was assessed using patient-reported outcomes using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and EQ-5D-5L visual analogue scale (VAS) (6). Patients treated with zanubrutinib showed greater improvements in health-related quality of life at weeks 12 and 24 compared with patients treated with bendamustine–rituximab. At 24 weeks, these differences were significantly higher for zanubrutinib in global health status, physical functioning, role functioning, and reduction in diarrhoea, fatigue and nausea/vomiting. The ALPINE trial was a randomized phase III trial comparing the efficacy and safety of zanubrutinib with ibrutinib in patients with relapsed/refractory CLL/SLL (7). Patients were randomized 1:1 to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg daily. After a median follow-up of 29.6 months, zanubrutinib was superior to ibrutinib for progression-free survival among 652 patients as assessed by investigators (HR for disease progression or death, 0.65, 95% CI 0.49 to 0.86). The results were similar for progression-free survival assessed by an independent review committee (HR 0.63, 95% CI 0.48 to 0.84). At 24 months, the investigator-assessed rates of progression-free survival were 78.4% in the zanubrutinib group and 65.9% in the ibrutinib group. Median progression-free survival was not reached in the zanubrutinib group and was 34.2 months (95% CI 33.3 to not estimable) in the ibrutinib group. Among patients with a 17p deletion, a TP53 mutation, or both, those who received zanubrutinib had longer progression-free survival than those who received ibrutinib (HR 0.53, 95% CI 0.31 to 0.88). Progression-free survival across other major subgroups consistently favoured zanubrutinib. At the data-cut-off date in the final analysis, results for overall survival showed fewer deaths in the zanubrutinib group than in the ibrutinib group (48 versus 60; HR for death 0.76, 95% CI 0.51 to 1.11). Median overall survival was not reached in either treatment arm. In the final analysis of the intention-to-treat population, overall response rates as assessed by the investigators were 83.5% in the zanubrutinib group and 74.2% in the ibrutinib group. The overall response rate as assessed by the independent review committee was 86.2% in the zanubrutinib group and 75.7% in the ibrutinib group. After a

median follow-up of 42.5 months, the progression-free survival benefit of zanubrutinib over ibrutinib was sustained (HR 0.68, 95% CI 0.54 to 0.84). Progression-free survival rates at 36 months were 65.4% and 54.4% in the zanubrutinib and ibrutinib groups, respectively. The progression-free survival benefit was also sustained in patients with (HR 0.51, 95% CI 0.33 to 0.78) and without (HR 0.79, 95% CI 0.61 to 1.02) 17p deletion/TP53 mutation, and in most other major subgroups and sensitivity analyses. Overall response rates were higher in the zanubrutinib group than in the ibrutinib group (85.6% versus 75.4%; response ratio (RR) 1.13, 95% CI 1.05 to 1.22). Median overall survival was not reached in either treatment group. There were 69 and 85 deaths in the zanubrutinib and ibrutinib groups, respectively (HR for overall survival 0.77, 95% CI 0.55 to 1.06) (8). Quality of life was measured using EORTC QLQ-C30 and EQ-5D-5L questionnaires (9). Patients receiving zanubrutinib experienced improvements in physical and role functioning, pain and fatigue in the EORTC QLQ-C30. Zanubrutinib-treated patients also reported lower diarrhoea scores. In the EQ-5D-5L, the mean change from baseline in EQ-VAS showed greater improvement in patients receiving zanubrutinib than patients receiving ibrutinib (mean change (standard deviation) 7.92 (18.245) versus 3.44 (16.972). Study BGB-3111-205 was a single-arm, open-label phase II study evaluating safety and efficacy of zanubrutinib in relapsed/refractory CLL/SLL (10). After a median follow-up of almost 34 months, investigator-assessed overall response rate was 87.9%, with 6.6% of patients achieving a complete response, 69.2% achieving a partial response, and 12.1% achieving a partial response with lymphocytosis. The overall response rate was generally consistent across all subgroups analysed, including patients with high-risk cytogenetics (11). Study BGB-3111-AU-003 was a phase I/II open-label, multiple dose, dose escalation and expansion study to investigate the safety and pharmacokinetics of zanubrutinib in patients with B-cell lymphoid malignancies, including 22 patients with treatment-naïve CLL/SLL and 101 patients with relapsed/refractory CLL/SLL (12). Patients received zanubrutinib 160 mg twice daily (n = 81), 320 mg once daily (n = 40) or 160 mg once daily (n = 2). After a median follow-up of 47.2 months, the overall response rate was 95.9% (100% for treatment naïve patients, and 95% relapsed/refractory), with 18.7% achieving complete response. Ongoing response at 3 years was reported in 85.7% of patients. The overall response rate in patients with 17p deletion)/TP53 mutation was 87.5%. The 2- and 3-year estimated progression-free survival was 90% (treatment naïve 90%; relapsed/refractory 91%) and 83%, respectively. Real-world studies The results of a retrospective study that evaluated real-world switching and sequencing to next line of therapy in patients starting a Bruton tyrosine kinase inhibitor as first- or second-line treatment of SLL/CLL were published in an abstract in 2024 (13). A total of 2816 and 1253 patients started a first- or second-line Bruton tyrosine kinase inhibitor, respectively, during the study period. First-line were 157 with zanubrutinib, 1238 with acalabrutinib and 1421 with ibrutinib; second-line were 107 with zanubrutinib, 672 with acalabrutinib, and 474 with ibrutinib. Median follow-up for the first-line was 123 days for zanubrutinib, 406 days for acalabrutinib and 637 days for ibrutinib. Regardless of the line of therapy, zanubrutinib-treated patients had a significantly lower switching rate within 90 days and a lower proportion of patients receiving next line of therapy at 180 days compared with acalabrutinib and ibrutinib.

