Schweizerische Eidgenossenschaft
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Federal Department of Home Affairs
Federal Office of Public Health FOPH
Health and Accident Insurance Directorate
Section Health Technology Assessment

Health Technology Assessment (HTA)

Stakeholder Feedback

Title	The CAR T-cell therapies tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) for the treatment of B-cell acute lymphoblastic leukaemia, diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma
Authors	Konstance Nicolopoulos, Magdalena Moshi, Ming Min, Danielle Stringer, Thomas Vreugdenburg Royal Australasian College of Surgeons
Technology	Tisagenlecleucel (Kymriah®) Axicabtagene ciloleucel (Yescarta®)
Type of Technology	Medical services
Date	9 July 2024

Conflict of Interest: The authors have no financial, academic, personal or any other conflicts of interest to declare in relation to this project.

Bundesamt für Gesundheit
Sektion Health Technology Assessment
Schwarzenburgstrasse 157
CH-3003 Bern
Schweiz
Tel.: +41 58 462 92 30
E-mail: hta@bag.admin.ch

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Appendix 29

Preface

This document details the authors' responses to stakeholder feedback regarding the HTA report on CAR T-cell therapies tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) for the treatment of B-cell acute lymphoblastic leukaemia (B-ALL), diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma (PMBCL).

The stakeholder feedback and corresponding author responses are detailed in tables. The tables are listed by stakeholder, in alphabetical order.

Stakeholders that provided a response as part of the consultation included:

1 Curafutura
2 Gilead Sciences Switzerland Sarl
3 Interpharma (IPH)
4 Lymphome.ch Patientennetz Schweiz
5 Medizinische Onkologie, Inselspital Bern
6 Novartis
7 Onkologiepflege Schweiz (OPS) und Akademische Fachgesellschaft (AFG)
8 Santésuisse
9 Swiss Blood Stem Cell Transplantation Group (SBST)
10 Swiss Society of Hematology (SSH)
11 Swiss Society of Medical Oncology (SSMO)

1. Curafutura

Comment	Author response
We would like to thank the authors for their detailed and well-founded report. Unfortunately, due to numerous reasons as the diseases indicated for CAR-T therapy, the small case numbers and the heterogeneous treatment approaches as well as the personalised nature of last-line therapies as comparators, there is a very poor evidence base and a high risk of bias, which this report cannot change. For this reason, as the authors write, no reliable statement can be made about the efficiency of the therapy or its cost-effectiveness, which of course is also based on the therapy efficiency. Accordingly, the report raises the following questions of a more general nature: 1. How can evidence be created for highly innovative therapies and low case numbers? (According to the present HTA, all ongoing clinical trials are single-arm cohort studies or case-control studies, and are therefore unlikely to alter the findings of this HTA (p.228)). 2. How can medical registries be better used and evaluated? How can the data from the registries be better linked (e.g. with clinical data, insurance data)? When is the next evaluation of the Swiss CAR-T register planned and who will carry it out? Should funding for the registry be reconsidered? What about the financial participation of the pharmaceutical industry? 3. How should we deal with newly approved CAR-T therapies or approval extensions in the future whose benefits may become even smaller and the evidence even more uncertain? 4. How can costs for CAR-T be made more transparent and reduced? (Disclosure of production costs, pay for performance etc.?) 5. How can the political and ethical discussion about highly innovative therapies and their costs (e.g. maximum costs of a QUALY) be conducted? Zusammenfassung HTA CAR-T: Im HTA-Bericht untersuchte Indikationen: 3.Linien Therapie für B-ALL und DLBCL, PMBCL (="LBCL"): KLV Appendix 1, provisorisch gelistet bis 31.12.2024 (tisagenlecleucel (Kymriah®)	1. Randomised controlled trials (RCTs) can be conducted on rare diseases, pooling samples across centres/countries. For example, ZUMA-7 is a multicentre RCT that investigates the use of axi-cel as a 2nd line therapy compared to standard of care in patients with LBCL (Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma - PubMed (nih.gov)). In the absence of prospective controlled trials, indirect comparisons using propensity score matching are the next best alternative. This requires access to individual patient data (IPD) from each cohort. Several of these study designs have been included in the present HTA. In the absence of this type of evidence, other non-randomised study designs could be considered, including studies of routinely collected administrative data (limitations in these study designs notwithstanding). Finally, indirect naïve comparisons between single-arm studies are the final alternative, which have questionable value for informing decision-making due to the strong likelihood of confounding; for this reason, indirect naïve comparisons have not been presented in the clinical evaluation of this HTA. 2. Due to the very general question without clear connection to the subject of the present HTA and the wide range of possible registries, it is not possible to provide a specific answer with respect to the present HTA. Concerning the Swiss CAR-T register: The register is part of an ongoing evaluation within coverage with evidence development. The Commission requires regular reports in order to obtain information for the re-evaluation of reimbursement. Evaluations are to be carried out or financed by the applicant (i.e. the body demanding coverage of services or providers of services). 3. Thank you for this feedback. It is noted for consideration by the commission.

	4. Thank you for this feedback. It is noted for consideration by the commission. 5. Thank you for this feedback. It is noted for consideration by the commission.

2. Gilead Sciences Switzerland Sarl

Comment	Author response
1. Stakeholder feedback form is limited to 4000 characters vs HTA of >600000.Gilead submitted more feedback & insists all is assessed by FOPH. Only a condensed version is in this form. 2. Feedback period is too short to review input, model & results. 3. Gilead is concerned about HTA procedure & quality. FOPH's HTA program focuses on divestment while CART are highly innovative & not compatible with divestment efforts. Ensuring equitable access to innovative treatments for patients(pts) in need is crucial. 4. Switzerland has no cost-effectiveness threshold that prevents pt access to a life-saving treatment.ICER cannot be used for decisions. 5. Despite method.issues,this HTA confirms axi-cel as cost-effective at majority of arbitrary thresholds,at the price used in the calculations.This aligns with HTAs in HTA countries,where axi-cel is recommended&permanently reimbursed due to signif.clinical benefit&value. 6. Economic model is not shared,preventing stakeholders to spot errors,critique inputs&interactions.Gilead requests transparency in sharing and a more collaborative process considering stakeholders as partners. 7. Pls use mixture cure model(MCM):No other HTA base case used spline models.MCM are more clinically supported,where a proportion is cured with CART. 8. Naïve comparison instead meta-analysis or MAIC results in biased estimates.Pls clarify why these methods were not used since it is best practice in other HTAs(eg.NICE manual).Pls exclude Pola&Pembro as alternative due to different populations,guidelines&expert feedb. “Exploratory” analyses&results are misleading&therefore irrelevant for decisions.	1. This stakeholder feedback form is the official document for the FOPH's HTA stakeholder process. Texts with a maximum of 4000 characters (including spaces) can be inserted and saved in this template. Comments submitted outside of the stakeholder form will be published without an author’s response (please see appendix). Comments from this extended feedback form that necessitated changes to the report have also been addressed 2. The official HTA process of the FOPH envisages a four-week stakeholder consultation period. For more information about the HTA process, visit the FOPH website. 3. HTA reports conducted for the Swiss HTA program are conducted in alignment with established methodological standards for conducting clinical, economic and auxiliary evaluations of healthcare interventions. For example, the analysis in the clinical evaluation was conducted in accordance with the Cochrane Handbook for systematic reviews of interventions and reported in accordance with the PRISMA checklist. The economic evaluation was conducted in accordance with the FOPH’s pre-specified template. Both the clinical and economic analyses were conducted in accordance with *a priori* protocols, that were reviewed by a panel of independent clinical and methodological experts. This HTA report was not produced with the preconceived intention of disinvestment, but to re-evaluate the evidence for clinical

9. Pls excl.Shadman22publ. as SCT is not a comparator in 3L(study design&population not matching HTA scope). 10. Pls evaluate base case as per trial(w/o bridging)&scenario w/ bridging in RWE,considering impact on probability of infusion,efficacy&AE. 11. Pls reflect shift of 3L to 2L LBCL CART&correct the outdated and overstated budget impact. 12. Pls review and correct inaccuracies in numbers quoted from registry&publ.:e.g.HTA states applicability concerns about disease stage of pts,but % &therefore statement is not correct.Tabl60:CART pts don't add up&further errors. 13. Pls use latest data.Gilead demands ITC & RWD publ.with >1000pts to be incl.for axi-cel (e.g.from DESCART(Bachy22),US(Jacobson20,Jacobson22)&Spiegel23. 14. Pls recognize learning curve observed in Boyle23:CART pts today more likely to achieve durable remission vs pts treated in initial period,therefore consider latest RWE as comparator if assessing clin.benefit vs alternatives. 15. Pls explain set discount rate. 16. Excl.Sim19,Figura21&Wright20 not meeting SLR criteria. 17. Incl.Neelapu21 ZUMA-1 vs SCHOLAR-1 publ.&compare vs SCHOLAR-1 instead CORAL.SCHOLAR-1 is commonly used in other HTA. 18. Verify/correct values and statement for "time betw.leukaph.&infusion" in registry&publ.:eg.526max.days seems like an odd unlikely coincidence for axi-cel&tisa-cel,while min.3d unrealistically short.LBCL can quickly progress&lead to pt drop-off.Pts w/o CART infusion often died due to progression.Shorter vein-to-vein times are associated with improved outcome(Locke22).Gilead has industry leading manufacturing turnaround(14-19 days)&success(96-99%). 19. Axi-cel costs only incur after infusion. 20. Verify all efficacy,AE,cost input,calc.&references to avoid errors:e.g.Tabl22 ICANS in JULIET="NR",but Schuster21 reported ICANS=20%&GR3-4=11%. IVIG following axi-cel(48%) vs tisa-cel(69%),but tisa-cel % used to be 69%,not 64%;Ino-code wrong etc. 21. Gilead disagrees with HTA epi&pt flow&budget impact. 22. Tabl61:Pls use CH-data,not UK. 23. Tabl62:Bass model uptake is more realistic vs linear.Some scenarios eg.8&9 very unrealistic. 24. Explain body weight assumption in LBCL vs trials. 25. Provide rationale for n<10 as SLR excl.criterion. 26. Clarify why HTAs (CAN,UK,NL) were prioritized vs other. 27. Report the ICER for axi-cel in DLBCL if different vs LBCL.	effectiveness, cost-effectiveness, and appropriateness to inform the continued reimbursement of a provisionally-reimbursed service. 4. It is acknowledged that Switzerland does not have a legally mandated ICER threshold for policy decisions. For this reason, probabilistic sensitivity analyses (PSAs) have been presented, that detail probability of cost-effectiveness at difference ICER thresholds. 5. Thank you for this feedback. It is noted for consideration by the commission. 6. The aim of the stakeholder consultation is to obtain a general opinion on the report. An in-depth review (for example on the economic model) is not provided for in the FOPH HTA stakeholder process. 7. It is acknowledged that prior HTAs have used a mixture cure model (MCM) for CAR T-cell therapy in base case. We note that the NICE 2023 review concluded the company's overall survival (OS) extrapolation (which used MCM) was appropriate. However, MCM requires specific patient-level data (baseline age, sex, country, censoring indicator, time under observation, year of enrolment; Felizzi 2021), which we did not have. No changes will be made. 8. We acknowledge that the NICE DSU TSD18 states that, where only single-arm trials are available, matching-adjusted indirect comparisons (MAIC) "*can be used to improve on "unadjusted" or naïve indirect comparisons*." The unadjusted comparisons undertaken in this HTA will "*include sampling error plus systematic error due to the imbalance in both prognostic factors and effect modifiers*". However, IPD (for at least one study arm) is needed for a MAIC, which we didn't have. We note the NICE DSU TSD18 also states "*MAIC and STC have been designed to meet a very specific situation applying to companies making submissions to NICE, in which companies have access to individual patient data (IPD) from their own trials…"* Data from published MAICs have not been used in the modelling. Progression-free survival (PFS) outcomes from the relevant MAIC populations were not available and, in the case of axi-cel, longer follow-up data has been published since the

28. Consider assessing axi-cel&tisa-cel in extended dominance framework,where axi-cel is dominant vs tisa-cel in DLBCL.	MAIC vs SCHOLAR-1 (Neelapu 2021). POLA-BR was identified via expert consultation as a relevant comparator, but we acknowledge there are population differences so the comparisons presented will have a high risk of bias due to cross-trial differences in patient characteristics. We have added a sentence to the conclusion to acknowledge this. Adjusting for these biases was not possible using the available aggregate data. However, we will retain the additional comparisons against POLA-BR in the HTA, with the intent to provide a potential range for the ICER. This is especially important as we identified applicability concerns with the historical control to contemporary Swiss practice. The comparison against pembrolizumab will be removed as a meaningful comparison cannot be made for the PMBCL population. 9. At the time of writing the HTA, CAR-T was recommended as a direct comparator to SCT in patients treated for LBCL, per Onkopedia guidelines. It is acknowledged that 18% of patients in the HCT arm were treated in 2nd line. This study has been excluded. 10. It is acknowledged that in the ZUMA-1 trial, "*systemic bridging chemotherapy was not allowed after leukapheresis and before administration of axi-cel*". However, in Swiss practice, bridging therapy is used (expert advice states in approx. 66-80% of patients), and model was based around real-world practices. Note most other studies include bridging. 11. This HTA is focused on evaluating the current reimbursement arrangements for tisa-cel and axi-cel in Switzerland; changes in use from 3L to 2L may occur in future, but do not exclude the possibility of treatment in 3L for a subset of patients. Feedback from SBST (presented below) suggests the budget impact understates uptake, based on their most recent data (not available to us at the time of writing). No changes. 12. The patient numbers reported in Table 60 have been reviewed. Errors were identified, due to 2 different populations cohorts being referred to (i.e. only patients with ≥2 lines of prior therapy recorded vs. all patients meeting KLV indication irrespective of recorded lines of therapy [according to advice from SBST registry, the latter can be used]). Table 60 has been adjusted to avoid any mismatches in patient number reporting. According to advice from

	SBST registry, all patients reported in amended Table 60 can be regarded as having had ≥2 prior lines of therapy (meeting the KLV indication for therapy). Data for the more restrictive cohort (patients with ≥2 recorded lines prior therapy) have been separated into a second table (Table 61). These annual data were included for the purpose of exploring trends in use of time. 13. Bachy will be included in the HTA. The other listed studies include patients and/or intervention characteristics that are outside the scope of the current HTA; reasons for excluding these studies are included in the appendices of the HTA. 14. Boyle 2023 does not meet the inclusion criteria for the HTA based on publication type (i.e. abstract/supplement) and intervention type (i.e. it reports combined data for tisa-cel and axi-cel). Boyle 2024 presents the full publication of the 2023 abstract, and would be excluded for the same reasons (i.e. combined interventions). No changes will be made. 15. Discount rate of 3% has been historically used in reports for the FOPH. EUnetHTA (Methods for health economic evaluations (eunethta.eu)) report most countries [European] use a discount rate between 3-5% for both costs and effect. No specific rates for Switzerland are provided. Most importantly, given the extended time horizon, we investigated the effect of different discount rates, including a rate of 0%. No changes. 16. We agree and acknowledge that Sim 2021 included radiotherapy as a bridging treatment prior to CAR T, noting that this does not preclude it from being included in the HTA; almost all included studies used some form of bridging therapy. Figura 2021 and Wright 2020 noted their inclusion criteria included patients with recurrent or refractory disease. It is noted and acknowledged that they did not clearly report how many prior lines of therapy patients received. These studies have been removed, noting that this decision had no significant impact on the overall treatment effects reported in the efficacy analyses of single-arm data. 17. Neelapu 2021 will be included in the HTA. 18. Time from leukapheresis to CAR T infusion have been checked and updated in the HTA, noting that in some cases approximations were required due to limitations in the reporting in primary studies.

