比较泽布替尼+利妥昔单抗和苯达莫司汀+利妥昔单抗治疗套细胞淋巴瘤(MCL)初治患者的疗效：III 期、随机、开放标签研究。

Trial in progress: A phase III, randomized, open-label study comparing zanubrutinib plus rituximab versus bendamustine plus rituximab in patients with previously untreated mantle cell lymphoma (MCL).

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背景：布鲁顿酪氨酸激酶（BTK）介导 B 细胞增殖、迁移和粘附。 BTK 抑制已成为靶向 B 细胞恶性肿瘤（包括套细胞淋巴瘤，MCL）的重要治疗策略。泽布替尼是新一代的 BTK 抑制剂，设计初衷旨在最大程度地提高对 BTK 的抑制率，并最大程度地降低对 TEC 和 EGFR 家族激酶的脱靶抑制，具有良好的药代动力学和药效学特性。泽布替尼单药疗法已在治疗 118 例复发/难治性 MCL 患者的两项单臂研究中（BGB-3111-206 和 BGB-3111-AU-003）进行了评估。两项试验中经独立审核委员会（IRC）评估的总缓解率（ORR）为 84%，中位缓解时间分别为 19.5 和 18.5 个月。MCL 的一线治疗未能治愈大多数患者，尤其是老年患者或不适合移植的患者，而基于化疗的治疗方法会导致长期累积风险。本研究旨在评估泽布替尼联合利妥昔单抗对比苯达莫

司汀联合利妥昔单抗在老年患者以及不适合干细胞移植且患有 MCL 合并症初治患者中的安全性和有效性。

方法：这项正在进行的 III 期、开放标签研究将招募约 500 名患者，以 1：1 的比例随机分组，并按 MCL 国际预后指数评分（低、中/高）、年龄（<70 岁、≥70 岁）和地域（北美/欧洲、亚太地区）进行分层。在 A 组中，患者将接受最多 6 个周期（28 天为一周期）的治疗：口服泽布替尼（160 mg/次，BID），并在每个周期的第 1 天静脉注射（IV）利妥昔单抗 375 mg / m^2。6 个周期后，泽布替尼将继续单药治疗，直到疾病进展、出现不可接受毒性或患者不再同意进行治疗为止。在 B 组中，患者将接受最多 6 个周期（28 天为一周期）治疗：每个周期的第 1 天和第 2 天静脉注射苯达莫司汀 90 mg/m^2，并在每个周期的第 1 天静脉注射利妥昔单抗 375 mg / m^2，然后进行观察。符合条件的患者必须患有经组织学证实的 MCL，年龄≥70 岁或 65-69 岁之间，且患有明确的合并症。根据 2014 年卢加诺分类对非霍奇金淋巴瘤的疾病缓解进行评估。主要终点是由 IRC 确定的无进展生存期（PFS）。关键的次要终点包括研究者评估得出的 PFS，ORR，缓解时间和持续时间，总生存期和安全性。患者招募正在进行中。

原文摘要：

Abstract

Background: Bruton tyrosine kinase (BTK) mediates B-cell proliferation, mi- gration, and adhesion. BTK inhibition has emerged as a strategy for targeting B-cell malignancies, including MCL. Zanubrutinib is a next-generation BTK inhibitor that was designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases, with favorable phar- macokinetic and pharmacodynamic properties. Zanubrutinib monotherapy has been evaluated in 118 patients (pts) with relapsed/refractory MCL in 2 single-arm studies: BGB-3111-206 [NCT03206970] and BGB-3111-AU-003 [NCT02343120]. The overall response rate (ORR) by independent review committee (IRC) in both trials was 84% with median durations of response of 19.5 and 18.5 months, respectively. First-line treatment for MCL has failed to cure most pts, particularly elderly or transplant-ineligible groups, and chemotherapy-based approaches result in cumulative, long-term risks. The study described herein is designed to evaluate the safety and efficacy of zanubrutinib plus rituximab versus bendamustine plus rituximab in elderly pts and pts with comorbidities with previously untreated MCL who are ineligible for stem cell transplant.

Methods: This ongoing phase 3, open-label study will enroll »500 pts to be randomized 1:1, stratified by MCL International Prog- nostic Index

score (low vs intermediate/high), age (, 70 vs $70 years), and geographic region (North America/Europe vs Asia-Pacific). In arm A, pts will receive up to six 28-day cycles of oral zanubrutinib 160 mg twice daily in combination with intravenous (IV) rituximab 375 mg/m2 on day 1 of each cycle. After 6 cycles, zanubrutinib will continue as a monotherapy until progressive disease, unacceptable toxicity, or withdrawal of consent. In arm B, pts will receive up to six 28-day cycles of IV bendamustine 90 mg/m2 on days 1 and 2 of each cycle and rituximab 375 mg/m2 on day 1 of each cycle, followed by observation. Eligible pts must have histologically confirmed MCL and be aged $70 years, or 65-69 years with defined comorbidities. Disease response will be assessed per the 2014 Lugano Classification for non-Hodgkin lym- phoma. The primary endpoint is progression-free survival (PFS) determined by IRC. Key secondary end points include PFS by investigator assessment, ORR, time to and duration of response, overall survival, and safety. Recruitment is ongoing. Clinical trial information: NCT04002297. Research Sponsor: BeiGene.