Recommendation Letter

To Whom It May Concern,

I am writing this supporting letter to strongly advocate the inclusion of , Brukinsa® (Zanubrutinib Capsules) on the WHO Essential Medicine List and I am in full support of the submitted application.

As senior vice president and head of chemistry research and development at Beigene, and inventor of Brukinsa® (Zanubrutinib Capsules), I strongly recommend and look forward to its inclusion in the WHO Essential List of Essential Medicines as soon as possible.

Introduction

1. The efficacy of a new generation of BTK inhibitor, Brukinsa® (Zanubrutinib Capsules), has been internationally recognized and has been approved for launching in many countries:
2. It was approved in the United States in November 2019 for the treatment of mantle cell lymphoma (MCL) patients who had received at least one prior treatment; During the approval process, it was certified by FDA for "Breakthrough Therapy" and "Accelerated Approval".
3. It was approved in China in June 2020 for the treatment of adult mantle cell lymphoma (MCL) patients who had received at least one prior treatment, and adult chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) patients who had received at least one prior treatment;
4. In February 2021, Brukinsa® was approved in the United Arab Emirates for the treatment of mantle cell lymphoma (MCL) patients who had received at least one prior treatment;
5. In March 2021, Brukinsa® was approved in Canada for the treatment of patients with Waldenstrom macroglobulinemia (WM).

Clinical Efficacy and Safety

1. For the treatment of R/R CLL/SLL patients, the ORR of Zanubrutinib monotherapy was as high as 85% with good safety, low incidence of grade ≥3 atrial fibrillation and other adverse events, and low discontinuation rate. The majority of CLL patients are elderly (≥65 years old), and the median age at diagnosis is 70 years old. The incidence of hypertension, coronary heart disease and atrial premature beats in the elderly population is significantly increased, and safer treatment drugs are urgently needed. For patients with CLL who require long-term treatment, a low discontinuation rate ensures treatment outcomes and prolonged survival.
2. In the treatment of R/R MCL patients, the CR rate of Zanubrutinib monotherapy was 78%, and the PFS was 22.1 months; The efficacy data were significantly better than the historical data of other BTK inhibitors and drugs in R/R MCL.
3. ASPEN, a large global Phase III head-to-head study, showed that Zanubrutinib was safer than Ibrutinib, especially in atrial fibrillation (3.0% vs 18.4%), and treatment discontinuation rates were significantly lower than Ibrutinib (4.0% vs 14.3%).
4. ALPINE, a global multicenter phase III head-to-head study, compared the efficacy and safety of Zanubrutinib versus Ibrutinib in adult R/R CLL/SLL, the interim analysis achieved positive results and the efficacy reached primary end point. The researchers evaluated that Zanubrutinib achieved ORR superiority compared with Ibrutinib, and the difference was statistically significant (P =0.0006).

Public Health Relevance

With better safety, Zanubrutinib can reduce treatment-related adverse reactions in patients, improve the quality of life, and reduce the burden of long-term management of patients by doctors and medical institutions.

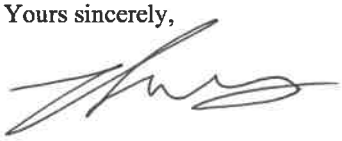
From the perspective of the Chinese healthcare system, the long-term (patient lifetime) economics of Zanubrutinib vs Ibrutinib in the treatment of relapsed/refractory mantle cell lymphoma were compared, and each patient in the Zanubrutinib group could obtain 3.043 QALYs and 4.164 LYs in a lifetime.1.228 more QALYs and 1.721 more LYs per patient than Ibrutinib group, respectively. Before being included in the national medical insurance, The total cost of Zanubrutinib group was 612,956.5 yuan, which was 75,947.3 yuan higher than 537,009.2 yuan in Ibrutinib group, and the incremental cost-effectiveness ratio (ICER) of the two groups was 61,848.6 yuan /QALY, lower than China's GDP per capita of 70,892.0 yuan in 2019. From March 1st, 2021, Brukinsa® has been officially included in National Medical Care Insurance Medicine Catalogue, with the new price of 6,336 yuan/box. The monthly treatment cost of Brukinsa® for CLL and MCL is only 11,880 yuan.

Cost-Effectiveness

In terms of cost-effectiveness, the 2020 ASH study confirmed the cost-effectiveness advantage of Zanubrutinib over Ibrutinib in the treatment of R/R MCL, with an incremental PFS LYs of 0.98 and incremental PFS QALYs of 0.77 compared to Ibrutinib. In probability analysis, the ICER and ICUR of Zanubrutinib were lower than the WTP threshold in the United States. At $100,000 WTP, the cost-effectiveness acceptability curve showed that the probability of Zanubrutinib and Ibrutinib being cost-effective was 34% and 16%, respectively, suggesting that Zanubrutinib, a new generation of BTK inhibitors, was more cost-effective than Ibrutinib in the treatment of R/R MCL.

In conclusion, Zanubrutinib has better efficacy, safety and pharmacoeconomic advantages in MCL and CLL treatment. It plays a positive role in public health care. We strongly recommend and look forward to its inclusion in the WHO Model List of Essential Medicines as soon as possible, so that more lymphoma patients in the world can benefit from it!

Yours sincerely,



Zhiwei Wang, Ph.D.
SVP, Head of Chemistry R&D
BeiGene