Zanubrutinib

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

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

ATC codes: L01EL03

Indication	Mantle cell lymphoma ICD11 code: 2A85.5
Medicine type	Chemical agent
List type	Complementary
Formulations	Oral > Solid: 80 mg
EML status history	Application rejected in 2021 (TRS 1035)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
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	Zanubrutinib
DrugBank	Zanubrutinib

Expert Committee recommendation

The Expert Committee noted that mantle cell lymphoma is a rare, aggressive variant of non-Hodgkin lymphoma, primarily affecting older people. The Expert Committee considered the application for inclusion of zanubrutinib on the EML for treatment of relapsed/refractory mantle cell lymphoma was premature. With regard to clinical efficacy, the Committee noted that only phase I and II trial data were currently available, and these are based on a small number of patients and limited follow-up. Data comparing the efficacy and safety of zanubrutinib with other treatments and studies assessing quality of life are also lacking. The Committee noted that zanubrutinib was associated with major haematological toxicity. Overall, the available data were considered insufficient to evaluate the clinical benefit and safety of zanubrutinib as an essential medicine at this time. The Committee also noted that the cost–effectiveness of zanubrutinib is unknown, and that currently global regulatory approval and availability of zanubrutinib are very limited. Therefore, the Committee did not recommend inclusion of zanubrutinib on the EML for the treatment of mantle cell lymphoma at this time.

Background

Zanubrutinib has not previously been considered for inclusion on the EML. The Model List does not currently include any medicines specifically for the treatment of mantle cell lymphoma.

Public health relevance

Mantle cell lymphoma is an uncommon subtype of non-Hodgkin lymphoma, accounting for between 2% and 10% of all non-Hodgkin

lymphomas (1). In 2018, the global incidence of non-Hodgkin lymphoma was 6.7 per 100 000 people (2). Mantle cell lymphoma has been reported to account for 7.8% of non-Hodgkin lymphoma in developed regions and 3.8% in developing regions (3). In Europe and the United States, average incidence rates for mantle cell lymphoma of about 0.5 cases per 100 000 person-years have been reported, with a male-to-female ratio of 2.3–5.0 to 1 and a median age at diagnosis of about 70 years (4). Mantle cell lymphoma is an aggressive disease with a poor prognosis and poor survival. During 2010 to 2016, the 5-year relative survival of patients with mantle cell lymphoma in the United States was 61.9%, and the relative survival was significantly correlated with age. The 5-year relative survival of patients with mantle cell lymphoma aged 20–64 years and > 65 years was 71.2% and 54.9%, respectively (5). Outcomes of treatment for mantle cell lymphoma vary widely. Patients can have an aggressive presentation and die from the disease in less than 6 months, or can have a slowly progressing clinical course with long survival of more than 10 years (6). More than 90% of patients present with advanced-stage disease (stage 3–4) (7). For several decades, the gold standard of first-line treatment was chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone, which has been used more recently in combination with the anti-CD20 antibody rituximab. Younger patients have been treated with more aggressive chemoimmunotherapy, with high doses of cyclophosphamide as part of a hyper-CVAD regimen (cyclophosphamide, vincristine, doxorubicin and dexamethasone). High doses of cytarabine were also used in other regimens for clinically fit patients with mantle cell lymphoma younger than 65 years old. Maintenance treatment with rituximab was shown to prolong response duration after rituximab-containing chemotherapy (8–11). Although standard chemoimmunotherapy is associated with a high overall response rate, treatment is not curative, and most patients will experience relapse. The rate of complete response is less than 50%, with median overall survival of 3–4 years (10,12). Median survival after first relapse of mantle cell lymphoma is 1–2 years (13). Allogenic haematopoietic stem cell transplantation may also be an option for the treatment of relapsed/refractory mantle cell lymphoma. However, many patients will not be candidates for such intensive treatment approaches due to advanced age and comorbid illness (13).

