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on non-Hodgkin lymphoma

Survival with axicabtagene ciloleucel in large B-cell lymphoma

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Pembrolizumab in relapsed or refractory primary mediastinal large B-cell lymphoma: final analysis of KEYNOTE-170

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Nature Medicine, 2023 July; 29(7):1710–7

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The Lancet Haematology, 2023 May; 10(5):e346–58

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Journal of Clinical Oncology, 2023 June 1; 41(16):3032–41

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Journal of Clinical Oncology, 2023 May 20; 41(15):2718–23

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SURVIVAL WITH AXICABTAGENE CILOLEUCEL IN LARGE B-CELL LYMPHOMA

The New England Journal of Medicine, 2023 July 13; 389(2):148–57

AUTHORS: Westin JR, Oluwole OO, Kersten MJ, Miklos DB, Perales MA, Ghobadi A, Rapoport AP, Sureda A, Jacobson CA, Farooq U, van Meerten T, Ulrickson M, Elsawy M, Leslie LA, Chaganti S, Dickinson M, Dorritie K, Reagan PM, McGuirk J, Song KW, Riedell PA, Minnema MC, Yang Y, Vardhanabhuti S, Filosto S, Cheng P, Shahani SA, Schupp M, To C, Locke FL, for the ZUMA-7 investigators and Kite members
CENTRE FOR CORRESPONDENCE: University of Texas MD Anderson Cancer Center, Houston, Texas, USA

BACKGROUND & AIM: Axicabtagene ciloleucel (axi-cel) is an autologous, anti-CD19, chimeric antigen receptor T-cell therapy for patients with early relapsed or refractory large B cell lymphoma. The phase-3 ZUMA-7 trial compared the efficacy of axi-cel and standard care as second-line therapy for these patients and found that event-free survival was significantly longer with axi-cel. The aim of this study was to assess the effect of axi-cel on overall survival 5 years after randomization in the ZUMA-7 trial.

STUDY DESIGN: Randomized controlled phase-3 study.

ENDPOINTS: Overall survival, progression-free survival, treatment-related death.

METHOD: The ZUMA-7 trial included 359 adults with large B-cell lymphoma that had relapsed within 12 months of first-line chemotherapy or was refractory to first-line treatment: 180 were randomized to axi-cel as second-line therapy, while 179 received standard care. Standard care consisted of two or three cycles of chemoimmunotherapy followed, in responders, by high-dose chemotherapy with autologous stem cell transplantation. A prespecified primary overall survival analysis was conducted in the intention-to-treat population no later than 5 years after randomization.

RESULTS: At a median follow-up of 47.2 months, 82 patients in the axi-cel group and 95 in the standard-care group had died. In the intention-to-treat population, which included a high proportion of patients with primary refractory disease and other high-risk disease characteristics, axi-cel was associated with significantly longer overall survival than standard care: the median overall survival time was not reached in the axi-cel group compared with 31.1 months in the standard-care group (hazard ratio for death 0.73, 95% confidence interval 0.54–0.98; p=0.03 in a stratified two-sided log-rank test). The estimated 4-year overall survival rate in the axi-cel and standard-care groups was 54.6% and 46.0%, respectively. In addition, the median, investigator-assessed, progression-free survival time was 14.7 months with axi-cel versus 3.7 months with standard care (HR for progression or death 0.51, 95% CI 0.38–0.67). The estimated 4-year progression-free survival rates for axi-cel and standard care were 41.8% and 24.4%, respectively. There were no new treatment-related deaths since the initial event-free survival analysis.

CONCLUSION: In patients with early relapsed or refractory large B-cell lymphoma, second-line treatment with axicabtagene ciloleucel was associated with significantly longer overall survival than standard second-line chemoimmunotherapy and autologous stem-cell transplantation at a median follow-up of 47.2 months.

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PEMBROLIZUMAB IN RELAPSED OR REFRACTORY PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA:

FINAL ANALYSIS OF KEYNOTE-170

Blood, 2023 July 13; 142(2):141–5

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BACKGROUND & AIM: In the phase-2 KEYNOTE-170 trial, the programmed cell death-1 inhibitor pembrolizumab demonstrated substantial antitumour activity and acceptable safety in patients with relapsed or refractory primary mediastinal B-cell lymphoma (PMBCL) over a period of 2 years. The aim of this final analysis of the KEYNOTE-170 trial was to evaluate the efficacy and safety of pembrolizumab in patients with relapsed or refractory PMBCL over approximately 4 years of follow-up.

STUDY DESIGN: Final analysis of an open-label phase-2 trial.

ENDPOINTS: Objective response rate and adverse events (primary endpoints), response duration, progression-free survival, overall survival.

METHOD: The efficacy analysis of the KEYNOTE-170 trial involved 53 adults with relapsed or refractory PMBCL whose disease had progressed after ≥2 previous lines of therapy and who progressed after, or were ineligible for, autologous stem cell transplantation. All received pembrolizumab, 200 mg intravenously every 3 weeks, for up to 2 years. Treatment responses, survival and adverse events were monitored at regular intervals. Objective responses and progression-free survival were assessed using International Working Group 2007 criteria.

RESULTS: After a median follow-up of 48.7 months (range 41.2–56.2 months), the objective response rate based on investigator assessment was 41.5%: 20.8% of patients achieved a complete response and 20.8% had a partial response. Although the median response duration was not reached, the estimated response rate at 48 months was 80.6%. Among patients who had complete responses, the median time to a complete response was 2.7 months – none of these patients had disease progression by data cut-off or had received subsequent therapy or consolidation stem cell transplantation. Among all patients, the median progression-free and overall survival times were 4.3 months and 22.3 months, respectively, and the 4-year progression-free and overall survival rates were 33.0% and 45.3%, respectively. Overall, 56.6% of patients experienced treatment-related adverse events: the most common were neutropenia (18.9%), asthenia (9.4%) and hypothyroidism (7.5%). In particular, 22.6% experienced grade-3 or -4 treatment-related adverse events and 7.5% discontinued treatment due to these events. There were no grade-5 events or deaths related to treatment.