	19. Acknowledged. Costs for leukapheresis and bridging incurred prior to infusion (and included for all patients); but CAR T-cell therapy product costs only incurred by patients who receive infusion. Sentence in Section 8.2.7 has been amended to clarify this in the report. 20. We acknowledge there was an error in Table 39; the proportion of patients with IVIG after tisa-cel (DLBCL population) should read 0.69 (not 0.64). Table has been updated. The correct value (0.69) was used in the modelling, so this error did not impact model results. Re: Ino-code, these have been amended in Table 47; this was a reporting error in the table, the correct codes were used in the costing, so this change has no impact on results. An additional sentence has been added above Table 46 to clarify blinatumomab costs. ICANS data was checked and is correct as reported in the HTA; the reported rates noted by the stakeholder are "neurological events" not ICANS specifically. 21. Noted as opinion. 22. UK data were used in the absence of Swiss data. No changes. 23. Acknowledge uptake is uncertain. Future utilisation of CAR T was projected based on historic trends in use (2019-2022) or assuming no further growth in uptake within eligible population in scenario analysis (i.e. by assuming population growth only). Acknowledge alternate models (e.g. Bass model) available and that the chosen approaches may have limitations. Also acknowledge, some uncertainty analysis scenarios, included as extreme cases, could be considered unrealistic. No changes. 24. Assumptions on body weight and body surface area (BSA) were required for the costings in the absence of published body weight/BSA from the trials used in the modelling. 25. The decision to exclude studies with a sample size <10 was a pragmatic one, which was made to balance the time and resource constraints of the HTA program against the relative impact of the excluded evidence on the results of the HTA. As noted previously, the efficacy results of the clinical evaluation for axi-cel in LBCL were primarily driven by the ZUMA-1 and ZUMA-9 studies (n=101, n=275). This inclusion criterion was listed as a limitation of the HTA's methodology in the discussion section. The addition of more

	single-arm studies with a sample size <10 would not have altered the conclusions of the HTA as they offer no additional information on relative safety or effectiveness. 26. The primary purpose of the HTA was to provide a de novo clinical, cost-effectiveness, financial impact and ethical, legal, social and organisational (ELSO) analysis within the Swiss context. In light of this, comparisons to existing HTAs were included in the discussion section to provide some context to the results in light of HTAs in other regions, noting that a comprehensive comparisons to *every* existing HTA on the topic is outside the scope of the HTA process. Comprehensive comparisons to other HTAs were not conducted in the existing HTAs. 27. Results were reported for the LBCL population, in line with the clinical evidence review chapter. Potential differences in cost-effectiveness (LBCL vs. DLBCL) were not assessed. The reconstructed IPD from the ZUMA-1 trial used in the modelling was for the combined LBCL population and could not be separated. No change. 28. Not appropriate. Scope of this HTA was clear in that no comparisons would be drawn between axi-cel and tisa-cel. Using the efficiency frontier would mean making a comparison *between* CAR T-cell therapy products.

3. Interpharma (IPH)

Comment	Author response
1. Bitte beachten Sie zusätzlich zu diesem Formular unser Schreiben, das wir Ihnen fristgerecht am 6. Februar 2024 zugestellt haben. Das Schreiben ist integraler Bestandteil der Stellungnahme von Interpharma. Im vorliegenden HTA werden zwei CAR-T-Zell-Therapien untersucht, die in Anhang 1 der Krankenversicherungs-Leistungsverordnung als "in Evaluation" aufgeführt sind. Dieses HTA ist Teil der Gesamtevaluation dieser beiden CAR T-Zell-Therapien gemäss dem Evaluationskonzept. Der Schwerpunkt des HTA-Programms des BAG liegt auf der Desinvestition, während CAR T-Zell-Therapien neue hochinnovative Produkte sind, die nicht	1. The focus of this HTA is on re-evaluating the evidence for the clinical effectiveness, cost-effectiveness, and appropriateness of provisionally-reimbursed CAR T-cell therapies, to inform a decision around their continued reimbursement. To this end, the HTA report presents evidence, it does not make or pre-empt policy recommendations. Changes in use from 3L to 2L may occur in future, but do not exclude the possibility of treatment in 3L for a subset of patients. No changes.

	mit den Desinvestitionsbemühungen vereinbar sind. Das Desinvestment kann für Patienten, die von einer Behandlung mit CAR-T-Zelltherapien profitieren, diskriminierend sein. Zudem hinterfragen wir den Nutzen eines HTA zu den CAR T Therapien, da in der sich schnell ändernden Therapielandschaft in diesem Bereich davon auszugehen ist, dass einige Erkenntnisse zum Zeitpunkt der Publikation des HTA-Berichts bereits wieder veraltet sind. In addition to this form, please note our letter, which we sent to you on time on February 6, 2024. The letter is an integral part of Interpharma's statement. The present HTA examines two CAR T-cell therapies that are listed as "in evaluation" in Appendix 1 of the Health Insurance Benefits Ordinance. This HTA is part of the overall evaluation of these two CAR T-cell therapies according to the evaluation concept. The focus of the BAG's HTA program is on divestment, while CAR T-cell therapies are new, highly innovative products that are not compatible with divestment efforts. Disinvestment may be discriminatory for patients who benefit from treatment with CAR T-cell therapies. We also question the benefit of an HTA for CAR T therapies, since in the rapidly changing therapeutic landscape in this area it can be assumed that some findings will already be out of date by the time the HTA report is published. **Policy** 2. Im Rahmen der wirtschaftlichen Beurteilung wurden als Ergebnisse Life Years (LY), Quality-Adjusted Life Years (QALYs) und die Incremental Cost-Effectiveness Ratio (ICER) verwendet. Für die damit verbundenen Schwellenwerte zur Beurteilung der Kosteneffektivität fehlen in der Schweiz gesellschaftlich und politisch breit abgestützte Rahmenbedingungen als Grundlage. As part of the economic assessment, Life Years (LY), Quality-Adjusted Life Years (QALYs) and the Incremental Cost-Effectiveness Ratio (ICER) were used as results. Switzerland lacks a broadly based social and political framework for the associated threshold values for assessing cost effectiveness. 3. Bei CAR T handelt es sich um eine hochkomplexe und individualisierte Therapie bei der sich die verschiedenen Wirkstoffe deutlich voneinander unterscheiden. Beim nun vorliegenden Bericht handelt es sich um ein Multi-HTA, in dem mehrere Wirkstoffe in einem Bericht zusammengefasst werden. Dieses Vorgehen setzt konsistente und vergleichbare Studiendaten zu den einzelnen Interventionen und Vergleichstherapien voraus, was im Fall der CAR T Zelltherapie nicht gegeben ist. In anderen Ländern wurde jedes CAR T Produkt jeweils konsequent separat beurteilt. CAR T is a highly complex and individualized therapy in which the various active ingredients differ significantly from one another. The present report is a multi-HTA in which several active ingredients are combined in one report. This approach requires consistent and comparable	2. It is acknowledged that Switzerland does not have a legally mandated ICER threshold for policy decisions. For this reason, probabilistic sensitivity analyses (PSAs) have been presented, that detail probability of cost-effectiveness at difference ICER thresholds. 3. While the report includes evidence for both tisa-cel and axi-cel in various populations, the drugs have not been compared within the report. For all intents and purposes, the report presents three separate HTAs in the same document (i.e. tisa-cel for B-ALL, axi-cel for LBCL, tisa-cel for LBCL). 4. Experts were included on the premise of anonymity. Names will not be disclosed (nor sub-specialty due to the risk of identification); however, their general field of expertise was relevant (e.g. oncology). Questionnaires/questions to the experts have been stated in the Appendix of the HTA protocol. 5. The involved experts have extensive experience in the use of CAR T therapies and meet therefore the requirements for the use of CAR T therapy defined by Swissmedic as part of the approval. 6. HTA reports conducted for the Swiss HTA program are conducted in alignment with established methodological standards for conducting clinical, economic and auxiliary evaluations of healthcare interventions. For example, the analysis in the clinical evaluation was conducted in accordance with the Cochrane Handbook for systematic reviews of interventions and reported in accordance with the PRISMA checklist. The economic evaluation was conducted in accordance with the FOPH's pre-specified template. Both the clinical and economic analyses were conducted in accordance with *a priori* protocols, that were reviewed by a panel of independent clinical and methodological experts. 7. The official HTA process of the FOPH provides for the stakeholder feedback to be published on the FOPH homepage. This can be done either by naming the stakeholder or in anonymised form.

study data for the individual interventions and comparative therapies, which is not the case in the case of CAR T cell therapy. In other countries, each CAR T product was consistently assessed separately. **Experteneinbezug (Expert involvement)** 4. Wir möchten festhalten, dass obwohl der Einbezug von Experten begrüsst wird, die Auswahlkriterien, die Liste der befragten Experten (Name Fachrichtung) und die gestellten Fragen/Fragebogen und die Antworten als Teil der Methodik offengelegt werden muss. We would like to note that although the involvement of experts is welcomed, the selection criteria, the list of experts interviewed (name of discipline) and the questions/questionnaires asked and the answers must be disclosed as part of the methodology. 5. Im vorliegenden Bericht wird auf den Experteneinbezug zur Beurteilung verschiedener Aspekte verwiesen. In Kapitel 8.2.5 wird beispielsweise darauf hingewiesen, dass drei Experten befragt wurden, zwei aus dem Fachbereich «Onkologie» und ein Experte aus dem Fachbereich «Pädiatrische Onkologie», weitere Informationen zu den Experten werden nicht aufgeführt. Die CAR T Therapie ist hochkomplex und muss gemäss Swissmedic Zulassung an einem «von der Zulassungsinhaberin qualifizierten Behandlungszentrum angewendet werden». Gerade bei hochkomplexen Therapien ist es zentral, dass die befragten Experten die von Swissmedic im Rahmen der Zulassung definierten Voraussetzungen für die Anwendung der Therapie erfüllen. This report refers to the involvement of experts to assess various aspects. For example, in Chapter 8.2.5 it is pointed out that three experts were interviewed, two from the “Oncology” department and one expert from the “Pediatric Oncology” department; further information about the experts is not listed. CAR T therapy is highly complex and, according to Swissmedic approval, must be used at a “treatment center qualified by the approval holder”. Particularly in the case of highly complex therapies, it is crucial that the experts interviewed meet the requirements for the use of the therapy defined by Swissmedic as part of the approval. **Methodik (methdology)** 6. Damit HTAs ein nützliches Ergebnis liefern, müssen sie nach wissenschaftlich festgelegten und standardisierten Methoden durchgeführt werden. Die Transparenz und der Zugang zu den verwendeten Methoden/Modellen muss dabei über alle Schritte hinweg gewährleistet sein. Für die gesundheitsökonomische Betrachtung wurden Studien aus Ländern eingeschlossen, in denen sich das Gesundheitssystem grundsätzlich von dem in der Schweiz unterscheidet (z.B. China), daher sollten solche Studien bzw. Daten nicht berücksichtigt werden.	

In order for HTAs to produce a useful result, they must be carried out according to scientifically established and standardized methods. Transparency and access to the methods/models used must be guaranteed throughout all steps. For the health economic analysis, studies were included from countries in which the health system is fundamentally different from that in Switzerland (e.g. China), therefore such studies or data should not be taken into account. **Vertrauliche Daten (Confidential data)** 7. Die Stellungnahmen der Zulassungsinhaber zum vorliegenden HTA-Bericht werden jeweils auf der Website des BAG publiziert. Dies verunmöglicht es den Zulassungsinhabern vertrauliche Daten und Preise in ihrer Stellungnahme aufzuführen. Es muss daher eine Möglichkeit geschaffen werden, dass diese Daten im Rahmen des Stakeholderfeedbacks zum Bericht einbezogen werden können, ohne dass die Vertraulichkeit gefährdet wird. The marketing authorization holders' statements on this HTA report are published on the BAG website. This makes it impossible for marketing authorization holders to list confidential data and prices in their statement. A possibility must therefore be created for this data to be included as part of stakeholder feedback on the report without jeopardizing confidentiality.	

4. Lymphome.ch Patientennetz Schweiz

Comment	Author response
Besten Dank für die Übermittlung der entsprechenden Unterlagen und die Möglichkeit eine Stellungnahme zur Stakeholderkonstultation HTA-Bericht abzugeben. Es ist für uns als Patientenorganisation noch eine ungewohnte Situation, doch wir schätzen diese Möglichkeit sehr. Thank you for submitting the relevant documents and the opportunity to submit a statement on the stakeholder consultation HTA report. It is still an unfamiliar situation for us as a patient organization, but we greatly appreciate this opportunity. **Kostenwirksamkeitsanalyse** **Cost-effectiveness analysis** 1. Gemäss dem HTA-Bericht gibt es für die Wirksamkeit von Kymriah und Yescarta keine Vergleichsmöglichkeiten, dies stimmt so nicht. Es gibt randomisierte Studien die den Vergleich zur Wirksamkeit von Standardtherapie zur Preisfestlegung ermöglichen.	1. The current HTA used systematic methods to identify all published evidence that directly addresses the PICO criteria. To date, no RCT evidence that address the use of CAR T-cell therapies in the target populations was identified. We welcome the nomination of specific studies that may have been missed in the systematic literature searches that could better address the research questions. 2. Treatment costs for CAR T-cell therapy and nominated comparators in the third-line setting were presented in the HTA. High dose chemotherapy + SCT was not a nominated comparator for relapsed/refractory lymphoma in the third-line. 3. In the absence of comparative clinical evidence, estimates for the relative rates of adverse events/toxicities cannot be accurately estimated.

According to the HTA report, there is no comparison possible for the effectiveness of Kymriah and Yescarta, this is not true. There are randomized studies that allow comparison of the effectiveness of standard therapy to determine prices. 2. Die Hochdosis-Chemotherapie war bisher als letzte Behandlungsoption bei Rezidiven bzw. refraktären Lymphomen der Standard. Auch diese Therapie ist einerseits mit grossen Risiken für den Patienten verbunden und andererseits ebenfalls kostenintensiv. Es erstaunt uns aber, dass die Kostenfrage bei der Hochdosis mit anschliessender Stammzellltransplantation kaum im Vordergrund steht. High-dose chemotherapy was previously the standard treatment option for relapses or refractory lymphomas. On the one hand, this therapy is also associated with major risks for the patient and, on the other hand, it is also cost-intensive. However, it surprises us that the cost issue is hardly a priority when it comes to high doses followed by a stem cell transplant. 3. Der Bericht hebt die Toxizitäten der Behandlung hervor, diese sind aber nicht stärker zu gewichten wie die Toxizitäten der vorangegangenen Chemotherapie bzw. der Hochdosis mit möglichen Folgen wie Hörverlust, Neuropathien, Fatigue, Herz-, Lungen-, Nieren- und Leberprobleme. The report highlights the toxicities of the treatment, but these are not to be given greater weight than the toxicities of the previous chemotherapy or the high dose with possible consequences such as hearing loss, neuropathies, fatigue, heart, lung, kidney and liver problems. **Budgetimpact-Analyse** **Budget Impact Analysis** 4. Diese CAR-T-Zell-Therapie ist unbestritten teuer. Mit einer Zulassung für weitere Indikationen sollte es jedoch möglich werden, die Kosten längerfristig zu reduzieren. Im Weiteren ist es für uns als Patientenorganisation müssig, jetzt über die Höhe der Preise zu diskutieren, über die ja von den Entscheidungsträgern entschieden wurde. Tatsache ist, dass die Therapie im Vergleich zur Standardtherapie klar besser ist, leider wird darauf im HTA-Bericht nicht eingegangen. This CAR T-cell therapy is undeniably expensive. However, approval for additional indications should make it possible to reduce costs in the longer term. Furthermore, it is pointless for us as a patient organization to now discuss the level of prices, which was decided by the decision-makers. The fact is that the therapy is clearly better compared to standard therapy, unfortunately this is not discussed in the HTA report. 5. Verglichen mit den Kosten einer Hochdosis-Chemotherapie mit anschliessender Stammzelltransplantation inklusive möglicherweise Komplikationen kann nicht a priori von höheren Kosten ausgegangen werden.	4. Thank you for this feedback. It is noted for consideration by the commission. The HTA report presents all available evidence supporting claims of clinical and economic effectiveness relative to alternative therapies. 5. Thank you for the feedback. The aim was to explore the costs associated with CAR T-cell therapy; higher costs were not assumed 'a priori'. No change' 6. Thank you for this feedback. It is noted for consideration by the commission. 7. Thank you for this feedback. It is noted for consideration by the commission. 8. Thank you for this feedback. It is noted for consideration by the commission. 9. The current HTA used systematic methods to identify all published evidence that directly addresses the PICO criteria. We would welcome the nomination of specific studies that may have been missed in the systematic literature searches. 10. Thank you for this feedback. It is noted for consideration by the commission. 11. Thank you for this feedback. It is noted for consideration by the commission.