Harms

Systematic reviews A 2024 systematic review and network meta-analysis of 10 randomized controlled trials (4171 participants) evaluated the safety profile of first-line targeted therapies (acalabrutinib, ibrutinib, obinutuzumab, ofatumumab, venetoclax and zanubrutinib) in an unfit subpopulation of elderly and/or comorbid CLL patients (14). The results of the network meta-analysis showed that ibrutinib + venetoclax was associated with a significantly higher risk of adverse events leading to treatment discontinuation than other evaluated therapies: versus zanubrutinib (odds ratio (OR) 16.50, 95% credible interval (CrI) 2.73 to 153.68); versus acalabrutinib (OR 12.56, 95% CrI 5.28 to 102.70); versus chlorambucil + obinutuzumab (OR 9.62, 95% CrI 20.2 to 78.15); versus acalabrutinib + obinutuzumab (OR 9.62, 95% CrI 2.02 to 78.15); and versus venetoclax + obinutuzumab (OR 6.67, 95% CrI 1.46 to 52.55). No significant differences were found between the remaining targeted therapies. Zanubrutinib had the highest probability of being the safest therapeutic option for this outcome based on surface under the cumulative ranking curves (SUCRA 86%). Adverse events of grade ≥ 3 were generally significantly more frequent in groups treated with combination therapies than monotherapy. Zanubrutinib had the highest probability of being the safest therapeutic option for this outcome (SUCRA 98%). Serious adverse events (any grade) were significantly less frequent with zanubrutinib than ibrutinib (OR 0.35, 95% CrI 0.20 to 0.59), acalabrutinib (OR 0.38,

