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on non-Hodgkin lymphoma

Three-year follow-up of KTE-X19 in patients with relapsed/refractory mantle cell lymphoma, including high-risk subgroups, in the ZUMA-2 study

Journal of Clinical Oncology, 2023 January 20; 41(3):555–67

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Journal of Clinical Oncology, 2023 February 1; 41(4):745–55

Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study

Blood, 2023 April 6; 141(14):1675–84

High-dose cytarabine and autologous stem-cell transplantation in mantle cell lymphoma: long-term follow-up of the randomized Mantle Cell Lymphoma Younger trial of the European Mantle Cell Lymphoma Network

Journal of Clinical Oncology, 2023 January 20; 41(3):479–84

The frequency of differentiated $CD3^{+}CD27^{-}CD28^{-}$ T cells predicts response to CART cell therapy in diffuse large B-cell lymphoma

Frontiers in Immunology, 2023 January 9; 13:1004703

Glofitamab for relapsed or refractory diffuse large B-cell lymphoma

The New England Journal of Medicine, 2022 December 15; 387(24):2220–31

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Cancer Immunology, Immunotherapy, 2023 January; 72(1):211–21

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Framingham bv
Postbus 1593
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Framingham *on non-Hodgkin lymphoma* is supported by **Gilead Sciences GesmbH,** Vienna, Austria
AT-TEC-0087

THREE-YEAR FOLLOW-UP OF KTE-X19 IN PATIENTS WITH RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA, INCLUDING HIGH-RISK SUBGROUPS, IN THE ZUMA-2 STUDY

Journal of Clinical Oncology, 2023 January 20; 41(3):555–67

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CENTRE FOR CORRESPONDENCE: Department of Lymphoma/Myeloma, University of Texas MD Anderson Cancer Center, Houston, Texas, USA

BACKGROUND & AIM: Brexucabtagene autoleucel (KTE-X19) – an autologous anti-CD19 chimeric antigen receptor T-cell therapy – was approved in the United States and Europe for use in adults with relapsed or refractory mantle cell lymphoma following publication of a primary efficacy analysis of the ZUMA-2 trial. The median follow-up period in the trial was 12.3 months. The aim of this study was to analyse the efficacy and safety of KTE-X19 in patients in the ZUMA-2 trial followed for 3 years, particularly those with high-risk characteristics.

STUDY DESIGN: Single-arm phase-2 trial.

ENDPOINTS: Objective response rate, response duration, progression-free survival, overall survival, safety.

METHOD: The ZUMA-2 trial involved adults with mantle cell lymphoma who relapsed on, or were refractory to, one to five prior treatment regimens, including anthracycline- or bendamustine-containing chemotherapy, an anti-CD20 monoclonal antibody and Bruton's tyrosine kinase inhibitor therapy. Of these, 68 underwent leukapheresis and conditioning therapy, with bridging therapy between the two as needed, before receiving a single intravenous infusion of KTE-X19 (target dose 2×10^6 chimeric antigen receptor T cells/kg). Outcomes were analysed in subgroups stratified by high-risk disease characteristics and type of prior Bruton's tyrosine kinase inhibitor therapy (i.e. ibrutinib, acalabrutinib or both).

RESULTS: At a median follow-up of 35.6 months (range 25.9–56.3 months), 68% of patients (46/68) had a complete response and 24% (16/68) had a partial response, giving an objective response rate of 91% (62/68). Responses were durable: the median duration was 28.2 months among the 62 responders (46.7 months in complete responders and 2.2 months in partial responders). The median progression-free survival time was 25.8 months (48.0 months in complete responders, 3.1 months in partial responders and 2.3 months in non-responders) and the median overall survival time was 46.6 months (not reached, 16.3 months and 8.5 months in the three response groups, respectively). There were no new safety concerns with longer follow-up. Objective response and survival rates in high-risk subgroups and patients treated with prior ibrutinib, acalabrutinib or both were generally similar to rates in the whole group. However, there was a trend towards shorter survival in patients who experienced disease progression within 24 months of their initial diagnosis.

CONCLUSION: Response rates remained high after around 3 years among patients with heavily pretreated, mantle cell lymphoma who received a single KTE-X19 infusion in the ZUMA-2 trial, including those with high-risk disease characteristics.

https://doi.org/10.1200/JCO.21.02370

SMART START: RITUXIMAB, LENALIDOMIDE, AND IBRUTINIB IN PATIENTS WITH NEWLY DIAGNOSED LARGE B-CELL LYMPHOMA

Journal of Clinical Oncology, 2023 February 1; 41(4):745–55

AUTHORS: Westin J, Davis RE, Feng L, Hagemeister F, Steiner R, Lee HJ, Fayad L, Nastoupil L, Ahmed S, Rodriguez A, Fanale M, Samaniego F, Iyer SP, Nair R, Oki Y, Fowler N, Wang M, Ma MCJ, Vega F, McDonnell T, Pinnix C, Griffith D, Lu Y, Tewari S, Sun R, Scott DW, Flowers CR, Neelapu S, Green MR
CENTRE FOR CORRESPONDENCE: Department of Lymphoma and Myeloma, University of Texas MD Anderson Cancer Center, Houston, Texas, USA

BACKGROUND & AIM: As first-line treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) reportedly fails in around 40% of patients with diffuse large B-cell lymphoma (DLBCL), new drugs are needed. In a previous study, targeted therapy with rituximab, lenalidomide and ibrutinib (RLI) produced responses in the majority of patients with relapsed non-germinal centre B-cell-like (GCB) DLBCL, both without and with chemotherapy – the response rate was higher with chemotherapy. The aim of this study was to investigate the efficacy of administering RLI alone followed by RLI combined with standard chemotherapy in patients with newly diagnosed non-GCB DLBCL, which allowed some evaluation of RLI alone in these patients.

