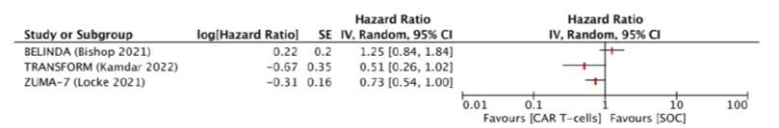
A.8	CD-19-directed CAR-T cell therapy – relapsed/refractory large B-cell lymphoma – EML
Draft recommendation	☐ Recommended ☒ Not recommended **Justification:** There is only low level of evidence that suggests that cellular immunotherapy with CAR T-cells may improve overall survival compared to the established treatment standard of immunochemotherapy, HDCT and ASCT. Research is still ongoing for this group. In addition these are highly expensive therapies requiring specialized skills and settings.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable **Comments:** Non-Hodgkin lymphomas (NHLs) are the 7th most common type of cancer and most common haematologic malignancy in the world, making up 4.3% of all cancers in the U.S. in 2015. The most common type of malignant lymphomas worldwide are diffuse large B-cell lymphomas (DLBCL) with 40% of all NHLs and 80% of all aggressive lymphomas. First-line treatment that consists of the combination of R-CHOP (Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone)-based immunochemotherapy. However, 30-40% of patients relapse or are refractory to first-line treatment. Even with the second-line treatments, which consists of salvage immunochemotherapy followed by ASCT, overall, approximately 60% of patients experience relapse. In patients with primary progressive disease or relapse within one year after first-line therapy PFS is about 25% at two years. Accordingly, prognosis for relapsed or refractory LBCLs remains poor.
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☐ Yes ☒ No ☐ Not applicable Comments: The evidence presented are from studies that are heterogenous resulting in low level of evidence.  *Figure 3. Overall survival* Studies are still ongoing, and evidence still being generated. Currently there is little superiority to the SOC.
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable **Comments:** CAR T-cell therapy might be associated with substantial toxicity (e.g. CRS or ICANS) there may be little to no difference in the occurrence of serious adverse events when compared to standard of care treatment.

Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable **Comments:** As per SOC with this group of patients and the toxicity of medications used in treatment
Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☐ No ☐ Not applicable **Comments:** Treatment with CAR T-cells is technologically demanding and resource intensive, requiring well-equipped facilities for its manufacturing and trained physicians to administer the treatment.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable **Comments:** Global availability of CAR T-cell therapy is limited. Thus far, it has not been introduced in lower- or middle-income countries (LMIC). The acquisition cost of CAR T-cell is between $373,000 to $475,000 per infusion, excluding extra procedures and facility costs.[1] [2]
Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☒ Yes ☐ No ☐ Not applicable **Comments:** Global availability of CAR T-cell therapy is limited. CAR T cell therapies have been approved in China, Australia, Singapore, the United Kingdom, and some European countries. In February 2022 Brazil approved tisagenlecleucel (Kymriah) treatment.
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments:

[1] Fiorenza S., Ritchie D.S., Ramsey S.D., Turtle C.J., Roth J.A. Value and affordability of CAR T-cell therapy in the United States. Bone Marrow Transpl. 2020;55:1706–1715. doi: 10.1038/s41409-020-0956-8

[2] Cummings Joyner AK, Snider JT, Wade SW, Wang ST, Buessing MG, Johnson S, Gergis U. Cost-Effectiveness of Chimeric Antigen Receptor T Cell Therapy in Patients with Relapsed or Refractory Large B Cell Lymphoma: No Impact of Site of Care. Adv Ther. 2022 Aug;39(8):3560-3577. doi: 10.1007/s12325-022-02188-0. Epub 2022 Jun 11. PMID: 35689726; PMCID: PMC9309131.