95% CrI 0.17 to 0.85), ibrutinib + obinutuzumab (OR 0.25, 95% CrI 0.11 to 0.57), ibrutinib + rituximab (OR 0.39, 95% CrI 0.22 to 0.67), ibrutinib + venetoclax (OR 0.28, 95% CrI 0.12 to 0.66) and acalabrutinib + obinutuzumab (OR 0.28, 95% CrI 0.13 to 0.62). Zanubrutinib had the highest probability of being the safest therapeutic option for this outcome (SUCRA 95%). The most frequently reported haematological adverse events were anaemia, thrombocytopenia, neutropenia and febrile neutropenia. Grade 1–5 anaemia was significantly less frequent with zanubrutinib than with chlorambucil + obinutuzumab, and acalabrutinib. No significant differences were observed between zanubrutinib and other investigated treatments for grade 1–5 anaemia. The risk of neutropenia was significantly lower for Bruton tyrosine kinase inhibitor monotherapy, particularly zanubrutinib and acalabrutinib. The rate of febrile neutropenia (any grade) was significantly lower for acalabrutinib compared with chlorambucil + obinutuzumab, but no significant differences were observed between other investigated therapies. The results of a 2023 systematic review and meta-analysis of 61 trials (6959 participants) that evaluated treatment-emergent adverse events of ibrutinib, acalabrutinib and zanubrutinib reported in clinical trials in B-cell malignancies were published as a conference poster (15). Most trials were in CLL/SLL (n = 36), mantle cell lymphoma (n = 9) or Waldenström macroglobulinaemia (n = 8). Compared with ibrutinib, the average incidence of all-grade adverse events was lower with acalabrutinib (relative risk (RR) 0.74, 95% CrI 0.62 to 0.85) and zanubrutinib (RR 0.83, 95% CrI 0.71 to 0.93). Similarly, compared with ibrutinib, the incidence of grade ≥ 3 adverse events was lower for both acalabrutinib and zanubrutinib. Zanubrutinib and acalabrutinib had similar average incidences of grade ≥ 3 adverse events. Grade ≥ 3 adverse events that occurred more frequently with acalabrutinib than zanubrutinib included anaemia (RR 0.58), infections (RR 0.76) and rash (RR 0.03). Grade ≥ 3 adverse events that occurred more frequently with zanubrutinib than acalabrutinib included cellulitis (RR 6.6), upper respiratory tract infection (RR 2.09) and neutropenia (RR 1.43). In the 2024 systematic review and meta-analysis that evaluated the efficacy and safety of acalabrutinib, zanubrutinib and tirabrutinib, alone or in combination with other treatments, for treatment-naïve and relapsed/refractory CLL/SLL, pooled rates of grade ≥ 3 neutropenia, anaemia and thrombocytopenia in acalabrutinib monotherapy were 14%, 7% and 5%, respectively. The pooled rates of grade ≥ 3 neutropenia, thrombocytopenia and anaemia in zanubrutinib monotherapy were 19%, and 4% and 2%, respectively. Zanubrutinib monotherapy had a similar pooled rate of grade ≥ 3 upper respiratory tract infection (2% versus 1%) and grade ≥ 3 hypertension (6% versus 4%) compared with acalabrutinib monotherapy (3). Clinical studies In the SEQUOIA trial, grade ≥ 3 adverse events were reported in 126 (52.5%) and 181 (79.7%) participants in the zanubrutinib and bendamustine–rituximab arms, respectively. Serious adverse events were reported in 88 (36.7%) and 113 (49.8%) participants, respectively. The most frequently reported grade ≥ 3 adverse events in the zanubrutinib arm were infections (16.3%), neutropenia (11.7%), other cancers (7.1%), hypertension (6.3%) and bleeding and major bleeding (both 3.8%). The most frequently reported grade ≥ 3 adverse events in the bendamustine–rituximab arm were neutropenia (51.1%), infections (18.9%), thrombocytopenia (7.9%) and hypertension (4.8%). Adverse events leading to treatment discontinuation were 8% and 14% in the zanubrutinib and bendamustine-rituximab arms, respectively (4). In the ALPINE trial, treatment discontinuation was lower with zanubrutinib (26.3%) than ibrutinib (41.2%), with most discontinuations due to adverse events (16.2% versus 22.8%) or progressive disease (7.3% versus 12.9%). A lower incidence of cardiac adverse events was reported in the zanubrutinib than the ibrutinib groups (21.3% versus 29.6%), with discontinuation due to cardiac disorders reported in 0.3% versus 4.3% of participants receiving zanubrutinib and ibrutinib, respectively. The rate of atrial fibrillation/flutter was lower with zanubrutinib than ibrutinib (any grade 5.2% versus 13.3%; grade ≥ 3 2.5% versus 4.0%). Neutropenia of any grade was reported in 29.3% and 24.4% in the zanubrutinib and ibrutinib groups, respectively. Incidences of neutropenia and febrile neutropenia of grade ≥ 3 were similar in the two groups. The incidence of infections were similar between treatment groups (any grade: 71.3% versus 73.1%; grade ≥ 3: 26.5% versus 28.1%). The incidence of hypertension (all grades and grade ≥ 3) was also similar between treatment groups (7). At 42.5 months median follow-up of the ALPINE trial, the most common non-haematological treatment-emergent adverse events of any grade with zanubrutinib versus ibrutinib were infections related to coronavirus disease 2019 (COVID-19) (46.0% versus 33.3%), upper respiratory tract infection (29.3% versus 19.8%), hypertension (27.2% versus 25.3%) and diarrhoea (18.8% versus 25.6%). The most commonly reported non-haematological grade ≥ 3 adverse events were COVID-19-related infections (17.9% versus 12.0%), hypertension (17.0% versus 16.0%) and pneumonia (7.7% versus 10.5%), respectively. Neutropenia was the most common haematological adverse event of any grade (31.5% versus 29.6%) and grade ≥ 3 (22.8% versus 22.8%) with

