受新型冠状病毒肺炎疫情影响，作为全球肿瘤领域的年度盛会，今年的美国临床肿瘤学会(ASCO)年会改为线上模式，于 2020 年 5 月 29 日顺利召开。2020 ASCO 共公布了 2215 项研究摘要，其中有哪些值得关注的亮点？大医编将以专题的形式，定期推送，带大家一览为快！

淋巴瘤专题-抗 PD-1 治疗

5 月 13 日，美国临床肿瘤学会（ASCO®）2020 年年会正式拉开帷幕，在线公布了研究摘要。近年来抗 PD-1 免疫治疗在淋巴瘤治疗领域惊喜不断，开启了淋巴瘤免疫治疗的新篇章。我国抗 PD-1 抗体药物的研发上市也紧追不舍，多个国产抗 PD-1 创新药喜讯频传。百济神州自主研发的抗 PD-1 抗体药替雷利珠单抗（商品名：百泽安®），已于 2019 年 12 月 27 日正式通过国家药品监督管理局（NMPA）批准，用于治疗至少经过二线系统化疗的复发或难治性经典型霍奇金淋巴瘤(R/R cHL)患者。今年的 ASCO 摘要中又有哪些值得关注的临床研究？现整理报道如下。

Alexander I 期研究：AUTO3—— 首个 CD19 / 22 双靶点 CAR-T 细胞疗法，联合 pembrolizumab 治疗复发/难治性（r / r）弥漫性大 B 细胞淋巴瘤（DLBCL)患者

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Phase I Alexander study of AUTO3, the first CD19/22 dual targeting CAR T cell therapy, with pembrolizumab in patients with relapsed/refractory (r/r) DLBCL

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背景：抗 CD19 的 CAR T 细胞对 r / r DLBCL 患者有效，但因 CD19 丢失或 PDL1 上调引起的肿瘤复发较为常见。AUTO3 是靶向 CD19 / 22 的 CAR T，具有有限的 PD-1 阻断作用。在这项研究中，我们评估了 AUTO3 的安全性和有效性。

方法：我们构建了双顺反子逆转录病毒载体，该载体编码带有人源化结合剂的抗 CD19（OX40 共刺激物）和抗 CD22（41BB 共刺激物）CAR。使用的细胞是在半自动和封闭环境中制造（CliniMACS Prodigy）。入组标准：r / r DLBCL（NOS）或转化（tDLBCL）的患者年龄≥18 岁；ECOG <2，有足够的器官储备功能。在 AUTO3 治疗之前，经 Flu / Cy 方案清除淋巴细胞。允许桥接治疗。给予 50、150 和 450 x 10^6 3 个剂量 CAR T 细胞。从第 14 天开始，患者只接受 AUTO3 或接受 3 次剂量的 pembrolizumab 200mg q3wk（方案 A）；或第 1 天开始接受单次剂量的 pembrolizumab 200mg（方案 B）。主要终点是 DLT 发生的频率和 3-5 级不良事件（AE），次要终点包括客观缓解率 ORR，完全缓解率 CRR 和生物标志物。

结果：截至 2020 年 1 月 21 日，有 28 例患者接受了白细胞分离术；其中 27 例成功，1 例正在进行，19 例接受了 AUTO3 治疗。中位年龄为 57 岁（28-71），先前治疗方案数目的中位数为 3（2-10）。89％为难治性病例，74％为 DLBCL NOS，26％为 tDLBCL。将 pembrolizumab 方案 A 和方案 B 的剂量从 50 个增加到 450 x 10^6 个细胞，没有发生 DLT。> 3 即的治疗性 AE 发生率> 15％，为中性粒细胞减少症（89％），血小板减少症（58％），贫血（47％），发热性中性粒细胞减少症（16％）和低血磷（16％）。在所有剂量水平上，有 0％的初次输注 sCRS 和 5％的严重神经毒性（sNT）（1/19），均已得到处理。在剂量>50×10^6 个细胞时没有发生 SCR 并且没有任何等级的神经毒性。评估了 18 名

患者的疗效。在剂量> 50 x 10^6 的 11 例患者中，ORR 和 CRR 分别为 64％和 55％，所有 CR 均在持续中（1-12 个月）。pembrolizumab 方案 B 的 3 例患者中 2 例在用 450 x 10^6 个细胞时达到了 CR。后续将介绍其他患者和更长的随访时间以及生物标记物。

结论：剂量大于 50 x 10^6 CAR T 细胞的 AUTO3 联用 pembrolizumab 可诱导完全缓解，未出现严重的 CRS 或任何级别的神经毒性。临床试验信息：NCT03287817

原文摘要：

Abstract

Background: CD19 directed CAR T cells are effective in patients with r/r DLBCL, however relapses due to CD19 loss or PDL1 upregulation are common. In this study, we evaluate the safety and efficacy of AUTO3, a CAR T targeting CD19/22 with limited duration of PD-1 blockade.

Methods: We constructed a bicistronic retroviral vector encoding both an anti-CD19 (OX40 co-stim) and an anti-CD22 (41BB co-stim) CAR with humanized binders. The cell product was manufactured in a semi-automated and closed process using CliniMACS Prodigy. Patients (≥ 18 years) with r/r DLBCL (NOS) or transformed (tDLBCL); ECOG <2, adequate organ function are eligible. Lymphodepletion was Flu/Cy prior to AUTO3. Bridging therapy was allowed. The three dose levels explored

are 50, 150, and 450 x 10^^{6} CAR T cells. Patients received AUTO3 alone, or with 3 doses of pembrolizumab (pem) 200 mg q 3 wks starting on D14 (regimen A), or with a single dose of pem 200 mg on D-1 (regimen B). The primary endpoint is frequency of DLTs and grade (G) 3-5 adverse events (AE) and secondary endpoints included ORR, CRR, and biomarkers.

Results: As of Jan 21, 2020, 28 patients underwent leukapheresis, 27 successfully manufactured, 1 being manufactured, and 19 patients treated with AUTO3. The median age was 57 (28 - 71) and median number of prior therapies was 3 (2 - 10). 89% had refractory disease, 74% were DLBCL NOS, and 26% were tDLBCL. Dose escalation from 50 to 450 x 10^6 cells with pem regimen A and B have been completed without DLTs. G > 3 treatment emergent AEs that occurred > 15% were neutropenia (89%), thrombocytopenia (58%), anemia (47%), febrile neutropenia (16%), and hypophosphataemia (16%). Across all dose levels, there were 0% sCRS with primary infusion and 5% severe neurotoxicity (sNT) (1/19), which resolved. There were no cases of sCRS and no neurotoxicity of any grade at > 50 x 10^6 cells. Eighteen patients were evaluable for efficacy. Among the 11 treated at dose > 50 x 10^6, the ORR and CRR were 64% and 55%, and all CRs are ongoing (1-12 mth). Two out of 3 patients achieved CR at 450 x 10^6 cells on pem regimen B. Additional patients and longer follow up, as well as biomarkers, will be presented.

Conclusions: AUTO3 at > 50 x 10^6 CAR T cells with pembrolizumab induces CRs without severe CRS or neurotoxicities of any grade. Clinical trial information: NCT03287817

参考文献：

Osborne W, Marzolini M, Tholouli E, Ramakrishnan A, Bachier CR, McSweeney PA, Irvine D, Zhang M, Al-Hajj MA and Pule M, et al: Phase I Alexander study of AUTO3, the first CD19/22 dual targeting CAR T cell therapy, with pembrolizumab in patients with relapsed/refractory (r/r) DLBCL. J CLIN ONCOL 38: 8001, 2020.