STUDY DESIGN: Open-label phase-II trial.

ENDPOINTS: Treatment response, progression-free survival, overall survival, adverse events.

METHOD: The study involved 60 adults (median age 63.5 years, 28% aged ≥70 years) with previously untreated, non-GCB DLBCL. All underwent two 21-day cycles of treatment with RLI alone followed by an additional six cycles of RLI with standard chemotherapy. The RLI regimen comprised rituximab, 375 mg/m^2 intravenously on day 1, lenalidomide, 25 mg orally once daily on days 1–10, and ibrutinib, 560 mg/day orally, in each 21-day cycle. Chemotherapy comprised etoposide, doxorubicin, vincristine, prednisone and cyclophosphamide (EPOCH) or CHOP.

RESULTS: In total, 42% of patients (25/60) were identified as high risk and 62% of those tested (24/39) expressed both MYC and BCL2 proteins. After two cycles of RLI alone, the overall response rate was 86.2%: 36.2% of patients had a complete response and 50.0% had a partial response. At the end of treatment, the overall response rate was 100% and the complete response rate was 94.5%. With a median follow-up period of 31 months, the estimated 2-year progression-free and overall survival rates were 91.3% (95% confidence interval 84.3–98.9%) and 96.6% (95% CI 92–100%), respectively. The most common adverse events were nausea (in 85.0% of patients), peripheral sensory neuropathy (83.0%), diarrhoea (78.0%) and mucositis (75.0%). Among other adverse events of interest, there was a grade-3 or higher rash in 16%, febrile neutropenia in 38% (52% with EPOCH and 24% with CHOP) and atrial fibrillation in 12%.

CONCLUSIONS: In patients with newly diagnosed, non-germinal centre B-cell-like DLBCL, treatment with rituximab, lenalidomide and ibrutinib alone for two 21-day cycles was associated with an overall response rate of 86.2%. Following the addition of standard chemotherapy, the complete response rate was 94.5% and the 2-year overall survival rate was 96.6%.

https://doi.org/10.1200/JCO.22.00597

FIVE-YEAR FOLLOW-UP OF ZUMA-1 SUPPORTS THE CURATIVE POTENTIAL OF AXICABTAGENE CILOLEUCEL IN REFRACTORY LARGE B-CELL LYMPHOMA

Blood, 2023 May 11; 141(19):2307–15

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BACKGROUND & AIM: The chimeric antigen receptor (CAR) T-cell therapy, axicabtagene ciloleucel (axi-cel), was approved for the treatment of large B-cell lymphoma (LBCL) after two or more lines of systemic therapy following the ZUMA-1 study. The results of the 5-year follow-up of ZUMA-1 are now available. The aim of this paper was to present findings on the long-term efficacy of axi-cel in patients with relapsed or refractory LBCL.

STUDY DESIGN: Phase 2 of a single-arm trial.

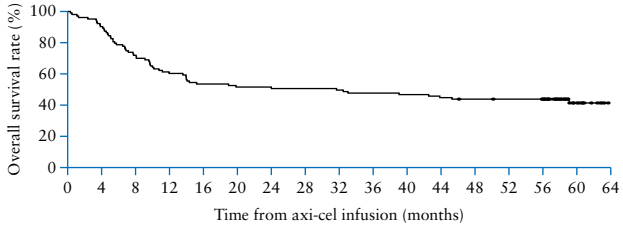
ENDPOINTS: Objective response (primary endpoint), response duration, progression-free and overall survival, adverse events, death.

METHOD: The study analysis involved 101 adults who had refractory LBCL or relapsed within 12 months of autologous stem cell transplantation and who subsequently received a single intravenous infusion of axi-cel at a target dose of 2×10^6 CAR T cells per kilogram body weight. Objective responses were assessed using International Working Group Response Criteria for Malignant Lymphoma. The median follow-up period was 63.1 months.

RESULTS: In the 101 patients, the objective response rate was 83% and the complete response rate was 58%. The median response duration was 11.1 months (95% confidence interval 4.2–51.3 months). At data cutoff, 31 patients (31%) had an ongoing objective response, of whom 30 (30%) had a complete response. Estimated 5-year progression-free and overall survival rates were 31.8% (95% CI 22.9–41.1%) and 42.6% (95% CI 32.8–51.9%; Figure), respectively. The median progression-free survival time was 5.9 months (95% CI 3.3–15.0 months) and the median overall survival time was 25.8 months (95% CI 12.8 months to not estimable). Among patients who achieved a complete response, the median overall survival time was not reached (95% CI 63.4 months to not estimable) and the 5-year overall survival rate was 64.4% (95% CI 50.8–75.1%). No new serious adverse events or treatment-related deaths occurred over the long term.