CONCLUSION: In the final analysis of the KEYNOTE-170 trial of pembrolizumab in heavily pretreated patients with relapsed or refractory primary mediastinal B-cell lymphoma, the estimated response rate at 48 months was 80.6% and the overall survival rate was 45.3%.

https://doi.org/10.1182/blood.2022019340

AXICABTAGENE CILOLEUCEL AS SECOND-LINE THERAPY IN LARGE B CELL LYMPHOMA INELIGIBLE FOR AUTOLOGOUS STEM CELL TRANSPLANTATION:

A PHASE 2 TRIAL

Nature Medicine, 2023 October; 29(10):2593–601

AUTHORS: Houot R, Bachy E, Cartron G, et al.
CENTRE FOR CORRESPONDENCE: Department of Hematology, University Hospital of Rennes, UMR U1236, INSERM, University of Rennes, French Blood Establishment, Rennes, France

BACKGROUND & AIM: A phase 3 trial demonstrated that CAR-T cell therapy with axicabtagene ciloleucel (axi-cel) was more effective than the standard of care for the second-line treatment of patients with high-risk, released/refractory (R/R) large B-cell lymphoma (LBCL) who were eligible for autologous stem-cell transplantation (ASCT). Event-free survival and overall survival were superior with axi-cel compared with standard of care. However, in clinical practice half of patients with R/R LBCL are not eligible for ASCT, and they generally have a poor prognosis with standard salvage chemoimmunotherapy. The aim of the current study was therefore to investigate the efficacy and safety of second-line axi-cel in patients with high-risk R/R LBCL considered ineligible for ASCT.

STUDY DESIGN: Phase 2, multicentre, open-label study.

ENDPOINTS: The primary endpoint was complete metabolic response at 3 months; secondary endpoints included objective response rate, progression-free survival, overall survival and safety.

METHOD: The study included 62 adults with R/R LBCL who were ineligible for ASCT but eligible for CAR-T cell therapy. Participants received a single axi-cel infusion and were followed up for 3 years. Complete metabolic response was assessed using the Lugano response criteria.

RESULTS: Among the 62 participants (median age 70 years, 24.2% female), most (98.4%) had an Eastern Cooperative Oncology Group performance status of 0 or 1, and most (83.9%) had a histological diagnosis of diffuse LBCL. Ineligibility for ASCT was due to older age, high haematopoietic cell transplantation-specific comorbidity index and/or previous ASCT. A complete metabolic response at 3 months after axi-cel infusion was achieved in 71.0% of participants (95% confidence interval 58.1% to 81.8%). The objective response rate at 3 months was 75.8% (95% CI 63.3% to 85.8%), while at 6 months 59.7% of patients still had a complete metabolic response. After a median follow-up of 12.0 months, the median progression-free survival was 11.8 months (95% CI 8.4 to not reached) and the median overall survival was not reached. The most common adverse event of grade 3 or higher was neutropenia (66.1%). Overall, 8.1% of patients experienced grade 3 to 4 cytokine release syndrome, and 14.5% experienced neurological events of grade 3 or 4. There were no unexpected toxicities.

CONCLUSIONS: A single axi-cel infusion had high anti-tumour activity and a manageable safety profile in patients with high-risk, R/R LBCL who were ineligible for ASCT, supporting its use as second-line therapy in this patient population.

https://doi.org/10.1038/s41591-023-02572-5

DETERMINANTS OF RESISTANCE TO ENGINEERED T CELL THERAPIES TARGETING CD19 IN LARGE B CELL LYMPHOMAS

Cancer Cell, 2023 January 9; 41(1):210–25.e5

AUTHORS: Sworder BJ, Kurtz DM, Alig SK, et al.
CENTRE FOR CORRESPONDENCE: Division of Oncology, Department of Medicine, Stanford University, Stanford, California, USA

BACKGROUND & AIM: Treatment with chimeric antigen receptor T cells that target CD19 (CAR19) on lymphoma cells is effective in patients with relapsed or refractory large B-cell lymphoma (LBCL) but over half will ultimately relapse. The mechanisms underlying resistance to treatment are not clear. The aim of this study was to identify determinants of resistance to CAR19 therapy in patients with relapsed or refractory LBCL by using a noninvasive technique that simultaneously assesses both tumour B-cell responses and anti-tumour T-cell dynamics during treatment.

STUDY DESIGN: Laboratory study.

ENDPOINT: Determinants of resistance to CAR19 therapy.

METHOD: The study involved 708 serial blood and tissue specimens from two independent cohorts of patients (n=65 and n=73, respectively) with relapsed or refractory LBCL who were treated with the CAR19 therapy axicabtagene ciloleucel. Samples were collected before treatment, after CAR19 infusion and at disease relapse. A novel tool was developed for simultaneous tumour and effector cell profiling that used the non-invasive integrated analysis of cell-free DNA (cfDNA) molecules to profile circulating tumour-derived cell-free DNA (ctDNA), CAR19-derived cell-free DNA (cfCAR19) from retroviral fragments and non-engineered T-cell receptor cfDNA levels at different time points. This enabled the integrated analysis of tumour- and effector-mediated factors that may determine CAR19 resistance.

RESULTS: A high pretreatment ctDNA level was significantly associated with shorter event-free survival (p=0.002). In addition, patients who had a ctDNA major molecular response 4 weeks after CAR19 therapy had significantly longer event-free survival (p<0.0001). Resistance to CAR19 therapy was associated with alterations in multiple classes of genes, including mutations in genes defining B cell identity (*IRF8* and *PAX5*), genes encoding immune checkpoint molecules (e.g. *CD274* encoding programmed cell death ligand 1) and genes affecting the immune microenvironment (e.g. *TMEM30A*). Reciprocal interactions that influenced outcomes were observed between the tumour and CAR19 T cells. Somatic tumour mutations were shown to impact CAR19 T-cell expansion and persistence by affecting the tumour microenvironment and CAR19 T cells influenced the tumour phenotype and genotype. A multivariable model comprising the ctDNA level at week 4 after therapy and the cfCAR19 level at week 1 was predictive of both event-free and overall survival.

