泽布替尼(BGB-3111)用于依鲁替尼治疗不耐受的 CLL/SLL 患者的 II 期、多中心、单臂研究。

Trial in progress: a phase II, multicenter, single-arm study of zanubrutinib (BGB-3111) in patients with previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma intolerant of prior treatment with ibrutinib.

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背景：依鲁替尼（ibr）是一种布鲁顿酪氨酸激酶抑制剂（BTKi），可改善慢性淋巴细胞白血病/小淋巴细胞淋巴瘤（CLL / SLL）的患者预后。然而，不良事件（AEs）是致使 ibr 治疗中断的最常见原因，复发/难治性（R / R）和初治患者中断治疗的比例分别为 50％和 63％（Haematologica.2018：103：874）。另一种 BTKi 泽布替尼经过了专门设计对选择性进行了优化，已获准用于治疗套细胞淋巴瘤。来自 6 项泽布替尼单药治疗 B 细胞恶性肿瘤临床试验的汇总临床数据（N = 682 例； R / R CLL / SLL [n = 91]）表明，泽布替尼单药治疗耐受性良好，并且因为不良事件导致的停药率低（9％; Tam，EHA 2019）。本文介绍的是一项正在进行中的试验，该试验旨在评估泽布替尼单药治疗是否可能成为对 ibr 不耐受的 CLL / SLL 患者的治疗选择。

方法：这是一项 II 期，多中心、单臂开放标签研究，对泽布替尼单药治疗（160mg/次，BID）作为先前 ibr 治疗不耐受的 CLL / SLL 患者进行评估。这项研究将从约 30 个社区医疗中心招募约 60 名患者。主要纳入标准包括在 ibr 治疗之前按照 CLL 国际研讨会标准（Blood. 2018; 131：2745）进行治疗的 CLL / SLL 患者，对 ibr 不耐受（定义为出现不可接受的不良事件，根据研究者的意见，尽管有最佳的支持疗法，ibr 治疗仍应停止），与 ibr 相关的 AE 分级≤1 级或基线 ECOG PS 0-2。主要排除标准包括用过 ibr 或泽布替尼进行癌症干预治疗，在 ibr 治疗至入组时有疾病进展记录，以及有中枢神经系统（CNS）出血史。主要终点是治疗方案指定的治疗相关不良事件（腹泻，肌痛，肌肉痉挛，关节痛，高血压，疲劳，皮疹，房颤和中枢神经系统出血以外的出血）的频率和严重程度。次要终点包括总体缓解率，无进展生存期和患者报告的结果。使用智能手机应用程序添加了一个探索性终点，以评估临床疗效（身体活动，与治疗相关的症状和生活质量）。患者招募正在进行中。

原文摘要：

Abstract

Background: Ibrutinib (ibr), a Bruton tyrosine kinase inhibitor (BTKi), was shown to improve patient outcomes in chronic lymphocytic

leukemia/small lymphocytic lymphoma (CLL/SLL); however, adverse events (AEs) were the most common reason for discontinuing ibr (50% and 63% of discontinuations in relapse/refractory (R/R) and frontline patients, respectively; Haematologica. 2018:103:874). Zanubrutinib, an approved BTKi for mantle cell lymphoma, was specifically engineered to optimize selectivity. Pooled clinical data from 6 zanubrutinib monotherapy trials in B-cell malignancies (N=682 patients; R/R CLL/SLL [n=91]) suggested that zanubrutinib monotherapy was well tolerated and demonstrated a low rate of treatment discontinuation from AEs (9%; Tam, EHA 2019). Presented here is a trial-in-progress that will evaluate whether zanubrutinib monotherapy may serve as a therapeutic option for patients with CLL/SLL who have become ibr intolerant.

Methods: The ongoing phase II, multicenter, US, single-arm, open-label study (NCT04116437, BGB-3111- 215) will evaluate zanubrutinib monotherapy (160mg twice daily) as a treatment option for patients with CLL/SLL intolerant to prior ibr treatment. Approximately 60 patients will be enrolled from ~30 community medical centers. Key inclusion criteria include CLL/SLL requiring treatment per In- ternational Workshop on CLL criteria (Blood. 2018;131:2745) before ibr therapy, intolerance to ibr (defined as an unacceptable AE for which, per investigator's opinion, ibr treatment should be discontinued despite optimal supportive therapy), resolution of ibr-related AEs to grade #1 or baseline, and an

ECOG PS 0-2. Key exclusion criteria include having an intervening cancer therapy between ibr and zanubrutinib, a documented disease progression during ibr treatment up to the time of enrollment, and a history of central nervous system (CNS) hemorrhage. The primary endpoint is frequency and severity of protocol-specified treatment-emergent AEs (diarrhea, myalgia, muscle spasm, arthralgia, hypertension, fatigue, rash, atrial fibrillation, and hemorrhage excluding CNS hemorrhage). The secondary endpoints include overall response rate, progression-free survival, and patient-reported outcomes. An exploratory endpoint was added to evaluate clinical effects (physical activity, treatment-related symptoms, and quality of life) using a smartphone app. Recruitment is ongoing. Clinical trial information: NCT04116437. Research Sponsor: BeiGene.