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# PD-1单抗在淋巴瘤中的研究

# AUTO3 Alexander I期研究，首个双重靶向CD19 / 22的CAR T细胞疗法，联合pembrolizumab治疗复发/难治性（r / r）DLBCL患者。



**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.** *First Author: Wendy Osborne, Newcastle, Newcastle, United Kingdom*

**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. Research Sponsor: Autolus Therapeutics.

# KEYNOTE-204:pembrolizumab (pembro)与brentuximab vedotin (BV)在复发或难治性经典霍奇金淋巴瘤(R/R cHL)中的随机、开放、III期研究。



**KEYNOTE-204: Randomized, open-label, phase III study of pembrolizumab (pembro) versus brentuximab vedotin (BV) in relapsed or refractory classic Hodgkin lymphoma (R/R cHL).** *First Author: John Kuruvilla, Princess Margaret Cancer Centre, Toronto, ON, Canada*

**Background:** PD-1 blockade via pembro monotherapy showed antitumor activity in R/R cHL. KEYNOTE-204 (NCT02684292) was a randomized, international, open-label, phase III study of pembro vs BV in R/R cHL. **Methods:** Patients (pts) were aged ≥18 y, were post−autologous stem cell transplant (auto-SCT) or ineligible for auto-SCT, and had measurable disease and ECOG PS 0 or 1. BV-naive and BV-exposed pts were eligible. Pts were randomized 1:1 to pembro 200 mg IV Q3W or BV 1.8 mg/kg IV Q3W and stratified by prior auto-SCT (yes vs no) and status after 1L therapy (primary refractory vs relapsed <12 mo vs relapsed ≥12 mo after end of 1L therapy). Primary end points: PFS by blinded independent central review (BICR) per International Working Group (IWG) criteria including clinical and imaging data after auto-SCT or allogeneic SCT (allo-SCT) and OS. Key secondary end points: PFS excluding clinical and imaging data after auto-SCT or allo-SCT (PFS-secondary), and ORR by BICR per IWG, PFS by investigator review per IWG, and safety. Exploratory end point: DOR by BICR per IWG. **Results:** 304 pts were randomized and 300 were treated (148, pembro; 152, BV); 256 discontinued. Median (range) follow-up: 24.7 (0.6-42.3) mo. 15 pts were BV exposed. Median (range) time on treatment was 305.0 (1-814) and 146.5 (1-794) days with pembro and BV, respectively. Statistically significant improvement was observed with pembro vs BV for primary PFS analysis (HR 0.65 [95% CI 0.48-0.88; $P$ =0.00271]; median 13.2 vs 8.3 mo); 12-mo PFS rates were 53.9% vs 35.6%, respectively. Benefit was observed in all subgroups tested, including pts with no auto-SCT (HR=0.61), primary refractory disease (HR=0.52), prior BV (HR=0.34) and BV naive (HR=0.67). Significant improvement in PFS-secondary was observed with pembro vs BV (HR 0.62 [95% CI 0.46-0.85]; median 12.6 vs 8.2 mo). Per investigator assessment, PFS was longer with pembro vs BV (HR 0.49 [95% CI 0.36-0.67]; median 19.2 vs 8.2 mo). ORR was 65.6% for pembro and 54.2% for BV; CR rates were 24.5% and 24.2%, respectively. Median (range) DOR was 20.7 mo (0.0+ to 33.2+) for pembro and 13.8 mo (0.0+ to 33.9+) for BV. Grade 3-5 TRAEs: 19.6% of pts with pembro and 25.0% with BV. One death due to TRAE occurred with pembro (pneumonia). **Conclusions:** In pts with R/R cHL, pembro was superior to BV and demonstrated statistically significant and clinically meaningful improvement in PFS across all subgroups, with safety consistent with previous reports. Pembro monotherapy should be standard of care for this pt population with R/R/cHL. Clinical trial information: NCT02684292. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

# 新型抗PD-1单克隆抗体Gls-010，用于中国复发或难治性经典霍奇金淋巴瘤患者:II期临床试验的初步结果。



**Gls-010, a novel anti-PD-1 mAb in Chinese patients with relapsed or refractory classical Hodgkin lymphoma: Preliminary impressive result of a phase II clinical trial.** *First Author: Yuqin Song, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), the Department of Lymphoma, Peking University Cancer Hospital & Institute, Beijing, China*

