KW-0761 (Mogamulizumab)和 MK-3475 (Pembrolizumab)联合治疗复发/难治性弥漫性大 B 细胞淋巴瘤的 I/II 期研究

A phase I and randomized phase II etctn study of KW-0761 (Mogamulizumab) and MK-3475 (Pembrolizumab) in relapsed and refractory diffuse large B-cell lymphoma

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背景：弥漫性大 B 细胞淋巴瘤（DLBCL）通过抑制 B2M 和 CD58 途径以及上调 PD-1 配体逃避宿主的免疫反应。然而，阻断 PD-1 的治疗结果令人失望，一种可能的机制是肿瘤内调节性 T 细胞（Tregs）的募集，Tregs 抑制了抗肿瘤免疫，同时抑制了 NK 细胞的细胞毒性作用。用靶向 Tregs 的 CCR4 抗体药物 mogamulizumab（KW-0761）代表了一种克服这种耐药性的分子策略。mogamulizumab 已与 pembrolizumab（MK-3475）联合用于患有实体恶性肿瘤的患者中，可安全施用，并可能促进淋巴瘤中 CD8 T 细胞依赖性效应和 NK 细胞依赖性细胞毒性。

方法：这是一项多中心 NIH-ETCTN Ib 期/II 期随机研究。I 期将评估 mogamulizumab 联合 pembrolizumab 治疗 R/R DLBCL 患者的安全性和

耐受性，并确定推荐的 II 期剂量（RP2D）。采用传统的 3 + 3 设计，在 21 天周期的第 1 天开始静脉注射 pembrolizumab 200mg，在第 1、8、15 天静脉注射 mogamulizumab 1mg / kg，然后每 21 天静脉注射 1.5mg / kg。第二阶段将通过 PFS（主要终点）、ORR 和 CR（次要终点）评估该双联方案的疗效。这将是一项允许交叉的 1：1 随机研究，将其与单药 pembrolizumab 进行比较。相关研究将评估肿瘤浸润性 CD8 T 细胞和 NK 细胞与治疗缓解率、B2M 和 CD58 中的体细胞突变以及在 DLBCL 细胞上 MHC-1 表达的相关性。 外周血中循环免疫细胞的功能表征以及促炎和抗炎细胞因子的测量将用于评估 Treg 和循环 T 细胞的水平、激活状态和效应功能。纳入标准包括可测量的疾病，≥2 个既往疗法，包括或不适合自体干细胞移植，ECOG≤2 和正常器官储备功能。排除标准是既往或计划进行的异源干细胞移植，先前使用过抗 PD-1 / PD-L1 / CTLA4 抗体的治疗，先前存在自身免疫性疾病或淋巴瘤累及中枢神经系统。该研究旨在第一阶段招募最多 12 名患者，在第二阶段招募最多 58 名患者，并且可以在任何 ETCTN 参与地点开放。迄今为止，它已经在两个地点开放，并且正在为第一阶段招募第一批患者。临床试验信息：NCT03309878

原文摘要：

Abstract

Background: Diffuse large B-cell lymphoma (DLBCL) escapes host immune responses via inhibition of the B2M and CD58 pathways and

upregulation of PD-1 ligands. However, treatment results with PD-1 blockade have been disappointing. One potential mechanism is the recruitment of intra-tumoral regulatory T-cells (Tregs) which suppress anti-tumor immunity and inhibit NK cell cytotoxicity. Targeting regulatory T cells with the CCR4 antibody mogamulizumab (KW-0761) represents a molecularly informed strategy to overcome this resistance. Mogamulizumab has been safely administered in combination with pembrolizumab (MK-3475) in patients with solid malignancies and may promote CD8 T-cell dependent effector and NK cell-dependent cytotoxicity in lymphomas.

Methods: This is a multi-center NIH-ETCTN phase Ib/randomized phase II study. The phase I will evaluate the safety and tolerability of mogamulizumab in combination with pembrolizumab in patients with R/R DLBCL and determine the recommended phase II dose (RP2D). A traditional 3+3 design with a starting dose of pembrolizumab 200mg IV on day 1 of a 21-day cycle and mogamulizumab 1mg/kg IV on days 1, 8, 15 and then 1.5 mg/kg IV every 21 days. The phase II will evaluate the efficacy of the combination by PFS (primary endpoint) ORR and CR (secondary endpoints). This will be a randomized 1:1 study with allowed crossover, comparing the combination to single agent pembrolizumab Correlative studies will evaluate the association of tumor infiltrating CD8 and NK cells with response to treatment, somatic mutations in B2M and

CD58 and with MHC-I expression on DLBCL cells. Functional characterization of circulating immune cells in the peripheral blood and measurement of pro and anti-inflammatory cytokines will be used to assess the levels, activation status and effector function of Tregs and circulating T cells. Inclusion criteria include measurable disease, ⩾2 prior lines of therapy including or ineligible for autologous stem cell transplant, ECOG ⩽ 2 and normal organ function. Prior or planned allogeneic stem cell transplant, as well as prior treatment with an anti PD-1/PD-L1/CTLA4 antibody, preexisting autoimmune disease or CNS involvement by lymphoma are exclusion criteria. The study aims to enroll up to 12 patients on the phase I and up to 58 patients on the phase II and can be opened at any ETCTN participating site. To date it has been opened at two sites and is accruing the first patients for the phase I portion. Clinical trial information: NCT03309878

参考文献：

Joffe E, Vardhana SA, Kumar A, Abedi M, Hoeg R, Sharon E and Younes A: A phase I and randomized phase II etctn study of KW-0761 (Mogamulizumab) and MK-3475 (Pembrolizumab) in relapsed and refractory diffuse large B-cell lymphoma. J CLIN ONCOL 38: S8072, 2020.