CONCLUSION: In patients with relapsed or refractory large B-cell lymphoma, dynamic reciprocal interactions between tumour phenotype and genotype and CAR19 T cells influenced responses to CAR19 therapy.

https://doi.org/10.1016/j.ccell.2022.12.005

RANDOMIZED PHASE III TRIAL EVALUATING SUBCUTANEOUS RITUXIMAB FOR THE FIRST-LINE TREATMENT OF LOW-TUMOR BURDEN FOLLICULAR LYMPHOMA:

RESULTS OF A LYSA STUDY

Journal of Clinical Oncology, 2023 July 1; 41(19):3523–33

AUTHORS: Cartron G, Bachy E, Tilly H, Daguindau N, Pica GM, Bijou F, Mounier C, Clavert A, Damaj GL, Slama B, Casasnovas O, Houot R, Bouabdallah K, Sibon D, Fitoussi O, Morineau N, Herbaux C, Gastinne T, Fornecker LM, Haioun C, Launay V, Araujo C, Benbrahim O, Sanhes L, Gressin R, Gonzalez H, Morschhauser F, Ternant D, Xerri L, Tarte K, Pranger D
CENTRE FOR CORRESPONDENCE: Département d'Hématologie Clinique, Centre Hospitalier Universitaire, Montpellier, France

BACKGROUND & AIM: Between 20% and 30% of patients with follicular lymphoma have a low tumour burden and are asymptomatic. A watch-and-wait approach is normally the standard of care but can lead to anxiety. Four-weekly rituximab induction therapy significantly improves progression-free survival and the time to next treatment compared with watching and waiting. The addition of rituximab maintenance therapy for 2 years improves these parameters even more but there are concerns about high costs and poor treatment adherence. The aim of this study was to assess the efficacy of a short maintenance course of subcutaneous rituximab in patients with asymptomatic, low-tumour-burden, follicular lymphoma.

STUDY DESIGN: Randomized phase-III clinical trial.

ENDPOINTS: Progression-free survival (primary endpoint), treatment response, overall survival, time to next treatment.

METHOD: The study involved treatment-naïve adults with histologically confirmed, $CD20^+$, low-tumour-burden, follicular lymphoma: 102 were randomized to receive intravenous rituximab, 375 mg/m^2, on days 1, 8, 15 and 22 (control arm), whereas 100 received intravenous rituximab, 375 mg/m^2, on day 1 followed by subcutaneous rituximab, 1400 mg, on days 8, 15 and 22, with subcutaneous rituximab maintenance treatment given at months 3, 5, 7 and 9 (experimental arm).

RESULTS: Over a median follow-up period of 50.2 months, the estimated 4-year progression-free survival rate was 58.1% (95% confidence interval 47.5-67.4%) in the experimental arm and 41.2% (95% CI 30.6-51.6%) in the control arm (hazard ratio for progression or death 0.59, 95% CI 0.39-0.87; p=0.008). At month 12, the overall response rate in the two arms was 73.0% (95% CI 63.2-81.4%) and 52.0% (95% CI 41.8-62.0%), respectively (p=0.002), and the complete response rate was 59.0% (95% CI 48.7-68.7%) and 36.3% (95% CI 27.0-46.4%), respectively (p=0.001). In the experimental and control arms, the estimated 4-year overall survival rate was 96.7% (95% CI 89.9-98.9%) and 95.0% (95% CI 88.5-97.9%), respectively. There was no significant difference between the groups in the time to next chemotherapy treatment. Rituximab exposure during the first 3 months was higher in the experimental arm and this was independently associated with a higher complete response rate, longer progression-free survival and a longer time to next treatment. Only four patients discontinued rituximab maintenance treatment.

CONCLUSION: In patients with low-tumour-burden follicular lymphoma, short maintenance treatment with subcutaneous rituximab following induction rituximab was associated with longer progression-free survival compared with intravenous rituximab induction alone.

https://doi.org/10.1200/JCO.22.02327

CD19 CAR T-CELL THERAPY AND PROPHYLACTIC ANAKINRA IN RELAPSED OR REFRACTORY LYMPHOMA:

PHASE 2 TRIAL INTERIM RESULTS

Nature Medicine, 2023 July; 29(7):1710–7

AUTHORS: Park JH, Nath K, Devlin SM, Sauter CS, Palomba ML, Shah G, Dahi P, Lin RJ, Scordo M, Perales MA, Shouval R, Tomas AA, Cathcart E, Mead E, Santomasso B, Holodny A, Brentjens RJ, Riviere I, Sadelain M

CENTRE FOR CORRESPONDENCE: Cellular Therapy Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA

BACKGROUND & AIM: Treatment with CD19-directed chimeric antigen receptor (CAR) T cells can lead to severe side effects, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Both increase morbidity, prolong hospitalization and result in intensive care unit admission. Previous studies reported all-grade ICANS in 55–69% of patients receiving axicabtagene ciloleucel or brexucabtagene autoleucel, with grade-3 or higher ICANS in 31–38%. In preclinical studies of CD19-directed CAR-T therapy, administration of the interleukin-1 receptor antagonist anakinra reduced the incidence of ICANS without impairing treatment efficacy. The aim of this clinical study was to assess the efficacy of prophylactic anakinra in preventing severe ICANS in patients receiving CD19-directed CAR T-cell therapy for B-cell lymphoma.

STUDY DESIGN: Interim analysis of data from a phase-II clinical trial.

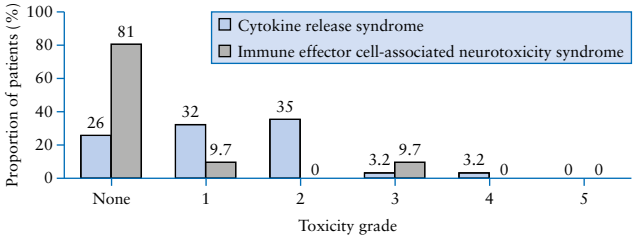
ENDPOINTS: ICANS (primary endpoint), CRS.

METHOD: The study involved 31 adults with relapsed or refractory large B-cell lymphoma (LBCL) or mantle cell lymphoma (MCL) who were receiving CD19-directed CAR T-cell therapy: 74% axicabtagene ciloleucel, 13% brexucabtagene autoleucel and 13% tisagenlecleucel. All were treated with anakinra, 100 mg subcutaneously every 12 hours for at least 10 days.