zanubrutinib and ibrutinib, respectively; febrile neutropenia was reported as 1.2% in both arms (8). In study BGB-3111-AU-003, the most frequently reported treatment-emergent adverse events (any grade) were infections (86.2%), contusions (52.0%), and cough and diarrhoea (both 35.8%). Grade ≥ 3 neutropenia was reported in 20.3% of participants. Twelve participants (9.7%) discontinued treatment due to adverse events (12). Study BGB-3111-215 was a phase II open-label, single-arm study that evaluated zanubrutinib in 67 patients with B-cell malignancies in the United States who were intolerant to prior treatment with ibrutinib and/or acalabrutinib (16). After a median follow-up of 12 months, 70% and 83% of ibrutinib- and acalabrutinib-intolerant adverse events, respectively, did not recur with treatment with zanubrutinib. Among recurring adverse events, 7/34 (21%) ibrutinib intolerance events and 2/3 (67%) acalabrutinib intolerance events recurred at the same severity with zanubrutinib, while the remainder recurred at a lower severity. Real-world studies Results of a retrospective study that evaluated real-world treatment patterns based on a formulary change from ibrutinib to zanubrutinib in patients in a community oncology practice in the United States were published in an abstract in 2024 (17). Of 281 patients who received zanubrutinib, 190 had switched from ibrutinib and 91 received only zanubrutinib. The primary reasons for switching to zanubrutinib were formulary change (73%) and disease progression (15%). Similar rates of treatment-emergent adverse events were seen with use of both therapies, with lower rates of treatment-limiting adverse events seen with zanubrutinib. The most common treatment-limiting adverse events were atrial fibrillation and fatigue with ibrutinib, and cytopenias and rash/bruising with zanubrutinib. Rates of cardiac adverse events were higher with ibrutinib, however rates decreased after switching from ibrutinib to zanubrutinib. Dose modification occurred in 34 patients treated with ibrutinib and in 50 patients treated with zanubrutinib. The results of a retrospective observational study that evaluated real-world cardiovascular adverse events, time to treatment discontinuation and time to next treatment in patients with CLL/SLL treated with Bruton tyrosine kinase inhibitors in the United States were published in an abstract in 2024 (18). In total, 3064 patients started a Bruton tyrosine kinase inhibitor as first- or later-line treatment during the study period (1389 on ibrutinib, 1223 on acalabrutinib, and 203 on zanubrutinib). Median follow-up was 20.5 months, 14.2 months and 6 months, for ibrutinib, acalabrutinib and zanubrutinib, respectively. Significantly more patients who received ibrutinib first-line experienced cardiovascular adverse events than those receiving acalabrutinib or zanubrutinib at 3, 6 and 9 months follow-up. The proportions of patients continuing treatment and the median time to next treatment was longer for patients who received zanubrutinib. Of patients treated with first-line ibrutinib, 12.7% discontinued and switched to a second-generation Bruton tyrosine kinase inhibitor. The median time to treatment discontinuation in the first-line setting was 13.7 months for ibrutinib, 19.2 months for acalabrutinib and 19.3 months for zanubrutinib. The associated probabilities of continuing the same treatment were higher with zanubrutinib (81.6%) than with ibrutinib (64.8%) or acalabrutinib (64.8%) at 6 months. In the first-line setting, the median time to next treatment was not reached for zanubrutinib and was 30.2 months for ibrutinib and 35.8 months for acalabrutinib.

Additional evidence

Median 5-year follow-up data from the SEQUOIA trial showed that median progression-free survival was not reached in the zanubrutinib group and was 44.1 months in the bendamustine–rituximab group (HR 0.29, 95% CI 0.21 to 0.40). The estimated 60-month progression-free survival for zanubrutinib and bendamustine–rituximab was 75.8% and 40.1%, respectively. Median overall survival was not reached in either treatment arm (HR 0.89, 95% CI 0.55 to 1.43) and the estimated 60-month overall survival rates were 85.8% and 85.0% in the zanubrutinib and bendamustine–rituximab arms, respectively (19).

Cost / cost effectiveness

Information on the cost of zanubrutinib in different settings was not presented in the application. The application identified six economic evaluation studies involving zanubrutinib in the treatment of CLL/SLL. A 2024 cost–utility analysis evaluated the cost–effectiveness of zanubrutinib versus ibrutinib in relapsed or refractory CLL from the commercial payer perspective in the United States based on survival curves from the ALPINE trial (23). Over a 10-year time horizon, the incremental cost–effectiveness ratio of zanubrutinib versus ibrutinib was 91 260 United States dollars (US$) per life-year gained and US$ 120 634 per quality-adjusted life-year (QALY) gained. Incremental