Compared to the costs of high-dose chemotherapy followed by stem cell transplantation, including possible complications, higher costs cannot be assumed a priori. **Resultate zu ethischen, legalen, sozialen und organisatorischen Aspekten** **Results on ethical, legal, social and organizational aspects** 6. Jeder Patient der entsprechenden Indikationen ohne weitere Studienoption soll von dieser Therapie profitieren können, solange sie der Person medizinisch zumutbar ist. Dies ist in jedem Fall vom behandelnden Arzt/Behandlungsteam zu beurteilen. Every patient with the corresponding indications without further study options should be able to benefit from this therapy as long as it is medically acceptable for the person. In any case, this must be assessed by the treating doctor/treatment team. 7. Sehr wichtig ist eine ausführliche Vorinformation über den Ablauf und die Risiken dieser Behandlung, damit der Patient und seine Angehörigen wissen, was bei der Behandlung auf sie zukommt und wie die Nebenwirkungen sein können. It is very important to have detailed prior information about the process and the risks of this treatment so that the patient and their relatives know what to expect during the treatment and what the side effects may be. 8. Eine Sorge sind die teilweise langen Wartezeiten, bis die Kostengutsprache durch die Vertrauensärzte der Versicherer erteilt wird und die Therapie zur Verabreichung vorliegt. Diese Verzögerungen werden auf dem Rücken der Patienten ausgetragen, die diese Behandlung dringend benötigen und vielfach keine Zeit zum Warten haben. Patienten befinden sich in dieser Situation in einem Ausnahmezustand und lange Wartezeiten sind aus medizinischen und psychologischen Gründen nicht zumutbar. Durch eine proaktive und vorausschauende und klare Regelung zum Zeitpunkt der Zulassung und Einführung hätte hier auf Seiten der Betroffenen seit 2019 viel erspart werden können, Wir erinnern an den Fall „Riebli“, der unsererseits grosses Unverständnis ausgelöst hat. One concern is the sometimes long waiting times until the insurer's medical examiner approves the costs and the therapy is available for administration. These delays come at the expense of patients who urgently need this treatment and often do not have time to wait. In this situation, patients are in a state of emergency and long waiting times are unacceptable for medical and psychological reasons. A proactive, forward-looking and clear regulation at the time of approval and introduction could have saved a lot for those affected since 2019. We recall the “Riebli” case, which caused a great deal of incomprehension on our part. **Feedback zu Ihren Fragen an die Patientenorganisation:** **Feedback on your questions for the patient organization:** 9. Zu wenig Berücksichtigung aktueller Studien.	

Too little consideration of current studies. 10. Diese Therapie ist teuer, es wird aber kostenmässig z. B. kein Vergleich mit der Hochdosistherapie mit anschliessender Stammzelltransplantation gemacht; diese Analyse wurde für eine bessere Beurteilung nicht gemacht. This therapy is expensive, but it is cost-effective e.g. B. no comparison was made with high-dose therapy followed by stem cell transplantation; this analysis was not done for a better assessment. 11. Der klare Benefit für den Patienten wird zuwenig betont (Einmalige Infusion versus Chemotherapien mit mehreren Zyklen) und kuratives Potential in 50%. The clear benefit for the patient is not emphasized enough (single infusion versus Chemotherapy with multiple cycles) and curative potential in 50%.	

5. Medizinische Onkologie, Inselspital Bern

Comment	Author response
Besten Dank für die Zustellung des HTA-Berichts. Wir antworten gerne als Zentrum mit der national grössten Erfahrung in der CAR-T Behandlung von Patient:innen mit hämatologischen Neoplasien. Der Bericht ist sehr umfangreich und kommt zu keinem klaren Schluss. Thank you for sending the HTA report. We are happy to respond as a center with the greatest national experience in CAR-T treatment of patients with hematological neoplasms. The report is very extensive and does not come to a clear conclusion. 1. Wir beschränken uns auf die medizinischen Aspekte. Das Ziel des HTA Reports ist die Erfassung von CAR-T Therapien in der 3. Linie. Wir entnehmen darin, dass die vorhandene Datenlage eine zuverlässige Analyse von Kosten und Wirkung schwierig macht. Der Bericht stützt sich weitgehend auf die Situation bei Zulassung von Kymriah und Yescarta. In der Zwischenzeit liegen für die 2. Linie zumindest für Lymphompatient:innen randomisierte Vergleiche mit der Standardtherapie (autologe Transplantation) vor. Zumindest liesse sich z.B. ein Kostenvergleich deutlich zuverlässiger ziehen. Diese randomisierten Studien haben auch den signifikanten Wert bzgl. Ansprechen und Ueberlebensrate von CARs klar gezeigt. Diese Aspekte sind im HTA-Assessment nicht berücksichtigt, dabei ist es das, was für die betroffenen Patienten ausschliesslich zählt. We limit ourselves to the medical aspects. The aim of the HTA report is to record CAR-T therapies in the 3rd line. We see that the existing data makes a reliable analysis of costs and	1. Indeed, the focus of the report is on the current reimbursed populations. Necessarily, this excludes evidence from RCTs of patients treated in 2L, as the population characteristics and treatment effects are likely to differ between 3L. 2. It is acknowledged that a range of alternative comparator options are available in the target populations, many of which are novel and patient-specific. The HTA was conducted using an *a priori* research protocol for the clinical and economic evaluations, that was informed through literature searches and input from a Swiss clinical expert, and were independently reviewed by a panel of Swiss clinical experts. No further changes incorporating other options will be made at this stage. 3. The focus of this HTA is on re-evaluating the evidence for clinical effectiveness, cost-effectiveness, and appropriateness to inform the continued reimbursement of a provisionally-reimbursed (regulated in Annex 1 of KLV) service. Changes in use from 3L to 2L may occur in future (and would be subject to a separate evaluation, with a different research question), but do not exclude

effects difficult. The report is largely based on the situation when Kymriah and Yescarta were approved. In the meantime, there are randomized comparisons with standard therapy (autologous transplantation) for the 2nd line, at least for lymphoma patients. At least a cost comparison, for example, could be made much more reliably. These randomized trials have also clearly demonstrated the significant response and survival value of CARs. These aspects are not taken into account in the HTA assessment, but it is what counts exclusively for the affected patients. 2. In der Zwischenzeit liegt mit Glofitamab eine zugelassene weitere Option für Patient:innen mit aggressiven Lymphomen nach 2 Therapielinien vor (Population des HTA). Dies sollte in einer mit den obigen Bemerkungen angepassten ergänzenden Analyse berücksichtigt werden. In the meantime, glofitamab is another approved option for patients with aggressive lymphomas after 2 lines of therapy (HTA population). This should be taken into account in a supplementary analysis adapted from the comments above. 3. Generell stellt sich unsererseits die Frage, ob die eingeschränkte Betrachtung des HTA sachgerecht ist, da das vorliegende HTA die jeweiligen Entwicklungen nicht zu berücksichtigen scheint. Neue Zulassungen und Indikationserweiterungen haben u.a. durch die Preisgestaltung eine Auswirkung auf das Kosten-/Nutzenverhältnis. In general, the question arises on our part as to whether the limited view of the HTA is appropriate, since the present HTA does not seem to take the respective developments into account. New approvals and indication expansions have an impact on the cost/benefit ratio through pricing, among other things. 4. Der Bericht berücksichtigt auch nicht die bei Einführung ungelösten legalen Fragen im Zusammenhang mit der Kostenübernahme durch die Krankenkassen und dem Label. Diese wurden im Wesentlichen erst 2023 gelöst, und haben bei einigen Patient:innen zu einer inakzeptablen Verzögerung einer potentiell kurativen Therapie auch in der 3. Linie geführt. The report also does not take into account the legal questions that were unresolved at the time of introduction in connection with the reimbursement of costs by health insurance companies and the label. These were essentially only solved in 2023 and have led to an unacceptable delay in potentially curative therapy, even in the 3rd line, for some patients. 5. Fazit: die Analyse ist leider lückenhaft und kommt eigentlich zu spät, da ihre Relevanz schon wieder überholt ist. Conclusion: the analysis is unfortunately incomplete and actually comes too late because its relevance is already outdated.	the possibility of treatment in 3L for a subset of patients. No changes. 4. The report focused on the assessment of the scientific literature regarding the PICO, as well as on ethical, legal, social and ethical issues that were current at the time the report was prepared. The legal regulation of the coverage by the mandatory health insurance already existed from 1 January 2020. FOPH is not aware of any unresolved legal questions regarding reimbursement of the two CART-products in the clinical situations investigated in this present HTA report. 5. Thank you for this feedback. It is noted for consideration by the commission.

6. Novartis

Comment	Author response
1. Es bestehen weiterhin grundsätzliche Bedenken bezüglich des beabsichtigten HTAs, welche wir nachfolgend erläutern und verweisen auf die Stellungnahme von Interpharma vom 06. Februar 2024 sowie auf unsere ausführliche Stellungnahme zum HTA Protokoll vom 23. Februar 2023, welche die Forschungsfrage, PICO, Datenbanken und Suchstrategie sowie die Datenextraktion, Analyse und Synthese kommentiert. Es fehlen klare Rahmenbedingungen sowie transparente Prozessstrukturen für eine Durchführung des HTA bei innovativen Medikamenten. There are still fundamental concerns regarding the intended HTA, which we explain below and refer to Interpharma's statement of February 6, 2024 as well as our detailed statement on the HTA protocol of February 23, 2023, which covers the research question, PICO, databases and search strategy as well the data extraction, analysis and synthesis are commented on. There is a lack of clear framework conditions and transparent process structures for carrying out HTA for innovative drugs. 2. Zudem bleibt auch beim abschliessenden Bericht das genaue Ziel des HTA unklar (Verweis Stellungnahme vom 23. Februar 2023 zum Kommentar zur Forschungsfrage). Dem vorliegenden HTA-Bericht kann entnommen werden, dass dieser erstellt wurde, um die verfügbare Evidenz zur Wirksamkeit und Sicherheit von den CAR-T-Zell-Therapien im Vergleich zur Standardbehandlung zu evaluieren. Zusätzlich sollen die Kosten, die Kosteneffizienz und der Budget Impact der CAR-T-Zell-Therapien und zusätzlich ethische, rechtliche, soziale und organisatorische Fragen im Zusammenhang mit ihrer Anwendung untersucht werden. Aufgrund der fehlenden Rahmenbedingungen sowie das Fehlen eines politisch und gesellschaftlich getragenen Schwellenwerts der bezüglich Kosteneffizienz herbeigezogen werden kann, sind die Ergebnisse einer solchen Auswertung schwierig zu kontextualisieren und somit limitiert aussagekräftig. In addition, the exact goal of the HTA remains unclear in the final report (reference statement from February 23, 2023 to the comment on the research question). This HTA report shows that it was prepared to evaluate the available evidence on the effectiveness and safety of CAR T-cell therapies in comparison to standard treatment. In addition, the costs, cost-effectiveness and budget impact of CAR T-cell therapies as well as ethical, legal, social and organizational issues related to their use will be examined.	1. The HTA has taken on board feedback from multiple stakeholders, as well as a panel of clinical and methodological experts. Feedback from all parties is considered during the protocol phase, and amendments are made accordingly. Reasons for accepting or not accepting changes recommended by parties during the protocol and HTA phases are published transparently. 2. Thank you for this feedback. It is noted for consideration by the commission. 3. In general, no confidential prices and tariffs are used in economic analyses of FOPH HTA reports. In the absence of confidential prices, we agree the analyses are speculative. 4. While the report includes evidence for both tisa-cel and axi-cel in various populations, the drugs have not been compared within the report. For all intents and purposes, the report presents three separate HTAs in the same document (i.e. tisa-cel for B-ALL, axi-cel for LBCL, tisa-cel for LBCL). 5. We re-iterate, CAR T-cell therapies have not been compared in the current HTA. 6. We re-iterate, CAR T-cell therapies have not been compared in the current HTA. For all intents and purposes, the report presents three separate HTAs in the same document (i.e. tisa-cel for B-ALL, axi-cel for LBCL, tisa-cel for LBCL). 7. Experts were included on the premise of anonymity. Names will not be disclosed (nor sub-specialty due to the risk of identification); however, their general field of expertise was relevant (e.g. oncology). Questionnaires to the experts have been stated in the Appendix of the HTA protocol. 8. The focus of this HTA is on re-evaluating the evidence for the clinical effectiveness, cost-effectiveness, and appropriateness of provisionally-reimbursed CAR T-cell therapies, to inform a decision around their continued reimbursement. To this end, the HTA report

Due to the lack of framework conditions and the lack of a politically and socially supported threshold that can be used in terms of cost efficiency, the results of such an evaluation are difficult to contextualize and are therefore of limited significance. 3. Als zu klärendes legales Grundproblem stellt sich weiterhin die Frage, wie im HTA die effektiven Nettopreise der betroffenen Präparate mit vertraulichen Preismodellen berücksichtigt werden können. Sensitivitätsanalysen können hinsichtlich vorhandener Schwellenwerte Hinweise liefern, sind im vorligenden HTA Bericht allerdings rein spekulativer Natur. Insbesondere die Spanne einer Preisreduktion von 0-100% verstärkt den spekulativen Charakter einer solchen Auswertung. The basic legal problem that still needs to be clarified is the question of how the effective net prices of the affected preparations can be taken into account in the HTA using confidential price models. Sensitivity analyzes can provide information regarding existing threshold values, but in the present HTA report they are purely speculative in nature. In particular, the range of a price reduction of 0-100% increases the speculative nature of such an evaluation. Die CAR-T Zelltherapien sind nicht alle gleich: Not all CAR-T cell therapies are the same: 4. Der HTA Bericht analysiert die beiden Therapien Kymriah® und Yescarta® in einem HTA Bericht. Dies steht im Gegensatz zu systematisch durchgeführten HTA Prozessen anderer ausländischer Institute, die die jeweiligen Therapien individuell bewerten. The HTA report analyzes the two therapies Kymriah® and Yescarta® in an HTA report. This is in contrast to the systematic HTA processes carried out by other foreign institutes, which evaluate the respective therapies individually. 5. Die Zulassungsstudien der CAR-T Zelltherapien weisen Unterschiede bezüglich der eingeschlossenen Patientenpopulationen auf, was die Vergleichbarkeit der Studiendaten und -Resultate stark limitiert. Die Durchführung und Analyse von Multi-HTAs (mehrere verschiedene Wirkstoffe in einem HTA) erfordert konsistente und vergleichbare Studiendaten zu den individuellen Interventionen und Vergleichstherapien. Diese Voraussetzung ist im vorliegenden HTA nicht gegeben. The approval studies of CAR-T cell therapies show differences in the patient populations included, which severely limits the comparability of the study data and results. The implementation and analysis of multi-HTAs (several different active ingredients in one HTA) requires consistent and comparable study data on the individual interventions and comparative therapies. This requirement is not met in the present HTA. 6. Bereits in der vorherigen Stellungnahme zum HTA-Protokoll hatten wir angemerkt, die Untersuchungsfrage auf spezifische Patientenpopulation und CAR-T Produkt zu limitieren und getrennte HTA Untersuchungen durchzuführen. Der Anmerkung wurde nicht Rechnung getragen.	presents evidence, it does not make or pre-empt policy recommendations.