RESULTS: Twenty-five patients (81%) began anakinra on day 2 after CAR T-cell infusion and six (19%) began it earlier because of grade-1 CRS. The median duration of anakinra treatment was 11 days (range 10–27 days). Overall, six patients (19%) experienced ICANS: three (9.7%) grade-1 ICANS and three (9.7%) grade-3 (i.e. severe) ICANS (Figure). In addition, 23 patients (74%) experienced CRS, which was mostly grade 1 or 2, although one (3.2%) had grade-3 CRS and one (3.2%) had grade-4 CRS. Among the 27 patients who received CD28-containing CARs (i.e. axicabtagene ciloleucel and brexucabtagene autoleucel), rates of severe ICANS and severe CRS were 11% and 7%, respectively.

CONCLUSION: In patients receiving CD19-directed CAR T-cell therapy for B-cell lymphoma, only 9.7% treated with prophylactic anakinra experienced grade-3 or higher immune effector cell-associated neurotoxicity syndrome.

CRS and ICANS with prophylactic anakinra in patients receiving CD19-directed CAR T-cell therapy for B-cell lymphoma



CAR = chimeric antigen receptor; CRS = cytokine release syndrome; ICANS = immune effector cell-associated neurotoxicity syndrome.

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INTERFERON ALFA-2B IN PATIENTS WITH LOW-GRADE LYMPHOMATOID GRANULOMATOSIS AND CHEMOTHERAPY WITH DA-EPOCH-R IN PATIENTS WITH HIGH-GRADE LYMPHOMATOID GRANULOMATOSIS:

AN OPEN-LABEL, SINGLE-CENTRE, PHASE 2 TRIAL

The Lancet Haematology, 2023 May; 10(5):e346–58

AUTHORS: Melani C, Dowdell K, Pittaluga S, Dunleavy K, Roschewski M, Song JY, Calattini S, Kawada JI, Price DA, Chattopadhyay PK, Roederer M, Lucas AN, Steinberg SM, Jaffe ES, Cohen JI, Wilson WH
CENTRE FOR CORRESPONDENCE: Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA

BACKGROUND & AIM: Lymphomatoid granulomatosis, a rare B-cell lymphoproliferative disorder associated with the Epstein-Barr virus, has no standard treatment and is associated with a median overall survival under 2 years. It has been suggested that low-grade lymphomatoid granulomatosis is immune-dependent and may respond to immunotherapy, whereas high-grade disease is immune-independent and requires chemotherapy. The aim of this study was to evaluate the activity and safety of immunotherapy for patients with low-grade lymphomatoid granulomatosis and standard chemotherapy for those with high-grade disease.

STUDY DESIGN: Open-label single-centre phase-2 trial.

ENDPOINTS: Overall response, 5-year progression-free survival rate, adverse events.

METHOD: The study involved 67 patients aged ≥12 years (median 46 years, 63% male) with untreated, or relapsed or refractory, lymphomatoid granulomatosis: 45 with low-grade (i.e. grade-1 or -2) disease received dose-escalated interferon alfa-2b, whereas 18 with high-grade (i.e. grade-3) disease received dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab (DA-EPOCH-R). Cross-over treatment was allowed for patients with residual or progressive disease after initial therapy.

RESULTS: Overall, 16 patients crossed over to DA-EPOCH-R and eight crossed over to interferon alfa-2b. In patients who initially received interferon alfa-2b, the overall response rate was 63.6% (61.4% with a complete response); among those who crossed over to interferon alfa-2b, the overall response was 62.5% (50.0% with a complete response). The 5-year progression-free survival rate was 48.5% (95% confidence interval 33.2–62.1%) after initial interferon treatment and 50.0% (95% CI 15.2–77.5%) after cross-over treatment. In patients who initially received DA-EPOCH-R, the overall response rate was 76.5% (47.1% with a complete response); among those who crossed over to DA-EPOCH-R, the overall response rate was 66.7% (46.7% with a complete response). The 5-year progression-free survival rate was 25.4% (95% CI 8.2–47.2%) after initial DA-EPOCH-R and 62.5% (95% CI 34.9–81.1%) after cross-over treatment. Serious adverse events occurred in 25.5% and 63.6% of patients receiving interferon alfa-2b and DA-EPOCH-R, respectively, with five treatment-related deaths.

CONCLUSION: Among patients with lymphomatoid granulomatosis, treatment of low-grade disease with interferon alfa-2b and of high-grade disease with DA-EPOCH-R chemotherapy, with treatment cross-over for residual or progressive disease, was promising and associated with 5-year progression-free survival rates ranging from 25.4% to 62.5%.

https://doi.org/10.1016/S2352-3026(23)00029-7

SAFETY AND EFFICACY OF AXICABTAGENE CILOLEUCEL VERSUS STANDARD OF CARE IN PATIENTS 65 YEARS OF AGE OR OLDER WITH RELAPSED/REFRACTORY LARGE B-CELL LYMPHOMA

Clinical Cancer Research, 2023 May 15; 29(10):1894–905

AUTHORS: Westin JR, Locke FL, Dickinson M, Ghobadi A, Elsawy M, van Meerten T, Miklos DB, Ulrickson ML, Perales MA, Farooq U, Wannesson L, Leslie L, Kersten MJ, Jacobson CA, Pagel JM, Wulf G, Johnston P, Rapoport AP, Du L, Vardhanabhuti S, Filosto S, Shah J, Snider JT, Cheng P, To C, Oluwole OO, Sureda A

CENTRE FOR CORRESPONDENCE: MD Anderson Cancer Center, Houston, Texas, USA

BACKGROUND & AIM: Older patients with relapsed or refractory large B-cell lymphoma (LBCL) often cannot tolerate second-line treatment with the standard of care, which may include high-dose chemotherapy and autologous stem cell transplantation (HDT-ASCT). Axicabtagene ciloleucel (axi-cel) is an autologous, anti-CD19, chimeric antigen receptor, T-cell therapy that has been approved for adults with relapsed or refractory LBCL who have failed on ≥2 lines of systemic therapy. In the ZUMA-7 trial involving these patients, second-line axi-cel was associated with longer event-free survival than the standard of care. The aim of this subgroup analysis of the ZUMA-7 trial was to report outcomes in participants aged ≥65 years.