CONCLUSION: Five-year follow-up of the ZUMA-1 study showed that axicabtagene ciloleucel continued to have survival benefits for patients with relapsed or refractory large B-cell lymphoma: the 5-year overall survival rate in complete responders was 64.4%.

Kaplan-Meier overall survival curve



axi-cel = axicabtagene ciloleucel

https://doi.org/10.1182/blood.2022018893

LISOCABTAGENE MARALEUCEL AS SECOND-LINE THERAPY FOR LARGE B-CELL LYMPHOMA:

PRIMARY ANALYSIS OF THE PHASE 3 TRANSFORM STUDY

Blood, 2023 April 6; 141(14):1675–84

AUTHORS: Abramson JS, Solomon SR, Arnason J, Johnston PB, Glass B, Bachanova V, Ibrahimi S, Mielke S, Mutsaers P, Hernandez-Ilizaliturri F, Izutsu K, Morschhauser F, Lunning M, Crotta A, Montheard S, Previtali A, Ogasawara K, Kamdar M, for the TRANSFORM investigators
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BACKGROUND & AIM: The standard of care for patients with relapsed or refractory, large B-cell lymphoma (LBCL) is platinum-based immunochemotherapy followed by, for responders, high-dose chemotherapy and autologous stem cell transplantation (ASCT). However, up to 50% do not proceed to transplantation because the disease is insensitive to chemotherapy. In an interim analysis of the TRANSFORM study (median follow-up 6.2 months), second-line treatment with the chimeric antigen receptor (CAR) T-cell therapy, lisocabtagene maraleucel (liso-cel), was more effective than the standard of care in patients with relapsed or refractory LBCL. The aim of this study was to report efficacy data from a longer follow-up of the TRANSFORM study.

STUDY DESIGN: Randomized open-label phase-III trial.

ENDPOINTS: Event-free survival (primary endpoint), treatment response, progression-free and overall survival, adverse events.

METHOD: The study involved 184 adults with refractory or early relapsed (i.e. within 12 months) LBCL: 92 were randomized to liso-cel, 100 × 10^6 CAR-positive T cells by infusion, while 92 received the standard of care (i.e. three cycles of platinum-based immunochemotherapy followed by, for responders, high-dose chemotherapy and ASCT).

RESULTS: In a median follow-up of 17.5 months, the median event-free survival time was not reached for liso-cel versus 2.4 months for the standard of care (hazard ratio 0.36, 95% confidence interval 0.24–0.52). The estimated event-free survival rate at 18 months was 52.6% and 20.8% in the two treatment groups, respectively, and event-free survival was longer with liso-cel in all prespecified subgroups. The complete response rate was 74% with liso-cel and 43% with the standard of care (p<0.0001). The median progression-free survival time was not reached versus 6.2 months in the two groups, respectively (HR 0.40; p<0.0001), and the median overall survival time was not reached versus 29.9 months (HR 0.72; p=0.099). After adjustment for the 57 patients who crossed over from the standard of care to liso-cel, the median overall survival time was not reached in both arms (HR 0.42, 95% CI 0.25–0.69) and the estimated 18-month overall survival rate was 73.1% for liso-cel and 54.1% for the standard of care. In both arms, the most common grade-3 or higher adverse events were neutropenia, thrombocytopenia and anaemia. In the liso-cel arm, any-grade cytokine release syndrome occurred in 49% of patients and neurological events occurred in 11%.

CONCLUSION: In patients with relapsed or refractory large B-cell lymphoma, second-line lisocabtagene maraleucel was associated with significantly longer event-free and progression-free survival than the standard of care.

https://doi.org/10.1182/blood.2022018730

HIGH-DOSE CYTARABINE AND AUTOLOGOUS STEM-CELL TRANSPLANTATION IN MANTLE CELL LYMPHOMA:

LONG-TERM FOLLOW-UP OF THE RANDOMIZED MANTLE CELL LYMPHOMA YOUNGER TRIAL OF THE EUROPEAN MANTLE CELL LYMPHOMA NETWORK

Journal of Clinical Oncology, 2023 January 20; 41(3):479–84

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BACKGROUND & AIMS: In the mantle cell lymphoma (MCL) Younger trial, patients with advanced MCL aged <66 years were randomized to either: (a) an alternating induction therapy schedule of rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) and rituximab plus dexamethasone, high-dose cytarabine and cisplatin (R-DHAP) followed by high-dose cytarabine-containing myeloablative radiochemotherapy conditioning and autologous stem cell transplantation (ASCT; R-DHAP arm); or (b) R-CHOP with standard myeloablative radiochemotherapy and ASCT (R-CHOP arm). At a median follow-up of 6.1 years, the time to treatment failure was significantly longer in the R-DHAP arm but there was no significant difference in overall survival. The main aim of this longer study was to confirm the initial efficacy results of the MCL Younger trial.