In the previous statement on the HTA protocol, we had already noted that we would limit the study question to a specific patient population and CAR-T product and carry out separate HTA studies. The comment was not taken into account. HTA-Prozess: HTA process: 7. Grundsätzlich begrüsst Novartis den Einbezug von Experten, allerdings sollten die Auswahlkriterien der Experten, deren Auflistung (Name und Fachrichtung) sowie die ausgehändigten Dokumente (z.B. Fragebogen und Auswahl der Alternativtherapien) im Rahmen des Protokolls ausgewiesen werden, um die Prozesstransparenz sowie die Validität des HTAs zu erhöhen. Dieser Anforderung wurde in dem abschliessenden HTA Bericht nicht nachgekommen. In principle, Novartis welcomes the involvement of experts, but the selection criteria of the experts, their list (name and field of expertise) and the documents handed out (e.g. questionnaire and selection of alternative therapies) should be stated as part of the protocol in order to ensure process transparency and the validity of the to increase HTAs. This requirement was not met in the final HTA report. 8. Generell stellt sich die Frage, ob aufgrund der fehlenden Klarheit hinsichtlich Zielvorgabe, die Durchführung des HTA der bereits etablierten CAR-T Zelltherapien einen Sinn ergibt. Eine gänzliche Streichung / Desinvestition einer dringend gebrauchten, innovativen Therapie aus dem Schweizer Versorgungskontext wäre mit dem Grundgedanken des KVG nicht vereinbar und ist auch rein ethisch äusserst fragwürdig. In general, the question arises as to whether it makes sense to carry out the HTA of the already established CAR-T cell therapies due to the lack of clarity regarding the target. A complete deletion/disinvestment of an urgently needed, innovative therapy from the Swiss healthcare context would be incompatible with the basic idea of the KVG and is also extremely questionable from a purely ethical perspective.	

7. Onkologiepflege Schweiz (OPS) und Akademische Fachgesellschaft (AFG)

Comment	Author response
1. The report is very detailed and comprehensive in regards to treatment efficacy. Hovewer as we are reviewing it from a nursing perspective our focus is more on the organisational, social and ethical issues. Only very few publications have addressed these, which in turn means that there is very little evidence presented. We do appreciate that the clinical practice recommendations and guidelines are listed in Appendix H but feel that they need to be much more detailed on aspects such as access to treatment, toxiticity management, patient education and psychosocial impact on patients. Examples: The EBMT Immune Effector Cell Nursing Guidelines on CAR-T Therapy (Ellard et al. 2022)	1. Thank you for this feedback. The aim of including the existing clinical practice guidelines is to summarise recommendations about the place of CAR T-cell therapies in the clinical management of patients with B-ALL, DLBCL and PMBCL. It is noted that the guidelines may provide other practical considerations around CAR T use, which are outside the scope of the HTA evaluation.

8. Santésuisse

Comment	Author response
1. Wichtige Aspekte zu medizinischen Grundlagen, PICO-Kriterien, HTA-Fragen und Methodik werden nachvollziehbar erläutert. Die Ergebnisse hinsichtlich Wirksamkeit und Sicherheit werden für die einzelnen CAR-T Zell Therapien nach Indikation aufgezeigt und mit Angaben zur QoE (GRADE) ergänzt. Die Evidenzbasis für die Wirksamkeit und Sicherheit der untersuchten CAR-T Zell Therapien aus den untersuchten 3 NRSI und 24 SA-Studien mit einer sehr tiefen QoE (true effect is likely to be substantially different) ist ohne qualitativ gute und robuste Vergleichsstudien weiterhin sehr schwach. Die konklusive Beantwortung der HTA-Fragen zur Wirksamkeit und Sicherheit im Vergleich mit Standardbehandlungen ist nicht möglich. Zur weiterhin hohen Unsicherheit tragen nebst der Vielfalt von Krankheitsbildern, Pathologien (z.B Histologie, Performance-Status etc.), Verläufen und Therapien (z.B. Vor-, Begleit- und Nachbehandlung, Therapie-Kombinationen, Follow-up etc.), die begrenzte Datenbasis aus einem kurzen Beobachtungszeitraum mit einer dynamischen Entwicklung (klinisch, prozessual) sowie methodische Einschränkungen (z.B. nur 3 NRSI, SA mit teilweise tiefen Fallzahlen, unterschiedlichen Vergleichstherapien, ungenügende Datengrundlage zu TFI, HRQoL und unerwünschten Wirkungen, ungenügende Berücksichtigung von ITT ab slot request und bridging-therapy, keine Subgruppen-Analysen, keine Berücksichtigung des Publication bias etc.) mit einem hohen RoB und hoher Varianz sowie teilweise widersprüchlichen Ergebnissen bei. Die Übertragbarkeit der Ergebnisse auf die Schweiz könnte aufgrund berichteter oder nicht berichteter demografischer bzw. klinischer	1. Thank you for this feedback, no changes required. 2. Thank you for this feedback, no changes required.

	Unterschiede (Versorgungspraxis) teilweise unsicher oder eingeschränkt sein (z.B. Alter, Geschlecht, Krankheitsstadium, slot-request bis CAR-T Infusion, Bridging, SCT-Anschlusstherapie etc.). Die zusätzliche Berücksichtigung von indirekten Vergleichsstudien und Netzwerk-MA würde möglicherweise die Evidenzbasis und damit die Aussagekraft des HTA verbessern. Die gemeinsame Analyse der LBCL-Population ohne Unterscheidung von DLBCL, PMBCL und tFL ist nachvollziehbar, könnte aber zusätzlich zur ungenügenden Evidenzbasis beitragen. Dabei zu beachten ist, dass nur Axi-cel für PMBCL zugelassen ist, welches in der NRSI nach 24 Monaten schlechtere Ergebnisse für OS zeigt als die Vergleichsbehandlung (HR 1.63). Von zusätzlichem Interesse wären (Zwischen-) Angaben zu Auswertungen aus nationalen oder internationalen Registern (SBST, DESCART, GLA, UK Cohort, CIBMTR, US CAR-T etc.). Die untersuchten ethischen, legalen, sozialen und organisatorischen Aspekte scheinen mehrheitlich für die Schweiz von untergeordneter Bedeutung. Important aspects of medical basics, PICO criteria, HTA questions and methodology are explained in a comprehensible manner. The results regarding effectiveness and safety are shown for the individual CAR-T cell therapies according to indication and supplemented with information on QoE (GRADE). The evidence base for the effectiveness and safety of the CAR-T cell therapies examined from the 3 NRSI and 24 SA studies examined with a very low QoE (true effect is likely to be substantially different) remains very weak without good quality and robust comparative studies. It is not possible to conclusively answer the HTA questions about effectiveness and safety in comparison with standard treatments. In addition to the variety of clinical pictures, pathologies (e.g. histology, performance status, etc.), courses and therapies (e.g. pre-, accompanying and post-treatment, therapy combinations, follow-up, etc.), the limited database contributes to the continued high level of uncertainty from a short observation period with a dynamic development (clinical, procedural) as well as methodological limitations (e.g. only 3 NRSI, SA with sometimes low case numbers, different comparative therapies, insufficient data on TFI, HRQoL and undesirable effects, insufficient consideration of ITT from slot request and bridging -therapy, no subgroup analyses, no consideration of publication bias, etc.) with a high RoB and high variance as well as sometimes contradictory results. The transferability of the results to Switzerland could be partially uncertain or limited due to reported or unreported demographic or clinical differences (care practice) (e.g. age, gender, stage of disease, slot request until CAR-T infusion, bridging, SCT follow-up therapy, etc.). The additional consideration of indirect comparative studies and network MA would potentially improve the evidence base and thus the validity of the HTA. The joint analysis of the LBCL population without distinguishing between DLBCL, PMBCL and tFL is understandable, but could additionally contribute to the insufficient evidence base. It should be noted that only Axi-cel is approved for PMBCL, which shows worse OS results in the NRSI after 24 months than the comparator treatment (HR 1.63). Of additional interest would be (interim) information on	

evaluations from national or international registers (SBST, DESCART, GLA, UK Cohort, CIBMTR, US CAR-T etc.). The majority of the ethical, legal, social and organizational aspects examined appear to be of minor importance for Switzerland. 2. Die relevanten Punkte zur Beurteilung der Wirtschaftlichkeit der beiden CAR-T Zell Therapien werden adressiert. Die Literatursuche kann nachvollzogen werden. Eine Kosten-Nutzen-Analyse wurde durchgeführt. Dabei wurden ICERs von ungefähr CHF 70'000 für Tisa-cel bei r/r B-ALL im Vergleich mit Blinatumomab und von CHF 88'000 bzw. CHF 130'000 für Axi-cel bei r/r LBCL und Tisa-cel bei r/r DLBCL im Vergleich mit Chemotherapie ermittelt. Im HTA wurden relevante Bedenken zur Plausibilität dieser Zahlen sowie zur Relevanz dieser Resultate für die Praxis in der Schweiz adressiert. santésuisse kann diese Überlegungen nachvollziehen und fordert, dass diese Lücken mit entsprechenden Massnahmen auf Stufe KLV umgehend geschlossen werden. Nur so können mittelfristig plausible Aussagen zur Wirtschaftlichkeit der beiden CAR-T Zell Therapien gemacht werden. Es sollte im HTA-Bericht explizit festgehalten werden, dass relevante Langzeitdaten zur Beurteilung der Wirtschaftlichkeit der beiden CAR-T Zell Therapien fehlen. Die geschätzten Kostenfolgen der betrachteten CAR-T Zell Therapien betragen rund CHF 40.7 Mio. im Jahr 2023 und rund CHF 64.7 Mio. Jahr 2027. Dabei ist von Kosten von rund CHF 500'000 pro Patient auszugehen. Die Berechnungen können nachvollzogen werden. The relevant points for assessing the economic viability of the two CAR-T cell therapies are addressed. The literature search can be traced. A cost-benefit analysis was conducted. ICERs of approximately CHF 70,000 for Tisa-cel in r/r B-ALL compared with blinatumomab and of CHF 88,000 or CHF 3. 130,000 determined for Axi-cel in r/r LBCL and Tisa-cel in r/r DLBCL in comparison with chemotherapy. The HTA addressed relevant concerns about the plausibility of these figures and the relevance of these results for practice in Switzerland. santésuisse can understand these considerations and demands that these gaps be closed immediately with appropriate measures at KLV level. This is the only way to make plausible statements about the economic viability of the two CAR-T cell therapies in the medium term. It should be explicitly stated in the HTA report that relevant long-term data to assess the economic viability of the two CAR-T cell therapies are missing. The estimated cost consequences of the CAR-T cell therapies under consideration are around CHF 40.7 million in 2023 and around CHF 64.7 million in 2027. Costs of around CHF 500,000 per patient can be assumed. The calculations can be understood.	

9. Swiss Blood Stem Cell Transplantation Group (SBST)

Comment	Author response
The authors need to be congratulated to this huge amount of work. The evidence for efficacy available until April 2023 is well described. Evidence gaps for comparisons with other treatments and economic evaluation are identified. Some points need to be emphasized and further commented on: 1. Comparisons are limited by the fact that during the period evaluated there was no clear priority list which ≥2 line-treatment would be applied to the patients with LBCL, i.e., there is no universal accepted standard of care to compare against it. Hence, the results should be interpreted with caution. Also for B-ALL the comparison of tisa-cel with blinatumomab can be considered controversial. Since the field is rapidly moving on, both the comparator as well as the place of CAR T-therapy within the treatment path of B-ALL and LBCL change and evolve continuously. 2. Digitization of published KM curves to illustrate efficacy is of questionable value and neglects the different patient characteristics and study designs. They should therefore be skipped from the report. 3. The authors conclude that comparisons suggest ICERs of approximately CHF 70'000 for tisa-cel for r/r B-ALL relative to blinatumomab, and of CHF 88'000 and CHF 130'000 for axi-cel for r/r LBCL and tisa-cel for r/r DLBCL, respectively, relative to historical salvage chemotherapy control. We agree with the authors concern, that the use of historical controls might be inappropriate and results misleading. It is furthermore difficult to understand that the calculations are based on the product prices of CHF 379'500 for axicel and CHF 370'755 for tisa-cel. These prices contribute the largest amount of the costs but are lower in real life. The authors are encouraged to calculated with more realistic estimates of surcharge codes. We support the authors' conclusions that there are important limitations underpinning the ICERs. Since the definition of the scope of this HTA, CAR T-therapy in Switzerland has been continuously evolving: 4. New products expand the use of CAR T-therapy, e.g. idecabtagen vicleucel for multiple myeloma, tisagenlecleucel for follicular lymphoma, brexucabtagen-autoleucel for mantle cell lymphoma and adult B-ALL. 5. The number of treatments for LBCL has been growing faster than expected in the HTA report. In 2023 the number is already in the range of the HTA estimates for 2025 (unpublished SBST data). For B-ALL the numbers are within the estimation. However, with the availability of brexucabtagen-autoleucel for adult patients the number of treatments for B-ALL is expected to increase more rapidly than suggested. 6. After introduction of ide-cel there were more patients than production slots. I.e. slot allocation became an important ethical issue that could be solved by the foundation of a national SBST	1. Thank you for this feedback. It is noted for consideration by the commission. 2. In the context that all included studies have met the inclusion criteria for the HTA (i.e. acknowledging that there is variability in patient demographics, but that they all broadly meet the PICO criteria for the HTA), the digitised KM curves illustrate a couple of useful piece of information. First, they show the variability in the spread of the reported survival outcomes, relative to sample size. Second, they show which studies had a relatively greater impact on the total survival curve. Third, they show the difference in survival reported in the NRSI and single-arm studies. Finally, they show survival outcomes in context relative to the duration of follow-up in the reported studies, and thus the limitations in length of follow-up. For these reasons, it is still useful to leave the KM curves in the report, noting that they present only single-arm data for CAR T and do not offer comparative evidence of efficacy. No changes. 3. We note SBST's agreement on concerns around the applicability of the historical control, and that there are important limitations underpinning the ICERs. Re: the product prices, these prices were used as inputs in the base case as information on the actual costs in practice were unavailable to us (due to confidentiality agreements). We acknowledge that these costs may be lower in real life and, for this reason, included the ICER as a function of CAR T product process plots for each comparison. No changes. 4. Thank you for this feedback. It is noted for consideration by the commission. 5. Estimates made based on current use (at time of HTA report), always uncertainty in modelling future use. Committee can take this feedback into consideration. 6. Thank you for this feedback. It is noted for consideration by the commission as relevant organisational issues related to CAR T use from unpublished sources.

CAR T-Myeloma board. Slots could be allocated in a sound and transparent process until the bottleneck was solved. 7. Overall, this HTA report is comprehensive and shows up major gaps in knowledge, particularly the lack of evidence by comparison. Finally, it should be noted that CAR T-therapies are an area with very high dynamics for treatment of a variety of disorders. The current focus on hemato-oncologic tumors is expected to expand to other malignant and non-malignant disorders in the future. Phase III trials are ongoing and will contribute to more mature data. Furthermore, outcome registries comparable to those of autologous and allogeneic transplant recipients will increase the knowledge on long-term efficacy and potential late effects. Therefore, outcome reporting needs to be acknowledged as an integral part of cellular therapies.	7. Thank you for this feedback. It is noted for consideration by the commission.

10. Swiss Society of Hematology (SSH)

Comment	Author response
The form contains an extract from the SSH statement. The complete statement can be found in the attached document. 1. Chimeric Antigen Receptor (CAR) T-cell therapy revolutionized the treatment of major B-cell malignancies, namely B-cell Acute Lymphoblastic Leukemia (B-ALL) in children and young adults and Diffuse Large B-Cell Lymphoma (DLBCL) in adults. Almost 7 years since their original approval by the FDA, thousands of patients including children received CAR T cell therapy, the favorable risk/benefit profile of which is clearly demonstrated. **Efficacy** 2. DLBCL is the major indication for CAR T cells worldwide and is therefore the disease in which most experience was acquired. Initially approved based on single-arm, non-comparative phase 2 studies with relatively short follow-up, the efficacy of CAR T cells in DLBCL is now supported by long term analyses and comparative data. Long term follow-up of the ZUMA-1 and JULIET pivotal clinical trials who lead to axicabtagene ciloleucel (axicel) and tisagenlecleucel (tisacel) approval in 3rd line show long term (more than 5 years) progression free survival (PFS) in about one third of treated patients. Importantly, a real-world series reported by the US-consortium at the last ASH meeting showed 5-year outcomes very similar to the ones of the pivotal clinical trials, and this despite the fact that a significant proportion of patients treated in the real-life setting did not fulfill the strict criteria of the clinical trials. Collectively the long-term results obtained both in clinical trials and real life	1. Thank you for this feedback. It is noted for consideration by the commission. 2. Thank you for this feedback. It is noted for consideration by the commission. 3. Thank you for this feedback. It is noted for consideration by the commission. 4. Thank you for this feedback. It is noted for consideration by the commission.

indicate that CAR T cells, even when administered in third line, can represent a curative option for DLBCL patients. 3. After their original approval in third line, CAR T cells have now been tested in well conducted, multicenter, randomized phase 3 clinical trials assessing their potential use in second line in comparison with salvage chemotherapy and high dose chemotherapy followed by autologous stem cell transplantation (HD-ASCT). These studies demonstrated that second line treatment with axicel improved PFS and overall survival (OS) when compared with salvage chemotherapy and HD-ASCT. To note, the OS benefit associated with CAR T cell use was demonstrated even though more than half of the patients in the HD-ASCT group received subsequent off-protocol third line CAR T cell therapy because of lack of response or disease progression. A similar trial performed with tisacel failed to show a positive impact of tisacel treatment over HD-ASCT. Based on these results, axicel treatment in second line became a new standard of care for patient with refractory or early relapsing DLBCL. 4. The need to have access to two different products, axicel and tisacel, for DLBCL is debatable. A propensity score matched analysis performed by the French colleagues on a large cohort of patients showed significantly improved PFS and OS in axicel treated patients compared to tisacel treated ones. However, axicel treatment was clearly associated with higher rates of toxicities. These and other retrospective results oriented most centers to privilege the use of axicel over tisacel in fit patients and to limit the use of tisacel to frail patients judged not eligible for axicel treatment because of toxicities. It is therefore of potential interest having access to both products at the national level if we want to increase the eligible population that can potentially benefit of such treatment. The increased use of lisocel (a product not part of this consultation) might solve this issue given its excellent toxicity and efficacy profile. Please find the complete statement in the attached document.	

