ASPEN：泽布替尼对比依鲁替尼治疗华氏巨球蛋白血症（WM）的 III 期随机对照试验

ASPEN: Results of a phase III randomized trial of zanubrutinib versus ibrutinib for patients with Waldenstro m macroglobulinemia (WM).

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背景：布鲁顿酪氨酸激酶（BTK）抑制是华氏巨球蛋白血症（WM）的新兴治疗标准。3 期随机试验研究 ASPEN 旨在比较强效高选择性 BTK 抑制剂泽布替尼（ZANU）与第一代 BTK 抑制剂依鲁替尼（IBR）对 WM 的疗效。

方法：将 MYD88 突变的 WM 患者按 1：1 随机分入 ZANU（160mg，BID）治疗组或 IBR（420mg，QD）治疗组。无 MYD88 突变的患者分配到一个独立组，接受 ZANU 治疗并单独报告。随机分层因素包括 CXCR4 突变状态和既往治疗次数（0 vs 1-3 vs >3）。主要终点为达到完全缓解或非常好的部分缓解（CR + VGPR）的患者比例。 计算样本量可提供 81％的功效，检测到在复发或难治性（R / R）WM 患者亚组中，ZANU 组的 CR + VGPR 比例为 35％，IBR 组为 15％。初步分析计划在最后 1 名患者入组后约 12 个月进行。

结果：从 2017 年 1 月至 2018 年 7 月，共纳入 201 例患者并随机分组。除了泽布替尼组者患者年龄较大（年龄大于 75 岁，33.3％vs 22.2％）和贫血发生率更高（血红蛋白≤110 g / L，65.7％ vs 53.5％）外，两组的其它基线因素平衡。中位随访时间为 19.4 个月，ZANU 组与 IBR 组的 CR + VGPR 比率分别为 **28.4％**和 **19.2％**（P = 0.09）。泽布替尼相较伊布替尼在耐受性上表现更好，房颤、挫伤、腹泻、外周水肿、出血、肌肉痉挛、肺炎和导致停药或死亡的不良事件（AE）的发生率较低。泽布替尼组的中性粒细胞减少率较高， 但是≥3 级的感染率相似（分别为 17.8％和 19.4％）。

评估, %	ZANU (n=102)	IBR (n=99)
CR+VGPR 比率	28.4	19.2
总人群中 12 个月时的 PFS/OS	89.7/97.0	87.2/93.9
R/R 人群中 12 个月时的 PFS/OS(n=83 vs 81)	92.4/98.8	85.9/92.5
≥3 级/ 5 级的不良事件	58.4 /1.0	63.3/4.1
导致停药的不良事件	4.0	9.2
心房颤动/扑动	2.0	15.3
高血压	10.9	17.3
大出血 [a]	5.9	9.2
中性粒细胞减少	29.7	13.3

PFS / OS，无进展生存期/总生存期

[a] 包括≥3 级出血和任何级别的中枢神经系统出血。

结论：ASPEN 是在 WM 患者中进行的最大型的 BTK 抑制剂 3 期试验，也是首次对 BTK 抑制剂进行的一对一对比试验。尽管在统计学上没有显著性，但泽布替尼倾向于有更高的 CR + VGPR 缓解率获益。并且与伊布替尼相比，泽布替尼在安全性方面显示出了临床优势。

原文摘要：

Abstract

Background: Bruton tyrosine kinase (BTK) inhibition is an emerging standard of care for WM. ASPEN is a randomized phase 3 study comparing zanubrutinib (ZANU), a potent and se- lective BTK inhibitor, versus ibrutinib (IBR), a first generation BTK inhibitor, in WM patients.

Methods: Patients with WM and MYD88 mutation were randomly assigned 1:1 to receive ZANU (160 mg twice daily) or IBR (420 mg once daily). Patients without MYD88 mutations were assigned to a separate cohort, received ZANU, and are reported separately. Random- ization was stratified by CXCR4 mutational status and the number of lines of prior therapy (0 vs 1-3 vs .3). The primary end point was the proportion of patients achieving a complete response or very good partial response (CR+VGPR). Sample size was calculated to provide 81% power to detect a difference in CR+VGPR rate of 35% vs 15% in the subset of patients with

relapsed or refractory (R/R) WM. Primary analysis was planned to occur at ~12 months after last patient enrolled.

Results: In total, 201 patients were randomized from Jan 2017 to Jul 2018. The treatment groups were well balanced for important baseline factors, except in the ZANU arm there were more elderly patients (aged .75 years, 33.3% vs 22.2%) and more anemia (hemoglobin #110 g/L, 65.7% vs 53.5%). At a median follow-up of 19.4 months, the rate of CR+VGPR was 28.4% vs 19.2% with ZANU vs IBR, respectively (2-sided P=0.09). Rates of atrial fibrillation, contusion, diarrhea, edema peripheral, hemorrhage, muscle spasms, pneumonia, and adverse events (AEs) leading to discontinuation or death were lower with ZANU. The rate of neutropenia was higher with ZANU (Table); however, grade $ 3 infection rates were similar (17.8% vs 19.4%).

Conclusions: ASPEN is the largest phase 3 trial of BTK inhibitors in WM and the first head-to-head comparison of BTK inhibitors in any disease. Although not statistically significant, ZANU was associated with a higher CR+VGPR response rate, and demonstrated clinically meaningful advantages in safety and tolerability compared to IBR. Clinical trial information: NCT03053440. Research Sponsor: BeiGene.