Benefits

The application presented the results of study BGB-3111-206, a single-arm, multicentre phase II trial that evaluated the efficacy and safety of zanubrutinib 160 mg twice daily in 86 participants with confirmed relapsed/refractory mantle cell lymphoma (14). The primary endpoint was overall response rate assessed by an independent review committee; secondary endpoints included duration of response, time to response, progression-free survival and safety. After median follow-up of 18.4 months, 72 participants (84%) achieved an objective response, with 59 participants (67%) achieving a complete response. After a median follow-up of 16.4 months from the initial response, the estimated median duration of response was 19.5 months. After a median follow-up of 19.2 months, the estimated median progression-free survival was 22.1 months with an estimated 76% of participants alive and without disease progression at 12 months. The application also presented a summary of results from phase I pharmacokinetic and dose-finding studies of zanubrutinib (15,16). Of 37 participants with relapsed/refractory mantle cell lymphoma in the phase I GBG-3111-AU-003 study, 32 (86%) achieved an objective response – 11 with complete response and 21 with partial response (15). Median progression-free survival was 15.4 months (16). Direct comparative data of zanubrutinib with other Bruton tyrosine kinase inhibitors for mantle cell lymphoma are lacking. The application presented indirect comparisons of efficacy reported for zanubrutinib (14), ibrutinib (17,18) and acalabrutinib (19). Objective response rates were 87% for zanubrutinib, compared with 80% for acalabrutinib and 72% for ibrutinib. Complete response rates were 69% for zanubrutinib, 40% for acalabrutinib and 19–21% for ibrutinib.

Harms

Safety results from phase I and II trials of zanubrutinib were presented (14,15,20). In study BGB-3111-206, 83/86 (96%) participants experienced at least one adverse event, with most events being grade 1 or 2 in severity; grade 3 and higher adverse events were reported in 34 (40%) participants. The most common haematological adverse events were neutropenia (49%), leukopenia (35%) and thrombocytopenia (33%). The most common non-haematological adverse events were upper respiratory infection (35%) and rash (34%). The most common grade 3 and higher adverse events were neutropenia (20%) and lung infection/pneumonia (9%). In total, 14/86 (16%) participants died during the study, seven within 30 days of the last study treatment (six due to complications of adverse events and one due to disease progression). Seven deaths occurred more than 30 days after the last dose of the study drug; five were due to progressive disease, one was due to complications of a fungal infection of the lungs and one was from unknown cause after receiving three additional lines of therapy (14). From an indirect comparison with ibrutinib in the treatment of relapsed/refractory mantle cell lymphoma, zanubrutinib was associated with a lower incidence of

atrial fibrillation (0% versus 6%) and treatment discontinuation due to adverse events (9.3% versus 11%) (14,21).

Cost / cost effectiveness

No cost–effectiveness analysis data for zanubrutinib were presented in the application. The price for zanubrutinib in the United States is US$ 12 935 per bottle (120 capsules), corresponding to 30 days of treatment at the recommended dose. The price for zanubrutinib in China is ¥ 11 300 per bottle (64 capsules). The monthly treatment cost is ¥ 22 600. Comparatively, the first-generation Bruton tyrosine kinase inhibitor, ibrutinib, is listed in China priced at ¥ 22 680 per month for patients with mantle cell lymphoma.

WHO guidelines

WHO guidelines for treatment of mantle cell lymphoma are not available.

Availability

Zanubrutinib has regulatory approval from the National Medical Products Administration of the People's Republic of China (2020) and the United States Food and Drug Administration (2019) for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy. Regulatory submissions have also been made in Australia, Canada, Europe and Israel.

Other considerations

The EML Cancer Medicines Working Group advised that it did not support the inclusion of zanubrutinib on the EML for treatment of relapsed/refractory mantle cell lymphoma at this time, noting that the available data for efficacy and safety are very limited (early phase trials, with small patient numbers and with short follow-up), important toxicity concerns, high cost and unknown cost–effectiveness. Zanubrutinib has been recommended as second-line treatment of mantle cell lymphoma in recent guidelines of the National Comprehensive Cancer Network (8) and the Chinese Society of Clinical Oncology (9). Comments were received from the WHO Department of Noncommunicable Diseases. The technical department advised that at the current time, there was insufficient evidence to support inclusion of zanubrutinib in WHO EML because of the lack of mature data substantiating a significant clinical effect and concerns about the toxicity profile (particularly rates of severe infections).

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