11. Swiss Society of Medical Oncology (SSMO)

Comment	Author response
Relevance of this report to SSMO community 1. Our core medical activity includes research in medical oncology for disease for which no curative therapies are available, as such CAR-T based therapies offer the opportunity to explore a novel powerful mean to tackle many of hematological but also solid tumor challenges (tumor heterogeneity, immunosuppressive microenvironment, non permissive tumor stroma). SAKK created a cell and gene therapy group to push forward these therapies in early phase trials. This is also important as CAR-T approaches will have to be included in the control arm of many trials to come as soon as CAR-T become a standard treatment. For these reasons SSMO representing medical oncologist in private and public practice should be involved in the discussion relative to this HTA. **Safety aspects** 2. CAR-T cells safety profile is well described at least for CD19 for leucemias and lymphomas and BCMA for multiple myeloma (which is not mentioned in this HTA report and is approved), and management algorithms for CRS and ICANs are clearly established in experienced centers. Insertional mutagenesis is recently described as potential risk of induced T cell leukemia as recently raised by the FDA, but it's important to state that over 30 000 patients treated worldwide, only 20 cases were observed. This is a lower incidence of leucemia when compared to other anti-cancer SOC therapies (chemotherapy, radiotherapy). Novel CAR designs including inducible (syn notch, etc.), switch-off, constructs are currently being tested in humans and will further improve safety profile. All of these aspects should at least be mentioned in the report. **Access and regulatory aspects** 3. Many programs are ongoing worldwide and science is advancing very fast thanks to regulatory agencies offering clear guidance of requirements to translate academic CARs to early phase trials. Due to very long IND approval times granted by Swissmedic for phase I trials and since Switzerland is lagging behind US, Australia, UK, China and other countries, it would be interesting to suggest the possibility to offer novel CAR-Ts already tested in the clinic elsewhere (with evidence of safety and efficacy) to Swiss patients with compassionate access. This aspect is not taken into account in the current HTA version. **Economical and efficacy aspects** 4. The HTA report concludes by stating a "Very low" certainty comparative evidence about efficacy and safety of tisa-cel and axi-cel compared to the current SOC for B-ALL, DLBCL and	1. Thank you for this feedback. It is noted for consideration by the commission 2. Thank you for this feedback. A statement regarding insertional mutagenesis has been added to the additional issues section of the HTA. 3. Thank you for this feedback. It is outside of the scope of the current HTA to comment on these issues. This feedback is noted for consideration by the commission. 4. It is acknowledged that defining the most relevant comparators was a key challenge for this HTA. Nonetheless, in the absence of CAR T, there are therapeutic options available. The purpose of the HTA is to present evidence for the relative efficacy and effectiveness of the CAR T treatments compared to other available options. The absence of robust, comparative studies limits the ability of the HTA to draw conclusions around relative treatment effects. Statements of the strength of evidence are based on an established evaluation framework (i.e. the GRADE approach), which considers study design, risk of bias, inconsistency, indirectness, imprecision, and other factors (e.g. risk of publication bias, etc.). 5. Thank you for this feedback. It is noted for consideration by the commission.

PMBCL due to the majority of the evidence base being single-arm. Indeed, that's exactly why the FDA created the "breakthrough designation" for these unprecendented clinical results in such refractory tumor indications. As such we shouldn't agree on this very strong statement suggesting that the selected studies were insufficient to inform about CART superiority as compared to SOC. Many patients especially in refractory LAL-B would have had a fatal outcome without CAR-T cells, since all available SOC had previously failed. 5. The poor outcome of conventional therapies for patients with LAL-B is documented in the SCHOLAR-1 study. This study on a patient-level analysis of outcomes of refractory DLBCL from 2 large randomized trials and 2 academic databases demonstrated poor outcomes in patients with refractory DLBCL, supporting a need for more effective therapies for these patients. The key findings were: For patients with refractory DLBCL, the objective response rate was 26% (complete response rate, 7%) to the next line of therapy, and the median overall survival was 6.3 months. Twenty percent of patients were alive at 2 years. (Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 studyM. Crump et al. Blood (2017) 130 (16): 1800–1808.) Please find the complete statement in the attached document.	

Appendix

Additional stakeholder comments

Gilead

Comment
General comments: **1** Gilead expresses concerns about the HTA procedure. In this HTA, two CAR T cell therapies listed as “under evaluation” in Annex 1 of the Health Insurance Benefits Ordinance are investigated. This HTA is part of the overall evaluation of these two CAR T cell therapies according to the evaluation concept. The focus of the FOPH's HTA program is on divestment while CAR T cell therapies are new highly innovative products not compatible to divestment-efforts. ATMPs such as CAR T cell therapies are seen e.g., by the European Medicines Agency (EMA) as "groundbreaking new opportunities for the treatment of disease". https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview **Divestment may be discriminatory for patients who benefit from treatment with axi-cel. This HTA may discriminate CAR T cell therapies like axi-cel and tisa-cel versus another CAR T that is not in scope of this HTA**. **It is of utmost importance that equitable access to innovative treatments for patients in need is possible.** **2.** We note that the chosen methodology results in **no conclusive statement** on the cost-effectiveness of CAR T therapies in LBCL or ALL. The authors classify the evidence base of the underlying studies as low and the economic models used show uncertainties or are based on rough assumptions. On this basis, the HTA's informative value is very limited. For this reason, we would **strongly advise against drawing up recommendations for action** on this basis, in particular if Pola-BR, Tafa-Len and/or SCT remain to be considered as comparators to CAR T in 3L+ LBCL. **3. There is no cost-effectiveness threshold value in Switzerland that could prevent patients to have access to a treatment bringing a life-saving opportunity.** In the absence of any legal binding threshold, incremental cost-effectiveness ratio (ICER) or incremental cost-utility ratio (ICUR) results cannot be used to decide on reimbursement on CAR T therapies. **4.** Despite methodological issues, errors, and unfavorable assumptions in this HTA, **Gilead acknowledges the current result of the HTA that confirms cost-effectiveness of axi-cel at the majority of arbitrary used thresholds already at the product price used in the calculations, in particular vs a historical cohort and favorable results of axi-cel vs tisa-cel.** **5. However, the results in this HTA are generally in line with analyses performed in HTA countries, in many of which axi-cel is recommended and reimbursed.** Multiple international HTAs recommend axi-cel. For example, the **National Institute for Health and Care Excellence** (NICE) has issued final draft guidance already last year in Jan’23 “**recommending the treatment be made routinely available on the NHS for suitable patients.** (…) NICE’s independent appraisal committee considered new evidence, including data from a clinical trial and from people having axicabtagene ciloleucel through the Cancer Drugs Fund (CDF) before making the recommendation. It suggests that people having axicabtagene ciloleucel live longer than people having chemotherapy and have longer before their condition gets worse.” https://www.nice.org.uk/News/Article/more-than-400-people-set-to-benefit-after-nice-approves-ground-breaking-car-t-therapy-to-treat-aggressive-form-of-blood-cancer **6. There are key methodological issues and unfavorable assumptions in this HTA that do not reflect real-world practice which are summarized in the following and addressed further below:**

- Not sharing the underlying economic model of the HTA resulting in the inability of stakeholders to spot errors, critique inputs and interactions of parameters.
- Not using mixed cure model (MCM) modeling framework. In fact, no other HTA has considered using spline models in their base case economic modelling assumptions. Cure models are more clinically supported given the mechanism of action of CAR T, whereby a proportion of the cohort are cured after receiving CAR T. This is best practice with UK NICE guidance and according to publications that were not considered in this HTA report.
- Using a naïve comparison (particularly vs Pembrolizumab and Pola-BR) instead of meta-analysis or matching adjusted indirect comparison (MAIC) leads to immeasurable biased estimates of effectiveness which interns will perpetuate into the economic model.
Further clarification is required as to why these methods were not considered as it is best practice in other HTAs and UK NICE guidance.
- Outdated budget impact assumptions (not considering shift from 3L to 2L LBCL CAR T treatments since 2023 in Switzerland)
- Not considering latest (comparative) data
7. No multi-HTA with multiple CAR T therapies in one HTA. A single HTA per product per indication is required. The HTA protocol assumed that all CAR Ts are the same, although clinical & real-world data proves the opposite. CAR T is a highly complex and individualized therapy. The implementation and analysis of multi-HTAs (several different active ingredients in one HTA) requires consistent and comparable study data on the individual interventions and comparative therapies. This requirement is not fully met in this HTA report. In countries with HTA institutions, each CAR T product was usually assessed separately (that is confirmed by most of the listed economic evidence in the appendix of the HTA protocol/report). The FOPH should provide at least a separate report by product.
8. The clinical heterogeneity of CAR T products and trials makes it difficult to compare these products and needs to be done with caution. The HTA process could result in inappropriate recommendations negatively impacting patient care and access in particular related to CAR T as potential curative treatment option vs treatments like Pola-BR in DLBCL and Pembrolizumab in PMBCL.
9. Confidential net price agreements have enabled reimbursement of CAR T cell therapies in Switzerland and other countries. In the case of this HTA report, the **confidentiality of the prices was maintained in order not to jeopardize the market access for patients in Switzerland**. We appreciate that relevant stakeholders in knowledge of the confidential net price will be able to conclude that the therapies are cost-effective already at the product price defined in the HTA report while the confidential net price is lower and further increasing cost-effectiveness. Nevertheless, we suggested in the HTA protocol feedback that the FOPH should consider providing the HTA results to the license holder before publication of the draft and final report to others so that the license holder company may assert any business secrets while the HTA report draft was shared with all stakeholders at the same time.
10. Confidential feedback: The comments of the marketing authorization holders on this HTA report are published on the FOPH website. This makes it impossible for marketing authorization holders to include confidential data and prices in their comments. A possibility must therefore be created for this data to be included in the stakeholder feedback on the report without jeopardizing confidentiality.
11. Consideration of most current and comparative data: CAR T cell therapy is a new, highly innovative drug for which new data is constantly being generated. Therefore, the current data (e.g., clinical data, guidelines, health economic data, current label) should be used for each product. In addition, current data is presented regularly, e.g., at the American Society of Hematology Congress (ASH) in December and at other congresses. These should be considered in the HTA. Please consider capturing latest data e.g., single long-term follow-up data points with a) conference abstracts and b) the current SMPC (aktuelle Fachinformation) approved by Swissmedic. If this HTA is needed to inform future reimbursement decisions, it should include contemporary, best available, evidence.
12. The **HTA report does not consider the further development of these therapies**. The use of axi-cel is already shifting to an earlier therapy line vs the line focused in the HTA

due to statistically significant favorable endpoints vs standard-of-care (EFS, OS & ORR) which was assessed in a phase III randomized controlled trial (RCT). YESCARTA is already recommended as second-line LBCL treatment in patients who relapse early after first-line chemoimmunotherapy. Generally, there is an expert consensus (e.g. DGHO guidelines), supported by clinical evidence, that whenever a patient is CAR T eligible, CAR T should be the preferred treatment choice vs any other treatment and as early as possible in an aggressive lymphoma like LBCL. **13. The majority of axi-cel LBCL** patients treated in Switzerland in **2023** was likely already **treated in 2L vs 3L+** therefore the **relevance** of this **HTA report**, in particular **budget impact** assumptions and results **are outdated and extremely overstated for 3L+ LBCL.**

14. Again, as already stated in the HTA protocol feedback (which was not considered), the license holder company should be involved in the development of the model (or provide the model for criticism), and where possible, data be made available commercial in confidence which is a standard practice in HTA like the NICE assessment. The **de-novo model** in this HTA is being developed and populated by a third-party, thus access to data is limited to what is publicly available. However, basic inputs, such as survival analysis using a cure model require individual patient level data to accurately estimate cost-effectiveness. Furthermore, resource use data collected in trials cannot be utilized. As a result, the cost-effectiveness model does not make use of the best available evidence and therefore may be unfit for decision making.

15. The **PMBCL comparison has major flaws and should be reworked before publication of the HTA because patient populations in the studies compared have only immaterial overlap** which may mislead stakeholders to wrong conclusions regarding efficacy and cost-effectiveness of axi-cel vs pembrolizumab in PMBCL.

16. The HTA protocol did not detail the areas in which the license holder company will be consulted, how the companies' comments are addressed and timelines for doing so. Gilead, as one of the two license holder companies in this HTA was only informed to provide stakeholder feedback related to the HTA protocol and report as part of the overall stakeholder feedback process. Feedback regarding the HTA protocol was acknowledged, but only partially considered (see further details in published HTA protocol feedback).

17. The HTA stakeholder feedback period should be extended to at least 2 months. It currently remains an unreasonably and insufficient short timeframe for a license holder company of the product in this HTA to review SLR results, clinical and economic assumptions, modelling and results within less than one month.

18. Involving experts: at various points in the HTA protocol, reference was made to a survey of experts (7.3.1.4 Relevant comparators to the Swiss context; 7.3.4 Cost inputs; 7.3.4.1 CAR T cell therapy costs). In principle, the involvement of experts is welcomed. However, if experts are involved, the selection criteria, the list of experts interviewed (name, discipline, treating experience with CAR T) and the questions/questionnaires asked must also be reported as part of the HTA protocol & report. Otherwise, potential conflict of interest may not be discovered. Furthermore, the expert feedback collected should be published like the questionnaire published in the appendix of the HTA report. Otherwise, a selection bias regarding expert feedback by the HTA vendor/FOPH cannot be ruled out.

19. Potential conflict of Interest of the authors, experts and/or vendors: The authors may have potential conflict of interest in relation to this project & other HTA assessments if regularly selected as HTA third-party vendor. Please comment if the selected third-party vendor was also used for other FOPH projects or in other HTAs related to CAR Ts or potential comparators, for which interventions/products and in which country.

Research question / Policy:

20. The clinical heterogeneity of CAR T products and trials makes it difficult to compare these products and needs to be done with caution. The HTA process could result in inappropriate recommendations negatively impacting patient care and access.

21. HTA protocol & report title is still mixing indications of both products not according to marketing authorization (Axi-cel is indicated in DLBCL/PMBCL) and reimbursement according to KLV annex 1. A single HTA and at least a separate HTA report per product per indication would have been required and clearer.