STUDY DESIGN: Long-term analysis of an open-label randomized phase-3 trial.

ENDPOINTS: Time to treatment failure, progression-free survival, overall survival, adverse events.

METHOD: This analysis involved 466 adults aged <66 years with previously untreated, Ann Arbor stage-II to -IV MCL who were suitable for ASCT and who took part in the MCL Younger trial: 234 were randomized to the R-CHOP arm and 232 to the R-DHAP arm.

RESULTS: After a median follow-up of 10.6 years, the median time to treatment failure was significantly longer in the R-DHAP arm than the R-CHOP arm: 8.4 versus 3.9 years, respectively (hazard ratio 0.59, p=0.038). At 10 years, an estimated 46% of patients in the R-DHAP arm had not experienced treatment failure compared with 25% in the R-CHOP arm. In addition, the estimated 10-year overall survival rate was 60% in the R-DHAP arm versus 55% in the R-CHOP arm (p=0.12). The difference in overall survival between the arms became significant when adjusted for MCL International Prognostic Index without or with the Ki-67 index: the p values were 0.038 and 0.0066, respectively. The severity and frequency of toxicities generally decreased over time in both treatment groups. At 10 years, the incidence of secondary haematological malignancies tended to be higher in the R-DHAP arm: 4.5% versus 1.4% in the R-CHOP arm.

CONCLUSIONS: This extended analysis of the MCL Younger trial in patients aged <66 years with previously untreated mantle cell lymphoma confirmed that the time to treatment failure was significantly longer with alternating R-CHOP/R-DHAP followed by high-dose cytarabine-containing myeloablative radiochemotherapy and ASCT than with R-CHOP followed by standard myeloablative radiochemotherapy and ASCT. Moreover, the 10-year overall survival rate was significantly higher after adjustment for prognostic factors.

https://doi.org/10.1200/JCO.22.01780

THE FREQUENCY OF DIFFERENTIATED CD3$^+$CD27$^-$ CD28$^-$ T CELLS PREDICTS RESPONSE TO CART CELL THERAPY IN DIFFUSE LARGE B-CELL LYMPHOMA

Frontiers in Immunology, 2023 January 9; 13:1004703

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BACKGROUND & AIM: Chimeric antigen receptor (CAR) T-cell therapy targeting the CD19 antigen on malignant B cells is effective in some patients with relapsed or refractory, diffuse large B-cell lymphoma (DLBCL). However, it is difficult to select those patients most likely to respond. The aim of this study was to identify pre-infusion blood and leukapheresis biomarkers that predict responses to CAR T-cell therapy in patients with relapsed or refractory DLBCL.

STUDY DESIGN: Clinical study.

ENDPOINT: Factors associated with a response to CAR T-cell therapy.

METHOD: The study included 33 heavily pretreated patients with relapsed or refractory DLBCL who were eligible for CAR T-cell therapy. Lymphocyte populations and their activation and differentiation status in peripheral blood and corresponding leukapheresis samples were compared between the DLBCL patients and 24 healthy controls matched for age and sex. Correlations were sought between peripheral blood or leukapheresis products and overall responses 3 months after CAR T-cell infusion in 26 DLBCL patients.

RESULTS: Compared with healthy controls, at leukapheresis patients with relapsed or refractory DLBCL had substantial lymphopenia due to low CD3$^-$CD56$^+$ natural killer and CD3$^+$CD4$^+$ T-helper cell numbers. However, patients with DLBCL also had a higher frequency of differentiated CD3$^+$CD27$^-$CD28$^-$ T cells than controls (28.7% versus 6.6%, respectively, p<0.001) and significantly more activated HLA-DR$^+$ T cells (mean 315 versus 113 × 10^6/L, respectively; p=0.005). Neutrophil, overall leukocyte, natural killer T-cell and cytotoxic CD3$^+$CD8$^+$ T-cell counts were similar in the two participating groups. There was an independent association between an overall response 3 months after CAR T-cell therapy and a low frequency of differentiated CD3$^+$CD27$^-$CD28$^-$ T cells at leukapheresis: the frequency was 23.3% in responders and 35.1% in nonresponders. This association became more pronounced for those who did or did not have a complete response (13.7% in responders versus 37.7% in non-responders; p=0.001). A complete response at 12 months was predicted with high accuracy by a CD3$^+$CD27$^-$CD28$^-$ T-cell frequency of 18% or less (p<0.001). *In vitro*, CD3$^+$CD8$^+$CD27$^-$CD28$^-$ CAR T cells had similar cytotoxicity for target CD19$^+$ B cells as CD3$^+$CD8$^+$CD27$^+$CD28$^+$ CAR T cells but the former were hypoproliferative and produced fewer cytotoxic cytokines (e.g. interferon-γ and tumour necrosis factor-α).