**Background:** classical Hodgkin lymphoma (cHL) are characterized by genetic alterations at the 9p24·1 locus and PD-L1 ligand overexpression. GLS-010 is a novel fully human anti-PD-1 mAb and exhibited favorable result in previous Phase I study. This multi-center, single-arm Phase II clinical trial is aimed to further evaluate the safety and efficacy profile of GLS-010 in Chinese patients (pts) with relapsed or refractory cHL. **Methods:** All pts enrolled received GLS-010 240mg every 2 weeks until disease progression, death, unacceptable toxicity or withdraw from the study. The primary endpoint was objective response rate (ORR) by independent review committee (IRC) per Lugona 2014. Adverse events (AEs) were graded by NCI CTCAE v4.03. **Results:** 85 pts with relapsed or refractory cHL who had received at least 2 lines of prior systemic chemotherapies were enrolled and treated. As of August 2 2019, data cutoff, pts received a median of 8 treatment cycles (1 cycle include 2 injections), with 12 pts discontinued and 73 pts were still in treatment. At a median follow-up of 6.57 months, an ORR was reported in 78 of 85 patients (91.76%, 95%CI, 83.77-96.62), by an IRC assessment, including 30(35.3%) pts with a complete response (CR) and 48 pts (56.5%) with a partial response (PR). Median duration of response (DoR) and progression free survival (PFS) were not reached yet. Treatment-related adverse events (TRAEs) of any grade occurred in 77 (90.6%) of 85 patients, most of which were Grade 1-2.The most common TRAEs were fever (26/85, 30.6%), neutrophil count decreased (16/85, 18.82%), white blood cell count decreased (15/85, 17.65%). ≥ Grade 3 TRAEs occurred in 23 (27.06%) pts, most commonly, hepatic function abnormal (5/85, 5.88%), hyperuricaemia (4/85, 4.71%). **Conclusions:** GLS-010 showed impressive anti-tumor activity (ORR = 91.96%) and manageable safety profile in Chinese patients with relapsed or refractory cHL, which could be a new safe and effective treatment option in this setting. Clinical trial information: NCT03655483. Research Sponsor: Guangzhou Gloria Biosciences Co,. Ltd.

# Sintilimab治疗复发/难治性经典霍奇金淋巴瘤:多中心、单臂II期定位-1研究的长期随访研究



**Sintilimab for relapsed/refractory classical Hodgkin's lymphoma: Long-term follow-up on the multicenter, single-arm phase II ORIENT-1 study.** *First Author: Hang Su, The Fifth Medical Center, Chinese PLA General Hospital, Beijing, China*

**Background:** Sintilimab, a programmed death-1 checkpoint inhibitor, has demonstrated efficacy in relapsed/refractory cHL after the primary analysis of the ORIENT-1 study. Here, we report the updated safety and efficacy profile after long-term follow-up. **Methods:** ORIENT-1 is a multicenter, single-arm, phase II study in China. Classical Hodgkin's lymphoma patients who had failed ≥2 lines of systemic therapy, including autologous hematopoietic stem cell transplantation (HSCT) were enrolled. Sintilimab, 200 mg IV was given every 3 weeks, until disease progression, death, unacceptable toxicity, or withdrawal from study. The primary endpoint objective response rate (ORR) by an independent radiological review committee (IRRC) per IWG 2007 has been reported before. The progression free survival (PFS) by IRRC follow-up data are reported herein. **Results:** 96 patients were treated. As of the data cutoff on 30 Sep, 2019, 57.3 % patients complete two-year treatment, with a median follow-up of 26.7 months. The median duration of treatment was 24.1 months (range: 0.7 to 24.8). Of 49 patients with progressive disease (PD) by investigator, 39/49 (79.6%) patients received treatment beyond PD, with a median treatment duration after PD of 8.0 months (range: 1.4 to 20.8). The median PFS was 18.6 months (95%CI: 14.4 to 22.3). Median overall survival has not been reached. Two-year OS rate was 96.3% (95%CI: 88.9% to 98.8%). The treatment-related adverse event (TRAE) was reported in 92/96 (95.8%) patients, most (71/96, 74.0%) of which were grade 1-2. The most common grade 3 or 4 TRAEs were pyrexia (3/96, 3.1%), lipase increased (3/96, 3.1%) and lymphocyte decreased (3/96, 3.1%). **Conclusions:** The results from long-term follow-up showed that, in addition to a high rate of response, sintilimab also demonstrated durable efficacy and favorable long-term safety profile. Considering the high rate (nearly 80%) of treatment beyond PD, IWG 2007 which was used to evaluate PFS may not be a suitable criteria for evaluating the efficacy of anti-PD-1 antibody in cHL. Further investigation and analysis are required. Clinical trial information: NCT03114683. Research Sponsor: Innovent Biologics, Inc., China National Major Project for New Drug Innovation (2017ZX09304015 and 2018ZX09301014009) and CAMS Innovation Fund for Medical Sciences (CIFMS) (2016-I2M-1-001)