22. There is no cost-effectiveness threshold value in Switzerland that could prevent patients to have access to a treatment bringing a life-saving opportunity. Incremental cost-effectiveness ratio (ICER) or incremental cost-utility ratio (ICUR) results cannot be used to decide on reimbursement on CAR T therapies.
23. Confidential net price agreements have enabled reimbursement of CAR T cell therapies in Switzerland and other countries. In the case of this HTA report, the **confidentiality of the prices was maintained in order not to jeopardize the access for patients in Switzerland**. We appreciate that relevant stakeholders in knowledge of the confidential net price will be able to conclude that the therapies are cost-effective already at the product price defined in the HTA report while the confidential net price is lower and further increasing cost-effectiveness. Nevertheless, we suggested in the HTA protocol feedback that the FOPH should consider providing the HTA results to the license holder before publication of the draft and final report to others so that the license holder company may assert any business secrets while the HTA report draft was shared with all stakeholders at the same time.
24. Societal costs (direct non-medicinal and indirect costs) of DLBCL are potentially material vs direct medicinal costs. We would like to highlight the importance of **widening the analysis beyond the health care payer perspective to capture the full benefit of this highly innovative therapy sufficiently**.
25. Efficacy and safety have already been evaluated by regulatory entities: Axi-cel is approved by Swissmedic, EMA, FDA etc. and is recommended in guidelines for treatment of 2L+ DLBCL with clinical data based on Phase 3 RCT vs SOC; for 3L+ DLBCL with indirect comparison to a historical cohort (SCHOLAR-1), therefore the efficacy, safety and clinical benefit profile has already been reviewed by the relevant regulatory authorities and also other international HTA institutions. As part of the marketing authorization approval process, questions regarding efficacy and safety were assessed in detail by Swissmedic.
26. Market share (MS) and price assumptions significantly influence the Budget Impact Analysis. **The current share and trend in DLBCL in the Swiss CART registry are in favor of axi-cel and shift from 3L+ to 2L LBCL must be considered in the HTA report.**

PICO:
27. It is r**ecommended combining DLBCL & PMBCL together** due to rare data/publications regarding PMBCL (in line with the conclusions of the initial search results in the HTA protocol). Guidelines generally suggest that r/r PMBCL is treated like r/r DLBCL.
28. Comparators need to be reviewed and compared carefully due to potential impact on the HTA results.
29. Outcome measurements & focus on clinically relevant parameters: The heterogeneity of definitions of PFS & other outcomes was not addressed. E.g., **the PFS definition for both products (timing and start point for evaluation) differs in the studies.**
30. Definition of grades in neurological events and how to manage adverse events (AEs) were different in the pivotal studies.
Databases and search strategy:
31. Please ensure the results are checked according to patient population, settings, age of study and other possible variables, which may affect the results.
32. Please ensure comparability of selected studies. Unadjusted patient populations from multiple studies were compared in this HTA report, therefore HTA results must be interpreted with utmost caution.
33. The **Swiss CAR T registry** is used as one of the data sources in this HTA (in HTA protocol: 7.3.2.1 The role of SCT, 7.3.4.1 CAR T cell therapy costs, 7.4.2.1 Patient numbers). As recorded in the protocol, this **data is not yet fully developed and must be interpreted with the utmost caution**. Comprehensive RWD from the USA and Europe are available, which are more meaningful than the Swiss registry data due to larger population and longer follow-up. It should also be noted that the Swiss registry data is not direct or indirect comparative data and that there was no matching-adjusted indirect comparison (MAIC) due to the small patient population. **An independent indirect comparison of axi-cel vs tisa-cel not yet considered in this HTA**

report is from the French CAR T registry highlighting stronger efficacy of axi-cel vs tisa-cel (Bachy et al. 2022: doi.org/10.1038/s41591-022-01969-y).
34. Consideration of most current and comparative data: CAR T cell therapy is a new, highly innovative drug for which new data is constantly being generated. Therefore, the current data (e.g., clinical data, guidelines, health economic data, current label) should be used for each product. In addition, current data is presented regularly, e.g., at the American Society of Hematology Congress (ASH) in December and at other congresses. These should be considered in the HTA.

Please consider capturing latest data e.g., long-term follow-up data points with a) conference abstracts and b) the current SMPC (aktuelle Fachinformation) approved by Swissmedic.
35. Appendix: HTA agency websites: missing agencies not searched as these are not on INAHTA member list but may contain relevant HTA publications: MSAC & PBAC for Australia, DMC for Denmark, AIFA for Italy, NOMA for Norway, TLV for Sweden, ICER for United States.

Data extraction, analysis, synthesis:
36. There is no cost-effectiveness threshold value in Switzerland that could prevent patients to have access to a treatment bringing a life-saving opportunity. In the absence of any legal binding threshold, incremental cost-effectiveness ratio (ICER) or incremental cost-utility ratio (ICUR) results cannot be used to decide on reimbursement on CAR T therapies.

37. Market share (MS) and price assumptions significantly influence Budget Impact Analysis. **The current share and trend in DLBCL in the Swiss CART registry are in favor of axi-cel and the shift from 3L+ to 2L LBCL must be considered in the HTA report.**
38. Long term efficacy (Overall Survival – OS) focus is key in 3L+ DLBCL/PMBCL with comparison outside RCT due to palliative setting. For ethical reasons all study patients should receive CAR T and not salvage chemotherapy in the trial, therefore indirect **comparison only according MAIC (comparable patient population) with historical cohort (SCHOLAR-1).**
39. The license holder company should be involved in the development of the model (or provide the model for criticism), and where possible, data be made available commercial in confidence which is a standard practice in HTA like the NICE assessment.
The **de-novo model** in this HTA is being developed and populated by a third-party, thus access to data is limited to what is publicly available. However, basic inputs, such as survival analysis using a cure model require individual patient level data to accurately estimate cost-effectiveness. Furthermore, resource use data collected in trials cannot be utilized. As a result, the cost-effectiveness model does not make use of the best available evidence and therefore may be unfit for decision making.
40. Despite methodological issues, errors, and unfavorable assumptions in this HTA, **Gilead acknowledges the current result of the HTA that confirms cost-effectiveness of axi-cel at the majority of arbitrarily pre-specified thresholds in the HTA report already at the product price used in the calculations, in particular vs a historical cohort and favorable results of axi-cel vs tisa-cel.**
41. However, the results in this HTA are generally in line with analyses performed in HTA countries, in many of which axi-cel is recommended and reimbursed.

Multiple international HTAs recommend axi-cel. For example, the **National Institute for Health and Care Excellence** (NICE) has issued final draft guidance already last year in Jan'23 "**recommending the treatment be made routinely available on the NHS for suitable patients.** (…) NICE's independent appraisal committee considered new evidence, including data from a clinical trial and from people having axicabtagene ciloleucel through the Cancer Drugs Fund (CDF) before making the recommendation. It suggests that people having axicabtagene ciloleucel live longer than people having

chemotherapy and have longer before their condition gets worse." https://www.nice.org.uk/News/Article/more-than-400-people-set-to-benefit-after-nice-approves-ground-breaking-car-t-therapy-to-treat-aggressive-form-of-blood-cancer

42. Section 7.1.2.3 in the HTA protocol stated that most studies assessing the cost-effectiveness of axi-cel considered a combined population of adults with LBCL. We recommend combining **DLBCL & PMBCL** accordingly and assuming PMBCL to be treated like DLBCL which is also stated in guidelines in this HTA report.

43. Comparators: Why is tisa-cel not evaluated against SCHOLAR-1 but axi-cel evaluated vs CORAL although the historical cohort was SCHOLAR-1? Please comment if and how imbalances are corrected. The comparator needs to be the same and all confounders accounted for. This is difficult to do without individual patient level data (IPD). A network meta-analysis assumes randomization accounts for trial imbalances when there is a common comparator. A full protocol and statistical analysis plan (SAP) must be provided for the license holder company to comment on it. Please find below a **network meta-analysis** from Locke et al. 2022 that was so far not considered in the HTA protocol or report: (3346 Network Meta-Analysis (NMA) of Chimeric Antigen Receptor (CAR) T-Cell Therapy for the Treatment of Relapsed/Refractory Diffuse Large B-Cell Lymphoma (DLBCL) after 2 Prior Treatments Using Published Comparative Studies)
https://ash.confex.com/ash/2022/webprogram/Paper169812.html This NMA leverages "(…) available evidence to conduct an adjusted indirect comparison of axi-cel, liso-cel, and tisa-cel using published comparative studies of CAR-T products to historical SoC cohorts. (…) The search identified 467 publications, of which 3 were included in the evidence base. (…) In the first study, axi-cel individual patient data (IPD) was compared to SCHOLAR-1 (a historical SoC cohort) IPD using propensity score methods. For the second, a matching adjusted indirect comparison (MAIC) was used to compare liso-cel IPD to SCHOLAR-1 summary data. For the third, tisa-cel IPD was compared to CORAL IPD, a historical SoC cohort (and a sub-cohort of SCHOLAR-1). The results from the ITT population of JULIET were used in this analysis. Available outcomes across all three studies included overall survival (OS) and overall response rate (ORR). Complete response (CR) was analyzed where possible. All three treatments were superior to SoC across all outcomes. (…) For OS, axi-cel had a significantly lower hazard ratio for death relative to liso-cel and tisa-cel. (…) Results of the analyses suggest that axi-cel leads to improved OS in r/r DLBCL relative to liso-cel and tisa-cel. Axi-cel and liso-cel were comparable with respect to response outcomes, showing favorable ORR relative to tisa-cel. These results are in line with MAIC results, where efficacy between CAR-T treatments have been directly compared but offer the advantage of being able to include a common comparator in the absence of placebo controlled RCTs." **44. Comparison**: **An inclusion of tafasitamab and polatuzumab as DLBCL comparators would lead to inconclusive results.** Section 7.3.1.4 in HTA protocol mentioned tafasitamab and polatuzumab as DLBCL comparators, but those were not listed under "comparator" section in page 10 of the HTA protocol. One important caveat about these products is that their studies include earlier treatment line patients and are also used as a bridge (Pola-BR) to CAR T in Switzerland. Why are these antibody treatments considered as comparators in the HTA report since their studies include only a small number of patients when we try to match the population to ZUMA-1 trial, we will end up with very small number of patients.

45. Section 7.3.4.1 in HTA protocol stated 80% of patients receive bridging. **The evaluation should be done as per trial** and a scenario analysis with bridging based on RWE. **Including bridging might affect the probability of infusion, efficacy, and adverse events (de-bulking approach to reduce tumor size ahead of CAR T infusion).** The assumptions for bridging in the HTA report are not product specific nor derived from RWE therefore results to be interpreted with utmost caution.

46. Discount rate is set at 3.0% in the HTA protocol and report. Please provide the rationale for the base case rate and the sensitivity range.

Detailed feedback - in order of the HTA report ("P98" means e.g. the page number in the PDF-file, not the page number of the HTA report itself):

47. More than sufficient evidence was already **generated globally** and **other international HTA organizations confirmed in final HTAs the high benefit & value of axi-cel in 3L+ DLBCL/PMBCL that led for example to permanent reimbursement for axi-cel in 3L+ DLBCL/PMBCL like UK NICE and other countries.**

48. Long-term OS data for axi-cel in ZUMA-1 for 3L+ DLBCL/PMBCL & RWE (5 years) was published & there is broad real-world evidence (RWE) with more than 15000 patients treated with axi-cel worldwide in clinical trials and in the commercial setting.

49. Gilead/Kite acknowledges that the robust **ZUMA-1 long-term data (5 years OS) was considered in this HTA**. Please be aware that also disease-specific long-term 5 years survival

data was published showing a KM-curve with a survival plateau for half of the pivotal study patients. This data was not considered in this HTA report. **50. ZUMA-1 was the pivotal study which led to regulatory approval and reimbursement** in Switzerland and many other countries for patients with high unmet need with supportive data from a historical cohort (SCHOLAR-1).

51. Importance and context of ZUMA-1 trial design & results:

• ZUMA-1 has the longest follow-up data on 3L+ LBCL CAR T patients. International regulatory authorities and HTA organizations accepted ZUMA-1 data for axi-cel in 3L+ DLBCL/PMBCL evaluation vs historical cohort (mainly SCHOLAR-1 data).

• ZUMA-1 was a single-arm study for ethical reasons. A RCT study design in an aggressive late line indication like 3L+ LBCL with patients receiving CAR T with potential of cure vs salvage chemo patients with quite certain death within 6 months already known from historical cohort results would not be approved by an ethics committee.

52. RWE confirms ZUMA-1 pivotal study outcomes: Swiss registry data and other RWE does not show any unexpected outcomes or results that would contradict to clinical studies performed so far or data collected elsewhere. RWE with 5 year long term follow-up data confirms ZUMA-1 pivotal study long-term data. (Spiegel et al. 2023 doi.org/10.1182/blood-2023-179868)

53. Please consider 3L to 2L treatment evolution shift for CART & materially reduced 3L+ CART budget impact respectively: ZUMA-7 data, a Phase III RCT vs SOC was published for axi-cel and led in Switzerland in 2023 to a shift of treatment line for CAR T to 2L vs 3L+ LBCL. CAR Ts were standard of care in 3L+ and now are standard of care in 2L setting with a one-time treatment/infusion. The ZUMA-7 RCT provides high certainty regarding clinical results vs SOC and demonstrated a statistically significant benefit in OS, EFS, ORR vs SOC. Budget impact assumptions regarding 3L+ LBCL are therefore outdated and extremely overstated (P6).

54. Please prioritize referring to guidelines & real-world-evidence for axi-cel: CAR T has been established as SOC in 3L+setting and is in use more than 5 years in clinical setting. RWE further confirms effectiveness and safety profile of CAR-T products. There are 2 examples of reliable sources for RWE from independent groups collecting data on all CAR Ts and publishing data: CIBMTR from the US and DESCAR-T from France. DESCAR-T is an independent registry sponsored by LYSA group. The publication of Bachy et al. is an independent data source where we see a robust ITC as the LYSA groups owned the data and based on the IPD as they have it for both products. The number of patients included in both registries makes them largest and longest follow-up for any CAR T.

55. Please exclude antibody treatments in general as comparator to CAR T: Antibodies' data is immature, and these treatments are not established as standard of care. RWE is very limited related to antibody-treatments like Pola-BR or tafa-len and these are currently **not** considered as **curative**. Any indirect treatment comparisons (ITC) vs antibody-treatments must be done with pivotal studies (not RWE) and population differences make it very difficult to run a robust ITC (such as there are post-CAR T patients in these studies etc.)

56. P5: **Exclusion of Pola-BR as comparator from clinical and economic analysis in 3L+ LBCL:**

• Pola-BR could theoretically be used in 3L+ DLBCL, but the population in clinical practice is likely not the same as 3L+ CAR T eligible population.

• Pola-BR can also be used in 2L restricted to transplant ineligible patients which is 30% of the pivotal study. Apparently this HTA did not adjust the Pola-BR data for 2L patients in Pola-BR study.

Furthermore, DGHO-guidelines do not recommend Pola-BR in 3L+LBCL, but only in 2L transplant ineligible population similar as Tafa-Len. Therefore Pola-BR should not be compared with 3L+ CAR T.

• P38: It is stated in the HTA that Pola-BR is used according to Swiss experts to bridge to CAR T rather than as alternate treatment option to CAR T.

• Pola-BR is only temporary listed on the specialty list for SCT-ineligible patients (in r/r DLBCL).
• Any conclusions in the HTA report related to CAR T vs Pola-BR as a comparator are therefore strongly biased in favor of Pola-BR.
• Pola-BR should be excluded as comparator for the reasons as stated above.
• No rationale was provided in this HTA why Tafa-Len was excluded which is another antibody-treatment with similar label/patient population data like Pola-BR. If Pola-BR is included as comparator, Tafa-Len should be included too, but as stated above there are multiple reasons to exclude both as potential comparators.

57. Exclusion of Tafa-Len as comparator:
• Tafa-Len could theoretically be used in 3L+ DLBCL, but the population in clinical practice is likely not the same as the 3L+ CAR T eligible population.
• Tafa-Len can be used in 2L setting restricted to transplant ineligible population.
• Objections related to a comparison in Nowakowski G. et al., Clin Cancer Res. 2022 Sep 15;28(18):4003-4017. doi: 10.1158/1078-0432.CCR-21-3648.: While CAR T is RWE in the analysis, there is a highly selected patient population in the RE-MIND2 study for Tafa-Len, many censored patients, therefore highly unreliable Kaplan Meier curves. Furthermore, it is not clear which CAR T product was administered.
• Ruckdeschel data regarding Tafa-Len from ASH 2023 conference, https://ash.confex.com/ash/2023/webprogram/Paper185992.html show that “the outcomes including ORR, PFS and OS in the real-world setting were lower than observed in the preceding phase II clinical trial (L-MIND).”
• No rationale was provided in this HTA why Tafa-Len was excluded which is another antibody-treatment with similar label/patient population data like Pola-BR. If Pola-BR is included as comparator, Tafa-Len should be included too, but as stated above there are multiple reasons to exclude both as potential comparators.