CONCLUSION: In patients with relapsed or refractory, diffuse large B-cell lymphoma, a favourable response to CAR T-cell therapy was predicted by a low CD3$^+$CD27$^-$CD28$^-$ T-cell frequency at leukapheresis.

https://doi.org/10.3389/fimmu.2022.1004703

RESOURCE UTILIZATION FOR CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY VERSUS AUTOLOGOUS HEMATOPOIETIC CELL TRANSPLANTATION IN PATIENTS WITH B CELL LYMPHOMA

Annals of Hematology, 2022 August; 101(8):1755–67

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BACKGROUND & AIM: Recently CD19-directed chimeric antigen receptor (CAR) T-cell therapy has become available for patients with relapsed or refractory B-cell lymphoma. Usually, eligible patients who respond to second-line salvage chemotherapy proceed to consolidation with high-dose chemotherapy and autologous stem cell transplantation (ASCT). Ineligible patients are offered CAR T-cell therapy. Although the use of CAR T-cell therapy has increased in recent years, there are concerns about its affordability and there is, thus, a need for a health economic assessment. The aim of this study was to compare the resource use and costs associated with CAR T-cell therapy and high-dose chemotherapy followed by ASCT in patients with relapsed or refractory B-cell lymphoma.

STUDY DESIGN: Health economic assessment.

ENDPOINTS: Number of processes, time, costs.

METHOD: A process model for B-cell lymphoma patients undergoing CAR T-cell therapy or ASCT was developed using the software tool ClipMed^{PPM} and data on standard operating procedures in a Swiss hospital. The model covered all activities and processes involved.

RESULTS: The model found that CAR T-cell therapy and ASCT involved a total of 1041 and 1535 individual processes, respectively, and required an average of 30 and 48 days of hospital care, respectively. The higher number of processes performed per day with ASCT than CAR T-cell therapy (i.e. 34.7 versus 32.0, respectively) was attributable to the higher proportion of days of in-patient care. The total time required for CAR T-cell therapy was 269 hours and 16 min, compared with 389 hours and 47 min for ASCT. The 31% shorter time required for CAR T-cell treatment was attributable to fewer chemotherapy cycles, fewer outpatient visits and shorter hospital stays. Compared with ASCT, total treatment costs were 63% higher for CAR T-cell therapy due to the high one-time production cost of CAR T-cells. When this cost was excluded from the calculation, the cost of CAR T-cell therapy was 29% lower than that of ASCT. In addition, staffing costs were 29% lower with CAR T-cell therapy, material costs were 69% lower and surcharge costs (which included overheads and the cost of other medical departments involved) were 9% lower.

CONCLUSIONS: In patients with relapsed or refractory B-cell lymphoma, treatment costs were higher for CAR T-cell therapy than high-dose chemotherapy followed by autologous stem cell transplantation due to the high one-time production cost of CAR T-cells. However, other costs were lower for CAR T-cell therapy and it took less time and used fewer hospital resources.

https://doi.org/10.1007/s00277-022-04881-0

THREE-YEAR UPDATE OF TISAGENLECLEUCEL IN PEDIATRIC AND YOUNG ADULT PATIENTS WITH RELAPSED/REFRACTORY ACUTE LYMPHOBLASTIC LEUKEMIA IN THE ELIANA TRIAL

Journal of Clinical Oncology, 2023 March 20; 41(9):1664–9

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BACKGROUND & AIM: In the primary analysis of the pivotal, phase-II ELIANA study, treatment with the anti-CD19 chimeric antigen receptor T-cell therapy, tisagenlecleucel, was found to induce a sustained high remission rate of 81% in children and young adults with relapsed or refractory, B-cell acute lymphoblastic leukaemia (B-ALL). Most adverse events occurred in the first 8 weeks after infusion. The aim of this paper was to report on the efficacy and safety of tisagenlecleucel in participants of the ELIANA study followed up for more than 36 months.

STUDY DESIGN: Open-label phase-II study.

ENDPOINTS: Disease remission, event-free survival, relapse-free survival, overall survival, adverse events, clinical improvement.

METHOD: The study involved 79 paediatric and young adult patients (median age 11 years, range 3–24 years) with relapsed or refractory B-ALL who were treated with tisagenlecleucel. Of the 79 patients, 48 (61%) had had a prior haematopoietic stem cell transplantation and the median number of lines of previous treatment was 3 (range 1–8). The median time from tisagenlecleucel infusion to data cut-off for this analysis was 38.8 months.

RESULTS: Overall, 65 of the 79 patients achieved a remission within 3 months, which corresponds to an overall remission rate of 82%. The median duration of remission was not reached. Among all patients, the median event-free survival time was 24 months and the median overall survival time was not reached. The estimated 36-month event-free survival rate was 44% (95% confidence interval 31–57%) and the estimated 36-month overall survival rate was 63% (95% CI 51–73%) among all patients. The estimated 36-month relapse-free survival rate, censored for allogeneic stem-cell transplant and further anticancer treatment, was 52% (95% CI 37–66%). Without censoring, the estimated 36-month relapse-free survival rate was 48% (95% CI 34–60%). The long-term safety profile of tisagenlecleucel was consistent with previous reports; there were no new or unexpected adverse events. The proportion of patients with grade-3 or -4 adverse events declined over time. Clinically meaningful improvements in patient-reported, health-related quality of life were seen as early as 3 months after infusion and continued throughout follow-up.

