PD-1 抗体联合表观遗传治疗，用于既往经多次治疗的外周 T 细胞淋巴瘤(PTCL)和皮肤 T 细胞淋巴瘤（CTCL)患者是有效且安全的

The Integration of PD1 blockade with epigenetic therapy is highly active and safe in heavily treated patients with T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL).

Enrica Marchi, Helen Ma, Francesca Montanari, Ahmed Sawas, Jennifer K Lue, Changchun Deng, Kareema T Whitfield, Sandra Klein, Luigi Scotto, Salvia Sanjay Jain, John Lister, Nora N Benanni, Mark A Francescone, Wonseog S Kim, Pier Luigi Zinzani, Owen A. O'Connor

背景：我们的研究小组已证明，表观遗传修饰剂的联合治疗在 PTCL 的临床前模型中产生有效的协同作用，并诱导癌症睾丸抗原的表达。这提示表观遗传修饰剂与免疫检查点抑制剂 pembrolizumab 联合治疗可能发挥一定作用。

方法：这是一项 pembrolizumab 联合普拉曲沙（双联，A 组），或 pembrolizumab 联合普拉曲沙与地西他滨（三联，B 组），或联合地西他滨（双联，C 组），治疗复发难治性 PTCL 和 CTCL 的 1b 期研究。在药物三联组（B 组）中应用标准的 3 + 3 剂量递增，而在双联组（A

和 C 组）中，在毒性的情况下应用递减剂量。药代动力学和药效学研究正在进行中。

结果：我们总共治疗了 12 例患者，每组中有 4 例患者。接受至少一剂药物的所有患者的毒性均可评估。每组都有剂量限制性毒性（DLT），包括长期的 3 级血小板减少症（A 组），发热性中性粒细胞减少症（B 组），3 级低钠血症和皮疹（C 组）。未发生与治疗有关的死亡。在分析中，12 例患者中有 6 例患者可评价疗效，其中 1 例患者完全缓解，2 例部分缓解，1 例病情稳定，2 例病情进展。有趣的是，所有的缓解都出现在普拉曲沙+地西他滨+ pembrolizumab 的三联组合中。下表总结了患者的特征、毒性和缓解率。

结论：初步临床数据表明，pembrolizumab 与表观遗传药物的整合是安全的，并且在 PTCL 和 CTCL 患者中显示出令人鼓舞的缓解疗效。临床试验信息：03240211

Median age, years (range)	65 (38 - 77)
Sex	
Male	6
Female	6
Race	
White/Non-Hispanic	6
White/Hispanic	1
Black	3
Asian	2
Histology	
PTCL, NOS	5
AITL	3
Mycosis Fungoides	2
ATLL	1
Sezary Syndrome	1
Stage at diagnosis	
I	1
II	1
III	4
IV	5
Tumor Stage	1
Median number of prior therapies (range)	2 (1-5)
Adverse Event, Grade 3/4, n (%)	
Thrombocytopenia	1
Neutropenia	2
Fatigue	1
Vomiting	1
Hyponatremia	1
Rash	1
	Evaluable/Total Patients (Best Response)
Arm A	2/4 (POD, POD)
Arm B	2/4 (CR, PR)
Arm C	1/4 (SD)

上图：患者特征，毒性和反应（n = 12）

原文摘要

Abstract

Background: Our group has demonstrated that combinations of epigenetic modifiers produce potent synergy in pre-clinical models of PTCL and induce the expression of cancer testis antigen, suggesting a role in the addition of the immune-checkpoint inhibitor, pembrolizumab.

Methods: This is a phase 1b study of pembrolizumab combined with

pralatrexate alone (Arm A), with pralatrexate + decitabine (Arm B), or decitabine alone (Arm C) in patients with relapsed and refractory PTCL and CTCL. A standard 3+3 dose-escalation is applied in the triplet Arm (Arm B) while in the doublet Arms (A and C) de-escalation is applied in case of toxicity. Pharmacokinetic and pharmacodynamic studies are ongoing.

Results: We treated a total of 12 patients with 4 patients in each Arm. All patients that received at least one dose of drug were evaluable for toxicity. There was a dose limiting toxicity (DLT) in each arm including prolonged grade 3 thrombocytopenia (Arm A), febrile neutropenia (Arm B), grade 3 hyponatremia, and rash (Arm C). There were no treatment-related deaths. Six patients out of 12 were evaluable for response at the time of this analysis. One patient achieved a complete remission, 2 had partial remission, 1 had stable disease, and 2 experienced progression of disease. Interestingly, all of the responses were seen in the triple combination of pralatrexate, decitabine, and pembrolizumab. Table summarizes the patient characteristics, toxicities, and response rates.

Conclusions: These preliminary clinical data suggest that the integration of pembrolizumab on an epigenetic backbone is safe and demonstrates encouraging responses in patient with PTCL and CTCL. Clinical trial information: 03240211

参考文献：

Marchi E, Ma H, Montanari F, Sawas A, Lue JK, Deng C, Whitfield KT, Klein S, Scotto L and Jain SS, et al: The Integration of PD1 blockade with epigenetic therapy is highly active and safe in heavily treated patients with T-cell lymphoma (PTCL) and cutaneous T-cell lymphoma (CTCL). J CLIN ONCOL 38: 8049, 2020.