STUDY DESIGN: Randomized open-label phase-3 study.

ENDPOINTS: Event-free survival (primary endpoint), objective response rate, overall survival, adverse events, quality of life.

METHOD: In the ZUMA-7 trial, 359 patients who had relapsed or refractory LBCL within 12 months of first-line chemoimmunotherapy were randomized 1:1 to curative-intent therapy with axi-cel or investigator-selected, standard-of-care chemoimmunotherapy followed by HDT-ASCT. Patient-reported, quality-of-life outcomes were assessed using two standard questionnaires (i.e. EORTC QLQ-C30 and EuroQoL).

RESULTS: Overall, 109 patients were aged ≥65 years: 51 were randomized to axi-cel and 58 received the standard-of-care. At a median follow-up of 24.3 months, the median event-free survival time in these patients was 21.5 months with axi-cel and 2.5 months with the standard of care (hazard ratio 0.28, 95% confidence interval 0.16–0.47; descriptive $p<0.0001$). The objective response rate was 88% and 52% in the two treatment groups, respectively (odds ratio 8.81, 95% CI 2.71–32.14; descriptive $p<0.0001$). In addition, overall survival was significantly longer with axi-cel (HR 0.52, 95% CI 0.28–0.96). All patients had at least one adverse event. Grade-3 or higher treatment-emergent adverse events were reported in 94% and 82% of patients in the axi-cel and standard-of-care arms, respectively, most commonly neutropenia (80% and 44%, respectively). The mean change in patient-reported outcome scores from baseline to days 100 and 150 favoured axi-cel over the standard of care for several measures.

CONCLUSIONS: Among patients aged ≥65 years who had relapsed or refractory LBCL after first-line chemoimmunotherapy, second-line curative-intent treatment with axicabtagene ciloleucel was associated with longer event-free survival, a higher response rate and longer overall survival than the standard of care. In addition, adverse events were manageable and patient-reported outcomes were better.

https://doi.org/10.1158/1078-0432.CCR-22-3136

SUGEMALIMAB MONOTHERAPY FOR PATIENTS WITH RELAPSED OR REFRACTORY EXTRANODAL NATURAL KILLER/T-CELL LYMPHOMA (GEMSTONE-201):

RESULTS FROM A SINGLE-ARM, MULTICENTER, PHASE II STUDY

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BACKGROUND & AIM: Although treatment for extranodal natural killer/T-cell lymphoma (ENKTL) has improved with the introduction of L-asparaginase-based chemotherapy, around 50% of patients relapse within 5 years and the median survival time of those with relapsed or refractory disease only just exceeds 6 months. There is no standard treatment for these patients. However, as tumour cells in patients with relapsed or refractory ENKTL often express programmed death ligand-1 (PD-L1), inhibition of programmed death-1/PD-L1 checkpoint signalling could be effective. Sugemalimab is a fully human, immunoglobulin-G4, monoclonal, anti-PD-L1 antibody that has been approved in China for advanced non-small cell lung cancer. The aim of this study was to investigate the efficacy and safety of sugemalimab in patients with relapsed or refractory ENKTL.

STUDY DESIGN: Single-arm phase-II trial.

ENDPOINTS: Objective response, response duration, overall survival, adverse events.

METHOD: The study involved 80 adults with histologically confirmed, relapsed or refractory ENKTL: 54 (67.5%) had stage-IV disease and 39 (48.8%) had previously received ≥2 lines of systemic treatment. All received sugemalimab, 1200 mg intravenously once every 3 weeks, for up to 24 months or until withdrawal of consent, intolerable toxicity, disease progression or death. Objective responses were assessed by an independent radiological review committee (IRRC) and by the investigators. The median follow-up period was 18.7 months.

RESULTS: The IRRC-assessed objective response rate was 44.9% (95% confidence interval 33.6–56.6%): 35.9% of patients had a complete response and 9.0% had a partial response. The median response duration was not reached. The investigator-assessed objective response rate was 45.6% (95% CI 34.3–57.2%): 30.4% of patients had a complete response and 15.2% had a partial response. Again the median response duration was not reached. In addition, the median overall survival time was not reached (95% CI 14.0 months to not reached). The overall survival rate was 79.2% at 6 months, 67.5% at 12 months and 57.9% at 18 months. Most treatment-emergent adverse events were grade-1 or -2. Grade-3 or higher events occurred in 40.0% and 7.5% (6/80) of patients experienced treatment-related serious adverse events, all but one of which resolved without sequelae.

CONCLUSIONS: In patients with relapsed or refractory, extranodal natural killer/T-cell lymphoma, sugemalimab treatment was associated with an objective response rate around 45% and a 12-month overall survival rate of 67.5%. Adverse events were manageable.

https://doi.org/10.1200/JCO.22.02367

SAFETY AND EFFICACY OF TISAGENLECLEUCEL PLUS PEMBROLIZUMAB IN PATIENTS WITH R/R DLBCL:

PHASE 1B PORTIA STUDY RESULTS

Blood Advances, 2023 June 13; 7(11):2283–6

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BACKGROUND & AIM: In the JULIET trial involving adults with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), treatment with the chimeric antigen receptor (CAR) T-cell therapy, tisagenlecleucel, was associated with a high response rate and manageable safety. However, CAR T-cell exhaustion was noted in patients with programmed cell death protein-1 (PD-1) overexpression, some of whom had a lack of response. It was suggested, therefore, that the PD-1 inhibitor, pembrolizumab, might increase the efficacy of CAR T-cell therapy. The aim of this paper was to report the final analysis of the PORTIA trial, which investigated the safety and efficacy of adding pembrolizumab to tisagenlecleucel in patients with relapsed or refractory DLBCL.

STUDY DESIGN: Open-label phase-1b study.

ENDPOINTS: Dose-limiting toxicities, treatment response, adverse events, tisagenlecleucel expansion.