CONCLUSION: Three-year follow-up of the ELIANA study showed that treatment with tisagenlecleucel in heavily pre-treated, paediatric and young adult patients with relapsed or refractory, B-cell acute lymphoblastic leukaemia was associated with a 36-month relapse-free survival rate of 52% and clinically meaningful improvements in quality of life.

https://doi.org/10.1200/JCO.22.00642

GLOFITAMAB FOR RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

The New England Journal of Medicine, 2022 December 15; 387(24):2220–31

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CENTRE FOR CORRESPONDENCE: Peter MacCallum Cancer Centre, Melbourne, Australia

BACKGROUND & AIM: Over one third of patients with diffuse large B-cell lymphoma (DLBCL) on standard first-line treatment either relapse or develop refractory disease. The prognosis is particularly poor for those who had at least two previous therapies. Glofitamab is a new T-cell-engaging, CD20 × CD3, bispecific antibody with a novel 2:1 tumour–T-cell binding configuration. The aim of this study was to assess the safety and efficacy of glofitamab in patients with DLBCL after at least two previous lines of therapy.

STUDY DESIGN: Phase-2 study.

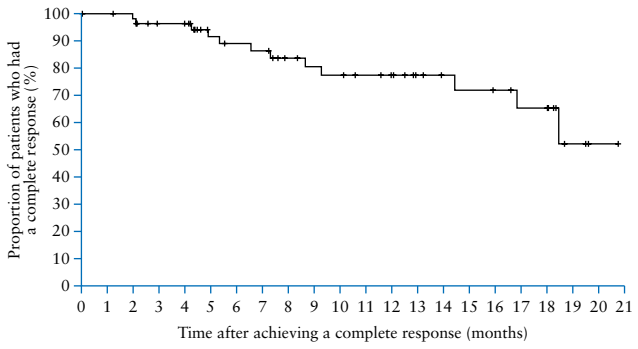
ENDPOINTS: Complete response (CR), response duration, adverse events.

METHOD: The study involved 154 patients (median age 66 years) with relapsed or refractory DLBCL who had received at least two previous lines of therapy: 110 had a confirmed diagnosis of DLBCL, 27 had transformed follicular lymphoma, 11 had high-grade B-cell lymphoma and 6 had primary mediastinal large B-cell lymphoma. Seven days before glofitamab administration, patients received intravenous obinutuzumab, 1000 mg, to mitigate cytokine release syndrome. Glofitamab was administered intravenously on day 8 (2.5 mg) and day 15 (10 mg) of the first 21-day cycle, then on day 1 (30 mg, the phase-2 dose) of cycles 2–12. Tumours were assessed at screening, after cycles 2, 5 and 8, at the end of treatment and every 6 months until disease progression.

RESULTS: In a median follow-up of 12.6 months, 22% (34/154) of patients had completed treatment, 8% (12/154) were still receiving treatment and 70% (108/154) had discontinued. The median duration of glofitamab treatment was 79 days. Overall, 39% (95% confidence interval 32–48%) of patients had a CR after a median of 12 treatment cycles. The median time to a CR was 42 days. In total, 78% of CRs were ongoing at 12 months (Figure). Grade-3 or higher adverse events occurred in 62% of patients and 9% discontinued glofitamab because of adverse events. The most common was cytokine release syndrome, in 63%.

CONCLUSION: Of 154 patients with previously treated, relapsed or refractory DLBCL who received glofitamab, 39% had a complete response. However, 62% had grade-3 or higher adverse events.

Proportion of patients with an ongoing complete response



https://doi.org/10.1056/NEJMoa2206913

EPCORITAMAB, A NOVEL, SUBCUTANEOUS CD3xCD20 BISPECIFIC T-CELL-ENGAGING ANTIBODY, IN RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA:

DOSE EXPANSION IN A PHASE I/II TRIAL

Journal of Clinical Oncology, 2023 April 20; 41(12):2238–47

AUTHORS: Thieblemont C, Phillips T, Ghesquieres H, Cheah CY, Clausen MR, Cunningham D, Do YR, Feldman T, Gasiorowski R, Jurczak W, Kim TM, Lewis DJ, van der Poel M, Poon ML, Cota Stirner M, Kilavuz N, Chiu C, Chen M, Sacchi M, Elliott B, Ahmadi T, Hutchings M, Lugtenburg PJ
CENTRE FOR CORRESPONDENCE: Assistance Publique & Hôpitaux de Paris, Hôpital Saint-Louis, Hémato-oncologie, Université de Paris, Paris, France

BACKGROUND & AIM: Epcoritamab is a bispecific monoclonal antibody that targets CD3 and CD20. In preclinical studies, the drug induced selective T cell-mediated cytotoxic activity against CD20+ malignant B cells. The recommended phase-II dose of epcoritamab was established in the dose-escalation phase of this study and no dose-limiting toxicity was observed in patients with relapsed or refractory, CD20+, mature B-cell non-Hodgkin's lymphoma. The aim of the dose-expansion phase was to evaluate the efficacy and safety of subcutaneous epcoritamab in patients with relapsed or refractory, large B-cell lymphoma (LBCL).