58. Exclusion of Shadman et al. 2022 publication due to ASCT comparator not applicable in 3L+DLBCL:
• P163: A rationale for exclusion is stated in the HTA: “No costs or disutilities for subsequent SCTs were incorporated into the LBCL models, based on feedback that subsequent SCTs do not apply for DLBCL or PMBCL, and that it would be very unlikely to perform a transplant following a comparator therapy in the third-line setting”.
• P5: AutoSCT is a 2L LBCL treatment modality. Even if it is possible to make autoSCT in 3L+, it is unlikely – this was confirmed also by the Swiss experts in this HTA report. Therefore, the publication of Shadman et al. should be excluded from the analysis due to study design and/or patient population not matching the scope of this HTA.
• Furthermore if the results in Shadman et al. are from patients who could reach out up until SCT which is not fair comparison vs axi-cel because more than half of the patients do not get SCT due to unresponsiveness to salvage chemo (if any, comparison in 3L vs autoSCT would have to be similar to ZUMA-7 study design: 3L+ CART should be

compared vs salvage chemo+/-HDT-SCT, but overall as mentioned SCT is uncommon and unlikely in 3L setting). • P25: SCT following standard care was excluded as comparator in PICO.
• Further limitations of Shadman et al. 2022 publication: retrospective, unbalanced in regard of treatment lines, difference in follow-up time.
• Axi-cel indication is based on early relapse in 2L and chemo refractory patients, Shadman publication only based on early relapse, other factors not evaluated.

59. Exclusion of pembrolizumab as a comparator to CAR T in 3L PMBCL:
• P5: Pembrolizumab it is not an established treatment alternative to CAR T in 3L+ PMBCL and there is no reasonable head-to-head comparison possible.
• Guidelines referenced in HTA report P31 state: “Options available for patients with PMBCL are the same as those available for patients with DLBCL.” The HTA report draft states further that “in addition, pembrolizumab is approved and reimbursed and will be given to patients who are fit enough (around 50%)

for a median duration of 6 months (8 cycles)." It remains unclear in the HTA report if pembrolizumab is really used in the same population as those patients eligible for CAR T treatment (3L PMBCL).
• Pembrolizumab is not reimbursed in r/r PMBCL if cytoreductive treatment is needed.
• DLBCL is characterized by rapid growth and a tendency to spread to various parts of the body, including lymph nodes, extranodal sites, and organs. It often presents at an advanced stage. PMBCL, on the other hand, typically manifests as a large mass in the anterior mediastinum (the area between the lungs) of young adults and children. Its presentation is more localized. DLBCL is therefore often regarded as more aggressive (worse outcomes/prognosis for patients) than PMBCL.
• From DGHO-PMBCL guidelines: "Due to the high efficacy of first-line PMBCL therapy, there are only a small number of primary refractory or relapsed patients, which makes it difficult to systematically develop an optimal therapy in relapsed or refractory patients. Patients who relapse after an initial chemosensitive disease should be treated with platinum-containing salvage therapy (R-DHAP, R-GDP or R-ICE) and, if at least a partial remission is achieved, with HD therapy according to the BEAM protocol and subsequent autologous stem cell transplantation. In a primarily chemorefractory situation, it is possible to treat with PD-1 blockade with or without brentuximab vedotin. PD-1 blockade (e.g. Pembrolizumab) has been approved for this indication in the USA and Switzerland. **Anti-CD19 CAR T-cell therapy is an option for the third line of therapy."**
• ZUMA-1 does only have 7% PMBCL patients included, so unadjusted comparison of ZUMA-1 full cohort results to KEYNOTE-107 (which is only PMBCL) is strongly biased. An adjustment would be very difficult to perform, and outcome would become highly uncertain.
• It appears reasonable as stated in the HTA report draft on P31 that the approach to salvage chemotherapy regimens in PMBCL should be like that used in the treatment of relapsed DLBCL.
60. P5: **Inclusion of indirect treatment comparisons (ITC) in the HTA for CAR Ts: Axi-cel vs tisa-cel** should be part of the analysis considering that **CAR Ts are standard of care in 3L+ DLBCL** setting. The HTA report does not consider indirect treatment comparisons (ITC) which prevents cross CAR T-comparison. Gilead/Kite demands that ITC is included in this HTA. Independent ITC is available in DESCAR-T cohort from Bachy et al. publication.
61. P3f.: **Please double check and provide more clarity in the summary tables of clinical data:** Different time ranges compared as displayed may lead to wrong conclusions. Long-term follow-up pivotal study data e.g. for OS is not visible here. How is the distribution of patients

and outcomes within the time range? The percentages vs participants displayed can be misleading to wrong conclusions/perceptions and should be interpreted with upmost caution or removed. **62.** P3f.: **Please add references in the summary tables of clinical evaluation.** It is not clear to what the results of axi-cel & tisa-cel are compared to.
63. P6: **Please be double check resource use CAR T vs ASCT in Ring et al. publication as it is probably related to 2L LBCL.** Ring 2022 publication is within Swiss healthcare context but focusing probably on 2L LBCL rather than 3L+. Nevertheless, the analysis demonstrates a favorable hospital resource use for CAR T vs SCT.
64. P7: **Please update wording for clarity of ICER results** instead "…*and of CHF88,000 and CHF130,000 for axi-cel for r/r LBCL and tisa-cel for r/r DLBCL…*" the more clearer wording "*and of CHF88,000 for axi-cel in r/r LBCL and CHF130,000 for tisa-cel in r/r DLBCL…"*. Please clarify and confirm if the ICER result stated in the summary for axi-cel in LBCL is the same as for axi-cel in DLBCL.
65. P25: **Please review and correct numbers of patients treated in Switzerland**: It seems that incorrect outdated unpublished 2021 SBST data is quoted. 2022 SBST report data should already have been available for HTA or 2023 data to be considered and to be correctly reported and quoted. The numbers quoted for axi-cel are materially incorrect in the HTA report draft. Potentially also tisa-cel numbers are incorrectly reported. **The following feedback to this list item should not be published due to confidential information, but to support further investigation and reconciliation with SBST, HTA vendor & FOPH** that correct numbers are considered as basis for budget impact analysis and to correctly inform on historical numbers: (……).

66. P27: **Please provide fair balance in the adverse event section:** As stated in the HTA report, severe adverse events can be life threatening, requiring urgent medical attention, but it is also to mention for a balanced view in regard of CRS and ICANS as quoted later in the HTA report on P172f. that the majority of CRS and ICANS adverse events is of short duration and reversible.
67. P32: **Please correct reimbursement status for tisa-cel**: tisa-cel is no longer reimbursed for DLBCL in the UK. The appraisal was terminated. https://www.nice.org.uk/guidance/ta933
68. P32: **Please correct reimbursement status for axi-cel:** axi-cel is reimbursed also in Norway in DLBCL & PMBCL. In Scotland, axi-cel is reimbursed in DLBCL & PMBCL. Multiple countries in the table have also 2L therapy regulatory status approved & reimbursement.

69. P42: **Please provide more clarity in the summary of clinical data and exclude SCT as comparator:** Different time ranges compared as displayed may lead to wrong conclusions. Long-term (e.g. 5y OS) data from pivotal study ZUMA-1 is not displayed here. How is the distribution within the time range? The percentages vs participants displayed may be misleading to wrong conclusions/perceptions.
70. P42: **Please also provide references of clinical evaluation**: It is not clear in the summary statement to what the results of axi-cel & tisa-cel are compared to.
71. P55: **Please include CIBMTR RWE publication**: Jacobson et al 2021 - Transplantation and Cellular Therapy 28 (2022) 581.e1581.e8 DOI: 10.1016/j.jtct.2022.05.026 It is a robust RWE from CIBMTR with more than 1200 axi-cel patients treated.
72. P55: Please include publication Boyle et al. 2023 DOI: 10.1111/bjh.19157 This large UK CAR T RWE shows improvement of outcomes over time for CAR T, with a 1-year PFS of 51% in axi-cel and 41% in tisa-cel treated patients after 2020, mirroring favorable results seen in large US real-world cohorts. This overall improvement occurred despite an increase in the number of elderly/less fit patients being treated. The data suggests changes in bridging therapy and toxicity management (to a proactive de-bulking approach) as the main drivers of improvement in survival. This publication highlights a learning curve - with patients being treated today more likely to achieve long-term remission than patients treated in the initial period of CAR T. Therefore, most recent RWE should serve as comparator outcomes for assessing the clinical benefit vs any potential alternative treatment options.
73. P55: Please include the publication providing RWE of 7 centers in the US from Jacobson et al 2020 - J Clin Oncol 38:3095-3106. DOI: 10.1200/JCO.19.02103
74. P55: Please include the publication on French RWE from DESCART from Bachy et al 2022; DOI: https://doi.org/10.1038/s41591-022-01969-y In addition to reporting comparative evidence for the two CAR T therapies, the **DESCAR-T study also report some data for these two interventions separately.**
75. P57/P59: The studies conducted by Figura et al (Figura 2021) and Wright et al (Wright 2020) in patients with recurrent or refractory LBCL were included in the HTA report, however, both these studies did not report the number of prior therapies and hence, did not meet the SLR inclusion criteria. Therefore, please exclude these publications.
76. P59: The study conducted by Sim et al (Sim 2019) was a case series and its primary objective was to assess the impact of radiation as a bridging strategy for CAR T cell therapy rather than assessing the efficacy and safety of CAR-T therapy itself. The inclusion of this study in the HTA report does not seem relevant. Therefore, please exclude this publication.
77. P56: Please double-check input for Benoit 2023 publication: Absolute and %-numbers seem not to be correct for “Stage III/IV at infusion: 80(12)”
78. P56: Bethge 2022 publication includes 67% of patients with 3 or more prior lines of therapy before CAR T and demonstrates CAR T outcomes below average. Poorer outcomes are indicated if patients are treated (too) late with CAR T. Similar observation in Grana 2021 and Sesques 2020 publications. Favorable outcomes for patients in earlier treatment lines were already observed in the ZUMA-1 pivotal trial by Locke et al. 2018 https://doi.org/10.1200/JCO.2018.36.15_suppl.30

79. P59: Please include ZUMA-1 vs SCHOLAR-1 publication in the HTA: Neelapu SS, et al. Comparison of 2-year outcomes with CAR T cells (ZUMA-1) vs salvage chemotherapy in refractory large B-cell lymphoma as it compares axi-cel against the historic SOC, Blood Adv. 2021 Oct 26;5(20):4149-4155. doi: 10.1182/bloodadvances.2020003848.

P59: Please be aware that compared with the registrational ZUMA-1 trial, 129 patients (43%) in ZUMA-9 study would not have met ZUMA-1 eligibility criteria because of comorbidities at the time of leukapheresis. This and RWE data shows that patients can benefit beyond inclusion criteria of the pivotal study. Therefore, experts and guidelines have established more generalized medical criteria regarding CAR T eligibility.
81. P64/74: Please exclude publication Yagi 2022 due to Japanese patient population as there are applicability concerns regarding a comparison with the Swiss population.
82. P72: Table 12: Please double check and correct the numbers reported:
• (…….)
• (…….)
• A sense check of specific patient characteristics does not match total numbers reported, for example: for “number of previous therapies” and Axi-cel 59 data sets are reported, but only 50 total patients included. Similar issue for tisa-cel. How is this possible?
• The percentage-value of “disease stage” for axi-cel patients is not correct: 39 of 51 patients is 76.5%, not 66.1%. Please review all values and update if applicable. This is of importance as these, and other Swiss patient characteristics are evaluated in the context of applicability in the included studies. On P74 it is stated in the HTA report that there are applicability concerns regarding the disease stage of patients in the included studies. This statement is not correct. Please check and update the statements if applicable.
83. P73-75: Please double check, update/correct the values and statement for “time between leukapheresis and CART infusion” for axi-cel & tisa-cel in the included studies including SBST registry. It is not clear where the referenced SBST data for 2019-2021 was reported and if the data is correct. Please use the latest available data reported to FOPH. 2022 unpublished SBST report to FOPH for CAR T stated the following numbers for 2021:
i. (……)
ii. (……..)

• The HTA report states that axi-cel patients in the included studies received CAR T infusion with a median time between leukapheresis and CAR T infusion of 17 to 42 days (range 17–526 days) while for tisa-cel patients a median of 32 to 54 days (range 3–526 days). 526 max. days seems like an odd unlikely coincidence for axi-cel with tisa-cel. Please double check studies included with reference numbers 133,134,136,141,142 to isolate the issue and correct as applicable. Furthermore, a minimum 3 days from apheresis to CAR T infusion seems unrealistically short. Please check and correct accordingly.
• Slot request/apheresis to CAR T infusion time is not fully in control of the CAR T manufacturer but depends also on patient status, treatment center capacity and potential other circumstances.

A study from Locke et al. 2022 assessed real-world impact of time from leukapheresis to infusion (vein-to-vein time) in 1,383 adult patients with relapsed or refractory (R/R) large B-cell lymphoma (LBCL) treated with axi-cel: The patients were identified from a non-interventional post-authorization safety study using the Centre for International Blood and Marrow Transplant Research (CIBMTR) registry. The analysis reported shorter vein-to-vein times associated with improved outcomes in patients treated with axicabtagene ciloleucel, adjusted for key prognostic factors. (https://doi.org/10.1182/blood-2022-155603)
• A European analysis of commercial manufacturing experience of axi-cel showed a median European manufacturing turnaround time of 19 days for patients with r/r DLBCL The analysis included data from 2,432 European patients who underwent leukapheresis and who received commercial axi-cel between 6 September 2020 and 5 September 2022 and was compared to data from 1,115 European patients who underwent leukapheresis between 6 September 2018 and 5 September 2020. The analysis showed a reduced median manufacturing turnaround time from 25 days to 19 days for European

patients with r/r DLBCL. An improvement in delivery success rate from 96% to 99% was also observed. 95% to 96% high manufacturing success rate was maintained during the analysis period. Manufacturing turnaround time is defined as time from day of leukapheresis to the day of product disposition for lots using fresh apheresis material. Delivery success rate is defined as the percentage of patients for whom a dose was shipped out of the total number of patients leukapheresed in the time period (excluding those patients lost in process and patients withdrawn). (Van de Wiel et al. "COMMERCIAL MANUFACTURING EXPERIENCE OF AXICABTAGENE CILOLEUCEL DELIVERY IN EUROPE: FROM THE FIRST 2 YEARS TO THE LATEST 2 YEARS." BONE MARROW TRANSPLANTATION. Vol. 58. No. SUPP 1., 2023.)

• Gilead/Kite just recently announced reduction of the turnaround time from apheresis to product release from previously 16 to now 14 days in the U.S. https://www.kitepharma.com/news/press-releases/2024/1/kite-receives-us-fda-approval-of-manufacturing-process-change-resulting-in-reduced-median-turnaround-time-for-yescarta-car-tcell-therapy

• Switzerland is materially in line within the European turnaround time of 19 days and further reduction of the median turnaround time is planned.

Gilead/Kite's short turnaround times, high manufacturing success rates of 96%-100% in clinical & commercial setting with reliable slot availability are industry leading results.

84. P73-74: Please double check patient characteristics with publications for axi-cel & tisa-cel in LBCL to avoid potential errors in the final HTA report.

85. P93ff.: Please double check effectiveness/efficacy & safety findings with publications for axi-cel & tisa-cel in LBCL to exclude potential errors and in particular comments in HTA report.

86. P104: Please consider the RWE HRQoL publication for axi-cel that contains patient reported outcomes for axi-cel with 64% of patients would have been eligible at apheresis for the ZUMA-1 pivotal axi-cel trial: https://ashpublications.org/blood/article/140/Supplement%201/5190/487526/Real-World-Patient-Reported-Outcomes-Among Real-world data suggest that axi-cel is associated with transient worsening of quality of life and symptoms at day 14, with statistically and clinically significant improvements thereafter in overall quality of life and several functional and symptom domains. These data are generally consistent with PROs reported from clinical trials of CAR T-cell therapy. However,
these findings extend previous research by reporting on patients' perspectives on CAR T-cell therapy received as standard of care in the real-world setting.