METHOD: The PORTIA trial involved 12 adults with relapsed or refractory DLBCL who had received at least two lines of prior therapy. All received a tisagenlecleucel infusion on day 1. In addition, pembrolizumab was initiated one day before tisagenlecleucel in four patients (D–1 group), on day 8 in four (D8 group) and on day 15 in four (D15 group). Pembrolizumab, 200 mg, was administered intravenously every 21 days for up to six doses until unacceptable toxicity or disease progression. Cellular kinetics and biomarkers were monitored alongside safety and efficacy. The median follow-up time after tisagenlecleucel infusion was 230 days.

RESULTS: Three of the 12 patients completed six cycles of pembrolizumab (one in the D–1 group and two in the D15 group). No dose-limiting toxicities were reported within 21 days of pembrolizumab initiation. Overall, 33.3% of patients had a complete response and 16.7% had a partial response. The overall response rate was highest in the D–1 group, at 75% (95% confidence interval 19.41–99.37%), with three of the four patients having a sustained complete response. All patients experienced at least one adverse event and two experienced serious treatment-related adverse events (i.e. febrile neutropenia in the D–1 group and cytokine release syndrome in the D8 group). Although pembrolizumab treatment did not result in the secondary expansion of tisagenlecleucel, peak tisagenlecleucel expansion was delayed in the D–1 group.

CONCLUSIONS: The addition of pembrolizumab to tisagenlecleucel in patients with relapsed or refractory DLBCL was not associated with dose-limiting toxicities within 21 days. Pembrolizumab did not increase the cellular expansion of tisagenlecleucel but did delay peak expansion if given one day in advance.

https://doi.org/10.1182/bloodadvances.2022007779

DIFFERENTIAL EFFICACY FROM THE ADDITION OF BORTEZOMIB TO R-CHOP IN DIFFUSE LARGE B-CELL LYMPHOMA ACCORDING TO THE MOLECULAR SUBGROUP IN THE REMoDL-B STUDY WITH A 5-YEAR FOLLOW-UP

Journal of Clinical Oncology, 2023 May 20; 41(15):2718–23

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BACKGROUND & AIM: The REMoDL-B study investigated the addition of bortezomib to rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) in patients with diffuse large B-cell lymphoma (DLBCL). Although the primary analysis at 30 months found that adding bortezomib had no effect on survival, a retrospective analysis identified an aggressive disease subtype that may benefit. The aim of this paper was to report the 5-year follow-up results of the REMoDL-B study in patients with DLBCL and known gene expression profiles.

STUDY DESIGN: Open-label randomized phase-3 trial.

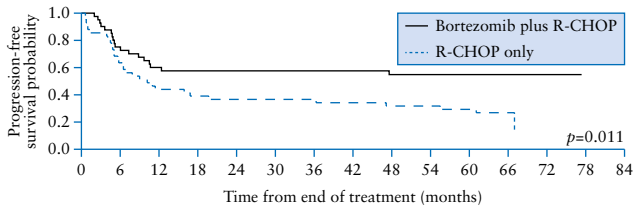
ENDPOINTS: Progression-free survival (PFS), overall survival (OS).

METHOD: The REMoDL-B study involved adults with a performance status ≤2 and measurable, bulky stage-I DLBCL or stage-II to -IV disease suitable for full-dose chemotherapy. Patients were randomized to either R-CHOP in cycles 1–6 or to R-CHOP in cycle 1 followed by R-CHOP plus bortezomib in cycles 2–6. Initial biopsies from 1077 patients underwent gene expression profiling to identify the cells of origin. The median follow-up was 64 months.

RESULTS: Overall, 801 patients were retrospectively classified as having either activated B-cell, molecular high-grade or germinal centre B-cell DLBCL. In those with activated B-cell DLBCL, the 5-year PFS rate was 69.4% in the R-CHOP plus bortezomib group versus 54.4% in the R-CHOP group (hazard ratio 0.65, p=0.041) and the 5-year OS rate was 80.4% versus 67.4%, respectively (HR 0.58, p=0.032). In patients with molecular high-grade DLBCL, the 5-year PFS rate was 54.9% with R-CHOP plus bortezomib versus 29.3% with R-CHOP (HR 0.46, p=0.011; Figure) and the 5-year OS rate was 60.0% versus 47.5%, respectively (HR 0.62, p=0.16). In contrast, there was no significant difference in PFS or OS between treatments in patients with germinal centre B-cell DLBCL, the most common molecular phenotype.

CONCLUSION: The addition of bortezomib to R-CHOP was associated with significantly longer progression-free and overall survival in patients with the molecular high-grade or activated B-cell subtypes of diffuse large B-cell lymphoma but not in those with the germinal centre B-cell subtype.

Kaplan–Meier progression-free survival curves in patients with molecular high-grade DLBCL, by treatment



DLBCL = diffuse large B-cell lymphoma, R-CHOP = rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone.

https://doi.org/10.1200/JCO.23.00033

QUALITY-ADJUSTED TIME WITHOUT SYMPTOMS OR TOXICITY:

ANALYSIS OF AXICABTAGENE CILOLEUCEL VERSUS STANDARD OF CARE IN PATIENTS WITH RELAPSED/REFRACTORY LARGE B CELL LYMPHOMA

Transplantation and Cellular Therapy, 2023 May; 29(5):335.e1–8

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CENTRES: Amsterdam University Medical Center, University of Amsterdam, Cancer Center Amsterdam, Amsterdam, the Netherlands; OPEN Health, Bethesda, Maryland, USA; Kite Pharma – a Gilead Company, Santa Monica, California, USA; Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA; and Department of Medicine, Weill Cornell Medical College, New York, New York, USA

BACKGROUND & AIM: The phase-3 ZUMA-7 trial in patients with relapsed or refractory large B-cell lymphoma (LBCL) found that treatment with axicabtagene ciloleucel (axi-cel) was associated with longer event-free survival (EFS) and a higher response rate than the standard of care (i.e. salvage chemotherapy with autologous stem cell transplantation). Estimating the quality-adjusted time without symptoms or toxicity (Q-TWiST) enables a patient's survival time to be adjusted according to their quality of life in a way that takes into account the strength of the patient's desire to avoid adverse events and EFS events. The aim of this analysis was to use Q-TWiST to compare the quality-adjusted survival time of patients in the ZUMA-7 trial treated with axi-cel versus the standard of care.