STUDY DESIGN: Open-label dose-expansion phase-I/II study.

ENDPOINTS: Treatment response (primary endpoint), response duration, adverse events.

METHOD: The study included adults with relapsed or refractory, CD20+ LBCL who had undergone at least two previous lines of treatment, including at least one anti-CD20 therapy. They were all ineligible for stem cell transplantation or it had previously failed. In the dose-expansion phase, patients received epcoritamab subcutaneously in 28-day cycles: the dose was stepped up on days 1 and 8 of cycle 1 and the full 48-mg dose was administered weekly from day 15 in cycle 1 until the end of cycle 3, once every 2 weeks in cycles 4–9 and once every 4 weeks from cycle 10 onwards. Responses were assessed using the Lugano criteria.

RESULTS: By data cut-off on 31 January 2022, 157 patients (median age 64 years) had been treated with epcoritamab, 96 of whom (61.1%) had primary refractory disease. Patients had received a median of three (range 2–11) previous lines of treatment and 61 (38.9%) had previously undergone chimeric antigen receptor T-cell therapy. At a median follow-up of 10.7 months in the 157 patients, overall and complete response rates were 63.1% (95% confidence interval 55.0–70.6%) and 38.9% (95% CI 31.2–46.9%), respectively. The Kaplan–Meier estimated, overall median response duration was 12.0 months; in complete responders, the median was not reached. Moreover, 88.7% of complete responders were still in remission at 6 and 9 months. The most common treatment-related adverse events were cytokine release syndrome (49.7% of patients), injection site reactions (19.7%) and neutropenia (17.8%). Immune effector cell-associated neurotoxicity syndrome developed in 10 patients (6.4%) – most were grade 1 or 2, with one fatal event.

CONCLUSIONS: In patients with relapsed or refractory, large B-cell lymphoma, epcoritamab was associated with overall and complete response rates of 63.1% and 38.9%, respectively. Moreover, 88.7% of complete responders were still in remission after 9 months.

https://doi.org/10.1200/JCO.22.01725

EFFICACY AND SAFETY OF CHIMERIC ANTIGEN RECEPTOR T-CELLS TREATMENT IN CENTRAL NERVOUS SYSTEM LYMPHOMA:

A PRISMA-COMPLIANT SINGLE-ARM META-ANALYSIS

Cancer Immunology, Immunotherapy, 2023 January; 72(1):211–21

AUTHORS: Lv L, Wu Y, Shi H, Sun X, Deng Z, Huo H, Li R, Liu Y
CENTRE: Department of Hematology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

BACKGROUND & AIM: The use of chimeric antigen receptor (CAR) T cells that target CD19 on B cells has revolutionized the treatment of refractory and recurrent, B-cell lymphomas. These CAR T cells have been detected in cerebrospinal fluid when administered intravenously, which suggests they could be effective in patients with a central nervous system lymphoma. However, the efficacy and safety of CAR T-cell therapy in these patients remains uncertain. The aim of this meta-analysis was to review what is currently known about the safety and efficacy of CAR T-cell therapy in patients with a central nervous system lymphoma.

STUDY DESIGN: Systematic review and meta-analysis.

ENDPOINTS: Treatment response, progression-free and overall survival, adverse events.

METHOD: The scientific literature was searched up to February 2022 for studies that investigated the use of CAR T-cell therapy in adults with a central nervous system lymphoma and that reported data on overall, complete and partial responses. Pooled response rates were calculated using a random-effects or fixed-effects meta-analysis model after double arcsine transformation according to whether between-study heterogeneity was either low or high, respectively.

RESULTS: The search identified eight cohort studies: five prospective and three retrospective trials that included a total of 63 patients aged 18–81 years. Following CAR T-cell therapy, the pooled overall response rate was 69% (95% confidence interval 56–81%) and the pooled complete and partial response rates were 51% (95% CI 37–64%) and 12% (95% CI 4–24%), respectively. Progressive disease after remission was reported in seven studies (pooled rate 38%, 95% CI 21–55%). Survival at 1 year was reported in four studies: the pooled, 12-month, progression-free and overall survival rates were 58% (95% CI 34–80%) and 75% (95% CI 42–98%), respectively. The main treatment-related adverse events were cytokine release syndrome and neurotoxicity. Severe (i.e. grade-3 or higher) cytokine release syndrome was reported in only one patient (11%) and the pooled rate of grade-3 or higher neurotoxicity was 12% (95% CI 3–24%). There were no reports of residual neurological impairment and no treatment-related deaths.

