ORIENT -4：Sintilimab 用于复发/难治性(r/r)结外 NK/T 细胞淋巴瘤(ENKTL)的多中心、单臂 II 期长期随访研究

Sintilimab for relapsed/refractory (r/r) extranodal NK/T cell lymphoma (ENKTL): Extended follow-up on the multicenter, single-arm phase II trail (ORIENT-4).

Jianyong Li, Rong Tao, Lei Fan, Yongping Song, Yu Hu, Wei Zhang, Yafei Wang, Linxinyu Xu, Xing Sun, Hui Zhou

背景：r / r ENKTL 患者在以门冬酰胺酶为基础的治疗方案失败后的预后较差。EBV 感染诱导的 PD-L1 过度表达是 ENKTL 逃避免疫监视的潜在机制之一。在对 ORIENT-4 研究进行初步分析后，全人源抗 PD-1 单克隆抗体 Sintilimab 已被证明在 r / r ENKTL 中具有疗效。在这项研究中，我们报道了延长随访后的疗效和安全性更新数据。

方法：入组经病理确诊为 r / r ENKTL 的患者，给予 Sintilimab 200 mg IV Q3W，直至疾病进展（PD）、死亡、出现不可接受的毒性或退出研究。允许超出 PD 的治疗。通过 PET-CT 和 CT / MRI 对比评估肿瘤缓解疗效。主要终点是根据 Lugano 2014 得出的客观缓解率（ORR）。此分析的数据截止日期为 2020 年 1 月 17 日。

结果：共有 28 位患者入组并接受治疗。中位随访为 26.9 个月（范围 23.3 至 28.6），中位治疗持续时间为 24.15 个月（范围 1.4 至 28.7）。根据 Lugano 2014 标准，20 例 PD 的患者中，19/20（95%）接受了超过 PD 的治疗。未达到中位 OS，24 个月 OS 率为 78.6%（95%CI，58.4%至 89.8%）。ORR 为 67.9％（95％CI，47.6％至 84.1％），其中 4 例在接受治疗前出现 PD。DCR 为 85.7％，其中 5 例在 SD 或缓解前出现 PD。中位缓解持续时间为 4.1 个月（范围从 1.9 到 15.2+）。治疗后，平均 EQ-5D-5L VAS 分数（从 79.3 到 90.8），EQ-5D-5L 指数值（从 0.8 到 0.9）和 EORTC QLQ-C30（从 70.5 到 87.3）均增加。发生 28 例（100％）任何级别的与治疗相关的不良事件（TRAE）；发生 11 例（39.4％）3 级与治疗相关的不良事件，最常见的是淋巴细胞计数减少（2 [7.1％]）和糖尿病（2 [7.1％]）；未发生 4-5 级的 TRAE。

结论：除了令人鼓舞的肿瘤缓解外，Sintilimab 还显示出长期的临床获益，24 个月 OS 率为 78.6%，长期随访后发现其具有良好的长期安全性。考虑到超过 PD 的高治疗率（95％），Lugano 2014 可能不是评估抗 PD-1 抗体在 r / r ENKTL 中疗效的合适标准。临床试验信息：NCT03228836

原文摘要：

Abstract

Background: Patients with r/r ENKTL have a poor prognosis after failing

an asparaginase-based regimen. The overexpression of PD-L1 induced by EBV infection is a potential mechanism for ENKTL to avert immune surveillance. Sintilimab, a fully human anti-PD-1 monoclonal antibody, has demonstrated efficacy in r/r ENKTL after the primary analysis of the ORIENT-4 study. Here, we report the updated efficacy and safety results with extended follow-up.

Methods: Patients with pathologically confirmed r/r ENKTL were enrolled. Sintilimab was given 200 mg IV Q3W, until PD, death, unacceptable toxicity, or withdrawal from the study. Treatment beyond PD is allowed. Tumor response evaluation was performed by both PET-CT and CT/MRI with contrast. The primary endpoint was objective response rate per Lugano 2014. Data cut-off date for this analysis was Jan 17, 2020.

Results: A total of 28 patient were enrolled and treated. With a median follow-up of 26.9 months (range, 23.3 to 28.6), the median treatment duration was 24.15 months (range, 1.4 to 28.7). Of 20 patients with progressive disease (PD) by investigator per Lugano 2014 criteria, 19/20 (95%) patients received treatment beyond PD. The median OS has not been reached and 24-month OS rate was 78.6% (95% CI, 58.4% to 89.8%). ORR was 67.9% (95% CI, 47.6% to 84.1%), including 4 pts who experienced PD prior to having a response. DCR was 85.7%, including 5 pts who experienced PD before SD or response. Median duration of

response was 4.1 months (range, 1.9 to 15.2+). After treatment, the mean EQ-5D-5L VAS Score (from 79.3 to 90.8), EQ-5D-5L Index Value (from 0.8 to 0.9) and EORTC QLQ-C30 (from 70.5 to 87.3) were all increased. The Treatment-related adverse events (TRAEs) of any grade occurred in 28 (100%) pts; grade 3 occurred in 11 (39.4%) pts, most commonly, decreased lymphocyte count (2 [7.1%]) and diabetes (2 [7.1%]); no grade 4-5 TRAE.

Conclusions: In addition to an encourage response, sintilimab also demonstrated long-term clinical benefit, with 78.6% of 24-month OS rate, and favorable long-term safety profile after extended follow-up. Considering the high rate (95%) of treatment beyond PD, Lugano 2014 may not be a suitable criteria for evaluating the efficacy of anti-PD-1 antibody in r/r ENKTL. Clinical trial information: NCT03228836

参考文献：

Li J, Tao R, Fan L, Song Y, Hu Y, Zhang W, Wang Y, Xu L, Sun X and Zhou H: Sintilimab for relapsed/refractory (r/r) extranodal NK/T cell lymphoma (ENKTL): Extended follow-up on the multicenter, single-arm phase II trail (ORIENT-4). J CLIN ONCOL 38: 8050, 2020.