抗PD1抗体药物联合表观遗传学药物治疗，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).** *First Author: Enrica Marchi, Center for Lymphoid Malignancies, Columbia University Medical Center, New York, NY*

**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. Research Sponsor: Merck.

**Patient characteristics, toxicities and responses (n = 12).**

| | |
|---|---|
| **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) |

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

8050 Poster Session (Board #383), Fri, 8:00 AM-11:00 AM

**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).** *First Author: Jianyong Li, Jiangsu Province Hospital, Nanjing, China*

**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. Research Sponsor: Innovent Biologics, Inc.

# 青少年和年轻人（AYA）晚期经典霍奇金淋巴瘤的组间协作研究：SWOG S1826.

**TPS8067** **Poster Session (Board #400), Fri, 8:00 AM-11:00 AM**

**An intergroup collaboration for advanced stage classical Hodgkin lymphoma (cHL) in adolescents and young adults (AYA): SWOG S1826.** *First Author: Sharon M. Castellino, Emory University, Aflac Cancer and Blood Disorders Center, Children's Healthcare of Atlanta, Atlanta, GA*

**Background:** Treatment for pediatric cHL varies considerably from that in adult cHL. Hence there are gaps in risk prediction and optimal therapy for de-novo advanced stage disease across the adolescent and young adult (AYA) age spectrum. Early access to novel agents for AYA could be facilitated via collaboration with adult research groups through the U.S. National Cancer Institute's National Clinical Trials Network (NCTN). The PD-1 inhibitor Nivolumab (Nivo) has safety and efficacy in relapsed and refractory disease in children and adults, but has not been evaluated in de-novo disease to date. **Methods:** North American cooperative group lymphoma chairs, Cancer Therapy Evaluation Program (CTEP) representatives and patient advocates met to establish consensus on the comparison arms and study design, based on recent historical approaches across adult and pediatric groups. Study champions were identified across North American cooperative groups and include expertise in imaging, radiation oncology, biology and patient-reported outcomes. A therapeutic study was designed with the primary aim being to compare progression-free survival with novel targeted agents in advanced stage cHL. S1826 (NCT03907488), led by SWOG Cancer Research Network, opened to accrual in July 2019. Eligibility criteria include age $>$ 12 years, and Stage III or IV cHL. Patients are randomized (1:1) to 6 cycles of either Nivo-Adriamycin, Vinblastine, Dacarbazine (AVD) or Brentuximab vedotin (Bv)-AVD. Enrollment is stratified by age, baseline International Prognostic Score, and provider intent to use involved site radiation therapy (ISRT). Protocol-prescribed ISRT is response-adapted, based on end of therapy imaging. The primary endpoint is a comparison of progression-free survival between arms. Secondary clinical endpoints include comparison of: overall survival, metabolic response at the end of therapy, physician-reported adverse events, patient-reported adverse events, and health-related quality of life (overall, and specific to fatigue and neuropathy). This unique intergroup collaboration demonstrates the process and the feasibility of consensus study designs toward early adoption of targeted therapies and harmonization of treatment approaches for AYA populations. Clinical trial information: NCT03907488. Research Sponsor: U.S. National Institutes of Health.

# KW-0761 (Mogamulizumab)和MK-3475 (Pembrolizumab)在复发、难治性弥漫性大b细胞淋巴瘤中的I期和随机II期etctn研究。

TPS8072 Poster Session (Board #405), Fri, 8:00 AM-11:00 AM

**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.** *First Author: Erel Joffe, Memorial Sloan Kettering Cancer Center, New York, NY*

**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. Research Sponsor: U.S. National Institutes of Health.