STUDY DESIGN: Analysis of data from a phase-3 trial.

ENDPOINT: Gain in Q-TWiST.

METHOD: In the Zuma-7 trial, 359 patients with relapsed or refractory LBCL were randomized to second-line treatment with axi-cel or the standard of care. Overall survival time was divided according to three health states: (a) time with ≥ grade-3 adverse events before an EFS event (TOX); (b) time without adverse events of interest before an EFS event (TWiST); and (c) time between the EFS event and death (REL). An EFS event was defined as disease progression, new lymphoma treatment or all-cause death. The Q-TWiST for each treatment group was calculated as the weighted sum of mean TOX, TWiST and REL values multiplied by state-specific, quality-of-life utility scores. A relative Q-TWiST gain >15% was regarded as clearly clinically important.

RESULTS: After a median of 23.5 months, the mean TWiST was 11.2 months in the axi-cel group versus 5.4 months the standard-of-care group: the corresponding mean times in the two groups were 1.2 and 0.7 months, respectively, for TOX; and 6.0 and 10.7 months, respectively, for REL. The resulting Q-TWiST was 14.8 months with axi-cel and 11.1 months with the standard of care: the difference of 3.7 months (relative gain 21.9%) was clearly clinically important. In subgroup analyses, the Q-TWiST gain with axi-cel was significant for different follow-up durations (4.9 months at maximum follow-up of 37.7 months), patient ages (3.1 months for <65 years and 5.2 months for ≥65 years) and relapsed or refractory statuses (3.2 months for primary refractory disease, 9.1 months for relapse within 6 months and 4.1 months for relapse in 6–12 months).

CONCLUSION: In patients with relapsed or refractory LBCL, treatment with axi-cel was associated with significantly longer quality-adjusted survival compared with the standard of care – this was considered clearly clinically important.

https://doi.org/10.1016/j.jtct.2023.01.008

Tecartus 0,4 – 2 × 10^8 Zellen Infusionsdispersion
Pharmakotherapeutische Gruppe: Sonstige antineoplastische Mittel, ATC-Code: L01XL06. **Qualitative und quantitative Zusammensetzung:** Mantelzell-Lymphom: Jeder patientenspezifische Tecartus-Infusionsbeutel enthält Brexucabtagen-Autoleucel in einer chargenabhängigen Konzentration autologer T-Zellen, die genetisch modifiziert wurden, um einen gegen CD19 gerichteten chimären Antigenrezeptor zu exprimieren (CAR-positive, lebensfähige T-Zellen). Das Arzneimittel ist in einem Infusionsbeutel abgepackt, der insgesamt eine Zell-Infusionsdispersion mit einer Zieldosis von 2 × 10^6 Anti-CD19-CAR-positiven, lebensfähigen T-Zellen pro kg Körpergewicht (Spanne: 1 × 10^6 – 2 × 10^6 Zellen/kg), mit maximal 2 × 10^8 Anti-CD19-CAR-positiven, lebensfähigen T-Zellen, die in einer Cryostor CS10-Lösung suspendiert sind, enthält. Jeder Infusionsbeutel enthält ca. 68 ml Infusionsdispersion.
Akute lymphatische Leukämie: Jeder patientenspezifische Tecartus-Infusionsbeutel enthält Brexucabtagen-Autoleucel in einer chargenabhängigen Konzentration autologer T-Zellen, die genetisch modifiziert wurden, um einen gegen CD19 gerichteten chimären Antigenrezeptor zu exprimieren (CAR-positive, lebensfähige T-Zellen). Das Arzneimittel ist in einem Infusionsbeutel abgepackt, der insgesamt eine Zell-Infusionsdispersion mit einer Zieldosis von 1 × 10^6 Anti-CD19-CAR-positiven, lebensfähigen T-Zellen pro kg Körpergewicht mit maximal 1 × 10^8 Anti-CD19-CAR-positiven, lebensfähigen T-Zellen, die in einer Cryostor CS10-Lösung suspendiert sind, enthält. Jeder Infusionsbeutel enthält ca. 68 ml Infusionsdispersion.
Sonstige Bestandteile: *Sonstige Bestandteile mit bekannter Wirkung:* Dieses Arzneimittel enthält 300 mg Natrium. Jede Dosis enthält 0,05 ml Dimethylsulfoxid (DMSO) pro ml Tecartus. Cryostor CS10, Natriumchlorid, Humanalbumin
Anwendungsgebiete: Mantelzell-Lymphom: Tecartus wird angewendet zur Behandlung von erwachsenen Patienten mit rezidiviertem oder refraktärem Mantelzell-Lymphom (MCL) nach zwei oder mehr systemischen Therapien, die einen Bruton-Tyrosinkinase-(BTK-)Inhibitor einschließen.
Akute lymphatische Leukämie: Tecartus wird angewendet zur Behandlung von erwachsenen Patienten ab einem Alter von 26 Jahren mit rezidivierter oder refraktärer B-Zell-Vorläufer akuter lymphatischer Leukämie (ALL).
Gegenanzeigen: Überempfindlichkeit gegen den Wirkstoff oder einen der genannten sonstigen Bestandteile. Die Kontraindikationen der Chemotherapie zur Lymphodepletion müssen berücksichtigt werden.
Inhaber der Zulassung: Kite Pharma EU B.V., Tufsteen, 2132 NT Hoofddorp, Niederlande.
Rezept- und apothekenpflichtig, NR.
Weitere Angaben zu Warnhinweisen und Vorsichtsmaßnahmen für die Anwendung, Wechselwirkungen, Schwangerschaft und Stillzeit, sowie Nebenwirkungen entnehmen Sie bitte der veröffentlichten Fachinformation.