cost–effectiveness ratios were considered cost-effective at a threshold of US$ 150 000 per QALY gained. The incremental cost–effectiveness ratio was most sensitive to drug acquisition costs and progression-free survival distributions. The probability of zanubrutinib being cost-effective was reported to be about 52.8%, with a 30.0% likelihood of dominance. The results from a cost-minimization analysis of zanubrutinib, acalabrutinib and ibrutinib in the treatment of relapsed/refractory CLL were published in an abstract in 2023 (24). The analysis used a three health-state (progression free, progressive disease, death) partitioned survival model from a United Kingdom National Health Service payer perspective over a lifetime time horizon. The model assumed equal efficacy of zanubrutinib, ibrutinib and acalabrutinib. Zanubrutinib was associated with cost savings of 7802 pounds sterling (£) per person versus acalabrutinib and an incremental cost of £19 677 per person versus ibrutinib. Acalabrutinib was associated with an incremental cost of £27 478 per person versus ibrutinib. Differences in treatment acquisition costs were the key reason for the cost differences between treatments. Zanubrutinib was associated with fewer management costs for adverse events than acalabrutinib and ibrutinib. A 2024 model-based study evaluated the cost–effectiveness of zanubrutinib and ibrutinib in relapsed and refractory CLL from the payer perspective in China and the United States (25). For Chinese payers, zanubrutinib had superior cost–effectiveness compared with ibrutinib, with an incremental cost–effectiveness ratio of US$ −88 068 per QALY. Zanubrutinib was a more affordable option for the United States, with an incremental cost–effectiveness ratio of US$ −284 485 per QALY. The results from a 2023 study comparing zanubrutinib and ibrutinib in relapsed/refractory CLL by calculating the number needed to treat to avoid one progression or death and associated incremental costs from a United States payer perspective were published as a conference poster abstract (26). Modelled results in the base case showed a number needed to treat of 8 for zanubrutinib compared with using ibrutinib. The total costs per patient treated were US$ 370 558 and US$ 430 150 for zanubrutinib and ibrutinib, respectively, with cost savings of US$ 59 593 associated with the use of zanubrutinib. The results from a 2022 budget impact analysis of zanubrutinib for the treatment of relapsed/refractory CLL from a United States payer perspective were published in an abstract (27). The modelled analysis compared a reference scenario with the current market mix (i.e. before the introduction of zanubrutinib) and a revised market mix in which uptake of zanubrutinib was included. The base-case analysis of a hypothetical 1-million-member health plan in which two patients were estimated to have relapsed/refractory CLL and started treatment showed that total health-care costs over 1 year were US$ 426 000 with zanubrutinib and US$ 430 000 without zanubrutinib, suggesting that adding zanubrutinib was associated with cost savings. One-way sensitivity analysis results showed that the budget impact on health-care costs over a 1-year time horizon were most sensitive to the zanubrutinib wholesale acquisition cost. The results from another 2022 budget impact analysis of zanubrutinib for treatment-naïve CLL/SLL from a United States payer perspective were published in an abstract (28). In a hypothetical health plan with 1 million members, 31 patients were estimated to receive active first-line treatment each year for CLL/SLL. Base-case scenarios of clinical practice with and without zanubrutinib were estimated. Total health-care costs were US$ 37.75 million with zanubrutinib and US$ 37.84 million without zanubrutinib. Over a 3-year time-horizon, the overall budget impact was a reduction of US$ 82 437, representing a 0.22% cost-saving with the use of zanubrutinib. Sensitivity analysis indicated that drug costs, payer perspective and treatment duration had the greatest impact on the financial budget of health-care costs.

WHO guidelines

WHO guidelines for the treatment of CLL/SLL are not currently available. Recommendations for the use of zanubrutinib as first- and later-line therapy of CLL/SLL are included in various national and international guidelines (20–22).

Availability

Zanubrutinib has regulatory approval in 40 countries/jurisdictions globally for use in the treatment of treatment-naïve and/or relapsed/refractory CLL/SLL. Most of these countries/jurisdictions are upper middle- and high-income settings.

Other considerations

The EML cancer experts group reviewed the application and provided its advice for the Expert Committee. The group did not support the inclusion of zanubrutinib on the EML for treatment of adults with treatment-naïve or relapsed/refractory CLL/SLL. The group noted that treatment for CLL/SLL is a rapidly evolving field, with ongoing studies evaluating combination regimens with zanubrutinib. Furthermore, while available data demonstrate better progression-free survival gains with zanubrutinib than ibrutinib, data for overall survival are less convincing. The group also considered that the improved safety profile of zanubrutinib versus ibrutinib was likely to be the effect of the comparison with the approved dose of ibrutinib. They noted that post-approval studies suggest that lower ibrutinib doses are as effective and that ibrutinib was therefore used at a dose that was too high, likely leading to an overestimate of the difference in adverse events. The cancer team within the Department of Noncommunicable Diseases, Rehabilitation and Disability reviewed and provided comments on the application. The technical department supported deferring the inclusion of zanubrutinib on the EML until further evidence for overall survival benefit and safety are available.