CONCLUSIONS: In patients with central nervous system lymphomas, CAR T-cell therapy was associated with an overall response rate of 69% and manageable adverse events. However, progressive disease occurred after remission in 38% of patients.

https://doi.org/10.1007/s00262-022-03246-w

IDE-CEL OR STANDARD REGIMENS IN RELAPSED AND REFRACTORY MULTIPLE MYELOMA

The New England Journal of Medicine, 2023 March 16; 388(11):1002–14

AUTHORS: Rodriguez-Otero P, Ailawadhi S, Arnulf B, Patel K, Cavo M, Nooka AK, Manier S, Callander N, Costa LJ, Vij R, Bahlis NJ, Moreau P, Solomon SR, Delforge M, Berdeja J, Truppel-Hartmann A, Yang Z, Favre-Kontula L, Wu F, Piasecki J, Cook M, Giralt S
CENTRE FOR CORRESPONDENCE: Department of Medicine, Adult Bone Marrow Transplantation Service, Memorial Sloan Kettering Cancer Center, New York, New York, USA

BACKGROUND & AIM: In patients with relapsed or refractory multiple myeloma who have previously been treated with three classes of drugs and who subsequently receive standard treatment, the median progression-free survival time is 3–5 months and the median overall survival time is <13 months. No standard of care has been established. Idecabtagene vicleucel (ide-cel) is a B-cell maturation antigen-directed, chimeric antigen receptor (CAR) T-cell therapy that produces deep and durable responses in heavily pretreated patients with relapsed or refractory multiple myeloma. The aim of this study was to compare ide-cel and standard treatment regimens in patients with triple-class-exposed, relapsed or refractory multiple myeloma.

STUDY DESIGN: Randomized open-label phase-III trial.

ENDPOINTS: Progression-free and overall survival, treatment response, response duration, adverse events.

METHOD: The study involved 386 adults (median age 63 years) with relapsed or refractory multiple myeloma who had received two to four previous lines of therapy and were refractory to the last regimen: 254 were randomized to ide-cel, 150–450 × 10^6 CAR-positive T cells, whereas 132 received one of five standard treatment regimens. Overall, 66% had triple-class-refractory disease and disease was refractory to immunomodulatory agents in 90% of patients, to proteasome inhibitors in 74% and to daratumumab in 95%.

RESULTS: Over a median follow-up period of 18.6 months, the median progression-free survival time with ide-cel and standard treatment was 13.3 and 4.4 months, respectively (hazard ratio for disease progression or death 0.49, 95% confidence interval 0.38–0.65; $p<0.001$). Overall, 71% of patients treated with ide-cel had a partial response or better compared with 42% on standard treatment (odds ratio 3.47, 95% CI 2.24–5.39; $p<0.001$); complete response rates were 39% and 5% in the two treatment groups, respectively. The median response duration was 14.8 months (95% CI 12.0–18.6 months) with ide-cel and 9.7 months (95% CI 5.4–16.3 months) with standard treatment. Overall survival data were immature. Grade-3 or -4 adverse events occurred in 93% of patients on ide-cel and in 75% on standard treatment and grade-5 events occurred in 14% and 6%, respectively. In the ide-cel group, 88% of patients experienced cytokine release syndrome (grade ≥3 in 5%) and 15% experienced investigator-identified neurotoxic effects (grade ≥3 in 3%).

CONCLUSION: In patients with triple-class-exposed, relapsed or refractory multiple myeloma, progression-free survival was significantly longer with ide-cel than standard treatment and the complete response rate was markedly higher.

https://doi.org/10.1056/NEJMoa2213614

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 BZell-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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AUSTRIAN CAR-T ACADEMY
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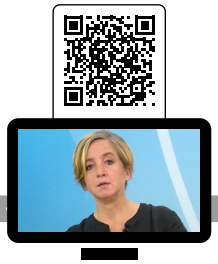
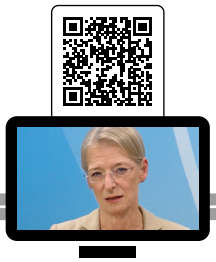
PATIENT SELECTION



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**
Med. Uni. Graz

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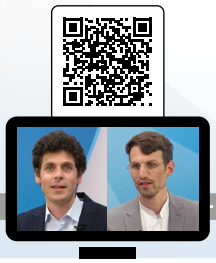
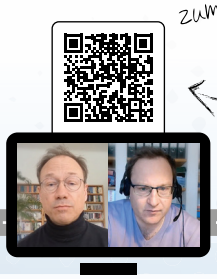
Value of CAR-T therapy in Mantle Cell Lymphoma
Prof. Thomas **Melchardt**
Med. Uni. Salzburg
Prof. Markus **Raderer**
Med. Uni. Vienna

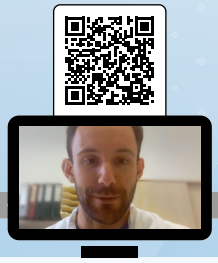


Value of CAR-T therapy in Large B-Cell Lymphoma
Doz. Josef **Singer**
UK Krems
OA. Gabriel **Kammerer**
UK St. Pölten

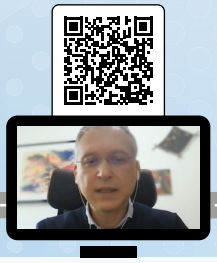


Value of CAR-T therapy in adult ALL
Doz. Johannes **Clausen**
Ordensklinikum Linz
Doz. Normann **Steiner**
Med. Uni. Innsbruck

INFUSION



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



Real World Evidence
OA. Jakob **Rudzki**
Med. Uni. Innsbruck

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