▼Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Jeder Verdachtsfall einer Nebenwirkung zu Tecartus ist zu melden an Gilead Sciences, E-Mail: Safety_FC@gilead.com, und/oder über das nationale Meldesystem an das Bundesamt für Sicherheit im Gesundheitswesen, Traisengasse 5, 1200 Wien, Österreich, Fax: +43 (0) 50 555 36207, Website: www.basg.gv.at

AT-TEC-0073

YESCARTA 0,4 – 2 x 10^8 Zellen Infusionsdispersion
Pharmakotherapeutische Gruppe: Sonstige antineoplastische Mittel, ATC-Code: L01XX70 **Qualitative und quantitative Zusammensetzung:** Jeder patientenspezifische Yescarta-Infusionsbeutel enthält Axicabtagen-ciloleucel in einer chargenabhängigen Konzentration autologer T-Zellen, die genetisch modifiziert wurden, um einen gegen CD19 gerichteten chimären Antigenrezeptor zu exprimieren (CAR-positive lebensfähige T-Zellen). Das Arzneimittel ist in einem Infusionsbeutel abgepackt, der insgesamt eine Zell-Infusionsdispersion mit einer Zieldosis von 2 × 10^6 Anti-CD19-CAR-positiven, lebensfähigen T-Zellen pro kg Körpergewicht (Spanne: 1 × 10^6 – 2 × 10^6 Zellen/kg), mit maximal 2 × 10^8 Anti-CD19-CAR-positiven, lebensfähigen T-Zellen, die in einer Lösung zur Kryokonservierung suspendiert sind, enthält. Jeder Infusionsbeutel enthält ca. 68 ml Infusionsdispersion.
Sonstige Bestandteile: *Sonstige Bestandteile mit bekannter Wirkung:* Jeder Beutel YESCARTA enthält 300 mg Natrium und 3,4 ml Dimethylsulfoxid (DMSO). Yescarta kann Reste von Gentamicin enthalten. Cryostor CS10 (enthält DMSO), Natriumchlorid, Humanalbumin.
Anwendungsgebiete: Yescarta wird angewendet zur Behandlung von erwachsenen Patienten mit diffus großzelligem B-Zell-Lymphom (DLBCL) und hochmalignem B-Zell-Lymphom (HGBL), das innerhalb von 12 Monaten nach Abschluss einer Erstlinien-Chemoimmuntherapie rezidiviert oder gegenüber dieser refraktär ist.
Yescarta wird angewendet zur Behandlung von erwachsenen Patienten mit rezidiviertem oder refraktärem (r/r) DLBCL und primär mediastinalem großzelligem B-Zell-Lymphom (PMBCL) nach zwei oder mehr systemischen Therapien.
Yescarta wird angewendet zur Behandlung von erwachsenen Patienten mit r/r follikulärem Lymphom (FL) nach drei oder mehr systemischen Therapien.
Gegenanzeigen: Überempfindlichkeit gegen den Wirkstoff oder einen der genannten sonstigen Bestandteile oder gegen Gentamicin (ein möglicherweise im Spurenbereich vorhandener Rückstand). Die Kontraindikationen der Chemotherapie zur Lymphodepletion müssen berücksichtigt werden.
Inhaber der Zulassung: Kite Pharma EU B.V., Tufsteen, 2132 NT Hoofddorp, Niederlande.
Rezept- und apothekenpflichtig, NR.
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▼Dieses Arzneimittel unterliegt einer zusätzlichen Überwachung. Jeder Verdachtsfall einer Nebenwirkung zu Yescarta ist zu melden an Gilead Sciences, E-Mail: Safety_FC@gilead.com, und/oder über das nationale Meldesystem an das Bundesamt für Sicherheit im Gesundheitswesen, Traisengasse 5, 1200 Wien, Österreich, Fax: +43 (0) 50 555 36207, Website: www.basg.gv.at

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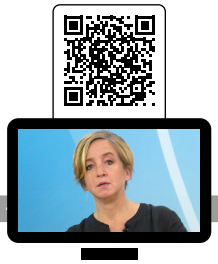
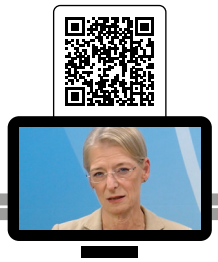


Patient selection
Prof. Antonia **Müller**
Med. Uni. Vienna



Previous therapies & washout phases
Prof. Nina **Worel**
Med. Uni. Vienna

Apheresis
Doz. Christoph **Grabmer**
Med. Uni. Salzburg

Value of CAR-T therapy in Follicular Lymphoma
Doz. Wolfgang **Willenbacher**
Med. Uni. Innsbruck
Doz. Daniel **Heintel**
Klinik Ottakring

Manufacturing process
KITE manufacturing video

Bridging therapies
Prof. Peter **Neumeister**
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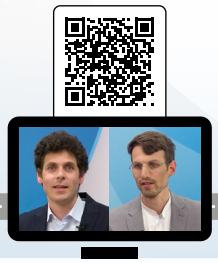
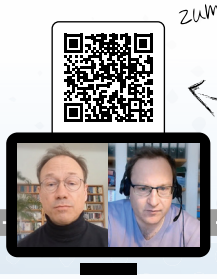
Value of CAR-T therapy in Mantle Cell Lymphoma
Prof. Thomas **Melchardt**
Med. Uni. Salzburg
Prof. Markus **Raderer**
Med. Uni. Vienna

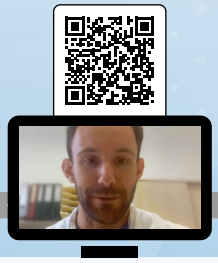


Value of CAR-T therapy in Large B-Cell Lymphoma
Doz. Josef **Singer**
UK Krems
OA. Gabriel **Kammerer**
UK St. Pölten

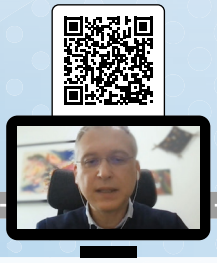


Value of CAR-T therapy in adult ALL
Doz. Johannes **Clausen**
Ordensklinikum Linz
Doz. Normann **Steiner**
Med. Uni. Innsbruck

INFUSION



Infusion & observation
OA. Michael **Leisch**
Med. Uni. Salzburg



Real World Evidence
OA. Jakob **Rudzki**
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