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.

I am Zhou Keshu, deputy director of the Department of Hematology, Henan Cancer Hospital, a doctoral supervisor at Zhengzhou University, and an advanced worker in the province's health and family planning system. As the PI of the zambutinib BGB-3111-206 study, I recommend Brukinsa® (Zanubrutinib Capsules) for the following reasons：

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. 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.

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.

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.

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

Kexu Zhou

12/May 2021

推荐信

简介

1. 新一代 BTK 抑制剂百悦泽®（泽布替尼胶囊）疗效得到国际认可，在多个国家获批上市：
2. 2019 年 11 月在美国获批用于治疗先前至少接受过一项治疗的套细胞淋巴瘤（MCL）患者；并在审批过程中获得 FDA “突破性疗法” 及 “加速审批” 认证。
3. 2020 年 6 月在中国获批用于治疗既往至少接受过一种治疗的成人套细胞淋巴瘤（MCL）患者、既往至少接受过一种治疗的成人慢性淋巴细胞白血病（CLL）/小淋巴细胞淋巴瘤（SLL）患者；
4. 2021 年 2 月，百悦泽®在阿拉伯联合酋长国获批用于治疗先前至少接受过一项治疗的套细胞淋巴瘤（MCL）患者；
5. 2021 年 3 月，百悦泽®在加拿大获批用于治疗华氏巨球蛋白血症（WM）患者。

临床疗效和安全性

1. 对于 R/R CLL/SLL 患者的治疗，泽布替尼单药治疗 ORR 高达 85%；且安全性良好，≥3 级房颤等不良事件发生率低，治疗中止率低。CLL 多为老年人 (≥65 岁)，诊断时的中位年龄为 70 岁，老年人群中高血压、冠心病和房性早搏发生率显著增加，亟需更安全的治疗药物；对于需要长期治疗的 CLL 患者来说，中止率低保证治疗效果，延长患者生存。
2. 对于 R/R MCL 患者的治疗，泽布替尼单药治疗 CR 率 78%，PFS 长达 22.1 个月；疗效数据显著优于其他已上市 BTK 抑制剂及药物在 R/R MCL 的历史数据。
3. 全球大样本量 III 期头对头 ASPEN 研究显示，泽布替尼安全性优于伊布替尼，尤其是房颤（3.0% vs 18.4%），治疗中止率显著低于伊布替尼（4.0% vs 14.3%）。
4. 全球多中心 III 期头对头 ALPINE 研究，在成年 R/R CLL/SLL 中，对比接受泽布替尼和伊布替尼疗效及安全性的，研究的中期分析取得积极结果，疗效达到主要终点。经研究者评估，与伊布替尼相比，泽布替尼达到 ORR 优效性，差异具有统计意义（p 值=0.0006）

批注 [YL1]: 【BGB-3111-205 研究】Xu W, et al. J Hematol Oncol 2020; 13(1):48.

批注 [YL2]: Https://seer.cancer.gov/statfacts/html/clyl.html

批注 [YL3]: 1. 胡盛寿等. 中国循环杂志 2019; 34(3):209-220.
2. Wang Y, et al. Frontier in Public Health 2020; 7:411
3. 朱晨. 医学理论与实践 2002; 15(4): 385-386.

批注 [YL4]: 【BGB-3111-206 研究】Song Y, et al. Clin Cancer Res. 2020 May 27.

批注 [YL5]: 【aspen 研究】Tam CS, et al. 2020 ASCO Abstract 8007.

批注 [YL6]: Hillmen P, et al. 61st ASH Annual Meeting (2019) Abstract No.4307.

https://clinicaltrials.gov/ct2/show/NCT03734016?term=BGB-3111&cond=CLL%2FSLL&draw=2&rank=4

公共卫生相关性

泽布替尼安全性更优可降低患者治疗相关不良反应，提高患者生活质量，减轻医生和医疗机构对患者长期管理的负担。

从中国医疗卫生系统角度出发，比较泽布替尼 vs 伊布替尼治疗复发/难治套细胞淋巴瘤长期（患者终生）的经济性，泽布替尼组每位患者终生可获得 3.043 个 QALYs、4.164 个 LYs，分别比伊布替尼组每位患者多获得 1.228 个 QALYs、1.721 个 Lys。泽布替尼组的总成本为 612,956.5 元，比伊布替尼组的 537,009.2 元高出 75,947.3 元，二者的增量成本效果比 (ICER)为 61,848.6 元/QALY，低于 2019 年中国人均 GDP 70,892.0 元。

批注 [YL7]: 泽布替尼 (百悦泽®)用于治疗复发/难治成人套细胞淋巴瘤的成本效果分析. 研究结果报告, 北京医药卫生经济研究会 2020 年 11 月.

成本效益

关于成本效益，2020 ASH 研究证实，泽布替尼对比伊布替尼治疗 R/R MCL 的成本效益优势，与伊布替尼相比，泽布替尼的临床疗效更好，增量 PFS Lys 为 0.98，增量 PFS QALYs 为 0.77。在概率分析中，泽布替尼的 ICER 和 ICUR 低于美国的支付意愿 (WTP)阈值； 在$100,000 的 WTP 下，成本-效果可接受曲线显示泽布替尼、伊布替尼具有成本-效益的概率分别为 34%和 16%，提示新一代 BTK 抑制剂泽布替尼对比伊布替尼治疗 R/R MCL 更具成本效益。

批注 [YL8]: Alrawashdh N, et al. 62nd ASH Annual Meeting (2020). Abstract No:2506.

2021 年 3 月 1 日起，百悦泽®正式纳入中国国家医保目录，执行新价格 6336 元/盒。百悦泽®月治疗 CLL 和 MCL 费用仅需 11,880 元。

综上所述，泽布替尼在 MCL 和 CLL 治疗上均具有更好的疗效、安全性和药物经济学优势。对公共医疗卫生事业起到积极影响的作用，强烈推荐并期待其能早日纳入 WHO 基本药物目录，让世界更多的淋巴瘤患者从中获益！

签名：

日期：2021.5.12