87.
P104: Please clarify the rationale of having an analysis of "treatment discontinuation". Categories missing in the HTA/evaluation which are of high relevance for CAR T-therapies are "manufacturing success rate" & "manufacturing/turnaround time" (from apheresis to product release). Publications to consider: EBMT 2023 poster 198 (Louis van de Wiel et al) & Tully S, Feng Z, Grindrod K, McFarlane T, Chan KKW, Wong WWL. Impact of Increasing Wait Times on Overall Mortality of Chimeric Antigen Receptor T-Cell Therapy in Large B-Cell Lymphoma: A Discrete Event Simulation Model. JCO Clin Cancer Inform. 2019 Oct;3:1-9. doi: 10.1200/CCI.19.00086. PMID: 31644324

88. P106: Table 19: Mian 2021 "SoC (auto-SCT)" is not correct. Please update according to publication.

89. P106ff.: Please double check axi-cel & tisa-cel values for safety evidence vs publications to avoid potential errors in the final HTA report.

90. P108: Table 20b: Please include "median duration of CRS" & "median duration of ICANS". Most of these events are reversible and of short duration as mentioned later in the HTA report.

91. P108: Table 20b: Please double check axi-cel & tisa-cel values for safety evidence vs publications to avoid potential errors in the final HTA report.

92. P117ff.: Please double check tisa-cel values for effectiveness & safety evidence vs publications to avoid potential errors in the final HTA report.

93. P125: Please double check if ICANS were reported in JULIET and correct accordingly in the updated version of the HTA report. This HTA report draft states in Table 22 that ICANS were not reported, but Schuster et al. (JULIET) in Lancet Oncol 2021 reported all ICANS = 20% and ICANS GR3-4 = 11%.

94. P127: 2 large data sets Bethge & JULIET show 13-23% CRS>3, but after weighting with other data sets, only 6% average CRS>3. This is driven by NCT03601442 data, the Out of Specification MAP for ALL or DLBCL Patients (1 of 84) & Pasquini (7/155). Please double check if only DLBCL patients were considered or mixed with pALL and comment if the out of spec study data had an impact on efficacy outcomes compared to JULIET & ELIANA studies.

95. P131ff.: Please double check GRADE summary of findings to avoid potential errors in the final HTA report.

96. P138: Economic part: "Naïve treatment comparisons were not included in the clinical evidence review; however, they were drawn in the economic evaluations to inform incremental cost-effectiveness ratio (ICER) calculations. This was considered appropriate given uncertainty analyses could be performed to explore the impact of various assumptions on cost-effectiveness outcomes." This HTA made no attempt to perform an indirect treatment comparison (ITC) which are considered essential when doing cross trial comparisons. The NICE HTA manual (https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741) recommends that 'When technologies are being compared that have not been evaluated within a single RCT, data from a series of pairwise head-to-head RCTs should be presented together with a network meta-analysis if appropriate....Alternative methods, such as meta-analysis and indirect comparisons (including, for example, observational studies with a comparator drawn from the population through a matching-adjusted indirect comparison) may be considered when an RCT was not possible.' Failure to do the above will lead to immeasurable biased estimates of effectiveness

which interns will perpetuate into the economic model. Further clarification is required as to why these methods were not considered. **97.** P138: "The probability of patients living into old age reflected by the modelled extrapolations suggests that the ICERs are likely optimistic." Please clarify if this was stated by other international HTAs or is author's assumption in this HTA report. Please provide references for this statement.
98. P138: "Other economic literature reviewed as part of this HTA highlighted the high cost burden of CAR T products." Please provide references for this statement.
99. P139: Please clarify why Inotuzumab is not a comparator in pALL while Blinatumomab was considered.
100. P139: Comparators with temporary listing only should not be included. These were also not available at marketing authorization of both CAR Ts and there are no head-to-head studies comparing these with CAR T.
101. P142: Please update missing reference - probably reference to table 29 & others to include.
102. P143ff.: Please double check economic results from studies for all indications vs publications to avoid potential error in the final HTA report.
103. P147: Please exclude economic analysis from Chinese healthcare system as there are applicability concerns vs Swiss healthcare system.
104. P155: Please clarify if the "CART to bridge to SCT"-model version applies only for pALL or also DLBCL? For DLBCL it would be unreasonable to model CAR T as bridge to SCT.
105. P157: Ring et al. 2022 analysis is likely related to 2L, not 3L – please exclude from 3L+HTA.
106. P157: alloSCT is not a comparator vs CART in 3L+LBCL. Please correct.
107. P161ff.: Please share the economic model for a critical appraisal on the modelling methodology & results.
In the spirit of transparency of the HTA process, it is typical for all stakeholders to have access to all relevant materials, particularly the economic model. The economic model contains innumerous interlined parameters and assumptions. It is impossible to give a comprehensive review of the economic results without access to the economic model and statistical code that underly the survival extrapolations (i.e. the TreeAge Pro file and the STATA/R code). Gilead requests that this file is shared with Gilead such that Gilead can robustly test the model, investigate all parameters, and do a comprehensive error check.
108. P162: Referenced data for "slot requests went without an infusion" from Swiss SBST registry is mixed for both CAR T. Please check and consider study data for axi-cel: 8% expected according to ZUMA-1 data, vs 12.5% mixed CAR T products data in SBST registry.
109. P164: Please double check methodology for extrapolation of survival data.

Extrapolation of survival data: The report states that "A retrospective comparison of the predictive accuracy of different survival extrapolation methods found mixture cure models (MCMs) and cubic spline models to generate more accurate survival predications for CAR T-cell therapies in r/r LBCL. A retrospective assessment of the accuracy of standard parametric survival models, spline models and MCMs fitted to OS data for immune-checkpoint

inhibitors found that spline models and MCMs generally demonstrate the potential to accurately reflect longer-term survival, but there are no definitive features that unquestionably support the use of one specific extrapolation technique." However, a study evaluating the predictive accuracy of different extrapolation methods on axi-cel specific long-term survival found that MCM models are superior to spline based models at predictive long-term survival. Ref: https://pubmed.ncbi.nlm.nih.gov/35667774/ It is not clear to Gilead why this article was not considered when choosing extrapolation methodology despite being directly applicable to the decision problem at hand. The use of mixture cure models (rather than cubic spline

models) has been further supported by the recent NICE re-evaluation of axi-cel in 3L+ LBCL Ref: https://www.nice.org.uk/guidance/ta872 and 2L LBCL, Ref: https://www.nice.org.uk/guidance/ta895 in which NICE agreed with the use of MCM over standard parametric models. In fact, no other HTA body has considered using spline models in their base case economic modelling assumptions. Cure models are more clinically supported given the mechanism of action of CAR T, whereby a proportion of the cohort are cured after receiving CAR T.
Knot points: Spline based models are considered flexible models as they are able to closely match the underlying hazard function. However, they are often subject to over-fitting, particularly when the hazards are complex. A key assumption of a spline model is the location of the knot points, which should be clinically and statistically determined as mentioned in NICE TSD 21. No details are provided in the report as to the justification of these knot points, and whether these were clinically validated. Furthermore, the hazard plots are not provided, this it is impossible to correctly determine whether these models actually fit the data well in the long-term. **Please could the hazard plots be shared (with short and long-term extrapolations fitted to the KM data) for all model classes (MCMs and Splines in particular), clinical validation methods used to pick the base case model, AIC/BIC values for the MCM, exact location of the knot points and sensitivity analysis with clinically led knot points.**
Proportionality: As per best practice stated in the NICE TSD 14, before independent models are fitted to each arm, a test of proportionality must be performed vs the SOC arm for all end points (OS and PFS/EFS). No such tests have been performed to justify independent model fitting. **Please could the HTA perform proportionality tests such as generation of log-log plots for each endpoint and arm, and Schoenfeld test of equality.**
110. P168: Please check body weight assumptions and provide rationale for different assumption: 75kg in HTA report vs >83kg in ZUMA-1.
111. P169: It seems that inpatient apheresis costs are lower CHF 18459 vs 24600 outpatient. It is not clear how the HTA report statement: "leukapheresis setting depends on the status of the veins; for axi-cel it is often performed in the inpatient setting due to constraints around the collection time of cells" was balanced with the HTA report statement: "Leukapheresis in adults most often in an outpatient setting (source: expert opinion)".
112. P170: Please review bridging assumptions and economic modeling: There was no bridging for axi-cel in ZUMA-1, therefore please model base case according to ZUMA-1 study and bridging as a scenario if ITT population is used for economic modeling because bridging might impact probability of infusion and outcomes. The referenced retrospective analysis for bridging (61%) at a single Swiss center included 21 tisa-cel of 23 total therapies, thereof only 2 axi-cel treatments. Bridging costs apply mainly for tisa-cel, but bridging assumption in the modelling for tisa-cel and axi-cel were 67% each which seems arbitrary. Bridging should have been reported in SBST registry by product if relevant for analysis.
113. P170: HTA-report states that Pola-BR is used for bridging in the outpatient setting. Therefore, please exclude Pola-BR as a comparator to CAR T in this HTA report.
114. P174: It is not clear when and where the data regarding use of tocilizumab was reported on product level in the unpublished SBST report. Please clarify and double check the reported values.

115. P175: There is less IVIG-use following axi-cel treatment (48%) vs tisa-cel (69%) in Swiss RWE, but the percentage-value used in tisa-cel IVIG-use cost calculations should be then also 69% and not 64%. Please correct the calculations accordingly.

116. P177f.: Please avoid arbitrary selections of comparators: pALL: Blinatumomab & Inotuzumab in both CEA and budget impact to consider as comparator or clarify why one is included and the other excluded. Same issue for DLBCL: Tafa-Len to consider in addition to Pola-BR as comparator if Pola-BR will not be excluded despite many objections already mentioned above. (p191: "No existing study has considered Inotuzumab as a comparator.")

117. P178: “Specifically, pembrolizumab costs were considered for 1.2% of the LBCL cohort (r/r PMBCL accounted for approximately 2.5% of all DLBCL/PMBCL patients” Please double check 2023 % of PMBCL vs DLBCL and cumulated % since the beginning in SBST reporting if possible. It is not clear where the number was derived from as it cannot be found in the unpublished SBST report to FOPH. Please confirm if and when individual analyses were performed with SBST registry data outside the yearly SBST reporting to FOPH.
118. P180: “Pola-BR is temporarily reimbursed on the Spezialitätenliste for the treatment of adult patients with r/r DLBCL who are ineligible for haematopoietic SCT” as stated in the HTA report, therefore it should be excluded as a comparator also due to different patient population vs CAR T. The Pola-BR patient population barely matches ZUMA-1 study population and should be therefore excluded as a comparator vs CAR T in 3L+ LBCL.
119. P181: “Tafasitamab in combination with lenalidomide and subsequent monotherapy is temporarily reimbursed on the Spezialitätenliste for the treatment of adult patients with r/r DLBCL after ≥1 prior line of systemic therapy for patients for whom autologous SCT is not possible.” is stated in the HTA report. This population barely matches with ZUMA-1 study population and should be therefore excluded as a comparator vs CAR T in 3L+ LBCL.
120. P182: “Pembrolizumab (Keytruda®) is listed on the Spezialitätenliste under a temporary limitation for use as a monotherapy in r/r PMBCL in adults with at least 2 previous treatments (one of which was rituximab) who are ineligible for autologous SCT or had relapse after transplantation.” is stated in the HTA report. This patient population does not match well with ZUMA-1 study population and should be therefore excluded as a comparator vs CAR T in 3L+ PMBCL.
121. P182: It is stated in the HTA report that Blinatumomab is not reimbursed for pediatric patients, but compassionate use according to Swiss expert advice. Please clarify if it means that only inpatient surcharges are included, but no product costs? Please clarify also in relation to table 46 where inpatient surcharges are included with addon payment Code ZE-2023-138.10. Please clarify if the following calculations assume Blinatumomab use only in the inpatient setting.
122. P183: Table 47: Please update inpatient surcharges code for Inotuzumab to ZE-2023-166.13. Code ZE-2023-138.10 is not correct.
123. P183: Please clarify why Inotuzumab Ozogamicin treatment costs were considered in the BIA; however, Inotuzumab Ozogamicin was not included as a comparator in the economic modelling.
124. P194: Please correct typo: “DMBCL” to DLBCL.
125. P195: Please add missing reference - probably related to objects in section 8.1.2.
126. P6 & P195: CORAL vs SCHOLAR-1 – Please clarify why CORAL data was used as a historical cohort and not SCHOLAR-1 data vs axi-cel? Recent NICE for axi-cel appraisal and other appraisals confirmed SCHOLAR-1 data as historical cohort, so why it has been ignored in this HTA report, particularly since it has been matched on an IPD basis?
127. P195: “To inform survival outcomes for a historical control for LBCL populations in the evaluation for this HTA, data were selected from the CORAL extension studies. OS curves from these 2 studies were digitized, and the reconstructed IPD was pooled to create a single

comparator population reflective of patients who may be eligible for CAR T-cell therapy.” is a weak assumption creating a substantial risk of bias, because:
• Some patients in CORAL may not be eligible for CAR T given the differences in patient pools in the trials. Whilst there is some overlap, the trial populations are different.
• Relative to CORAL EXT 1 & 2, ZUMA-1 has slightly older patients, more previous lines of treatment, and a higher proportion of patients with stage 3 or 4 disease.
• Nonetheless, there were a few important differences between the two trials. First, there were roughly 25% with prior ASCT in ZUMA-1 compared to around 50% in CORAL EXT 1 & 2. Second, there were much more patients that were refractory to the last line of therapy in ZUMA-1 (65.3% in the FAS population and 65.8% in the ITT population) than CORAL EXT 1 & 2 (34.9% in the FAS population and 41.3% in the ITT population), which was to be expected given that the ZUMA-1 trial focused on enrolled patients with chemotherapy-refractory disease.

128. P196: OS: historical controls for LBCL: “Model diagnostics for the fitted curves indicated the spline models with 2 knots provided the best fit for the data (i.e. showed the lowest AIC values).” Vadgama et al 2022 doi: 10.1016/j.jval.2021.10.015 proving that using IPD cure models are best fits. Please model accordingly.

129. P198: Pola-BR (or Tafa-Len) study data should not be compared vs ZUMA-1 due to substantial risk of bias: **It is not possible to remove or reduce observed between-trial differences for some important baseline characteristics.** Results of naïve comparisons and MAIC of ZUMA-1 versus L-MIND (Tafa-Len) and GO29365 (Pola-BR) should be interpreted with a high degree of caution, as failure to account for differences in all clinically relevant covariates across trials can lead to misleading estimates of relative treatment effects. ZUMA-1 included much more heavily pretreated patients compared to L-MIND and GO29365: ZUMA-1 required patients to have previously received a regimen containing an anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy regimen; L-MIND required patients to have one to three prior systemic regimens (including at least one anti-CD20 therapy); and GO29365 required patients to have at least one prior therapy. Consequently, there was only a small (3%) percentage of patients in ZUMA-1 with one prior line of therapy compared to about half of L-MIND study population and one-third of GO29365 study population. In addition, both L-MIND and GO29365 were restricted to transplant ineligible patients only whereas this was not an eligibility criterion in ZUMA-1. Arguably, a high proportion of patients in ZUMA-1 may have been considered transplant ineligible based on individual variables such as best response to prior treatment (>93% PD or SD) and lines of treatment (>96% in third or subsequent lines). However, information on transplant eligibility was not available for ZUMA-1 patients and there is no standard definition or hard objective criteria that would reliably categorize ZUMA-1 patients post-hoc as transplant-eligible or transplant-ineligible. This highlights two distinct differences between the study populations which cannot be adjusted for in a MAIC, rendering any estimated treatment effects at substantial risk of bias.

In addition to differences in eligibility criteria, the distribution of available patient characteristics also presents challenges for effective matching between the study populations, and several relevant prognostic factors cannot be included. For the comparison of ZUMA-1 and L-MIND, extreme differences in several baseline patient characteristics can be noted. It is important to highlight that it is not feasible to match on prior lines of systemic therapy, which is ranked as having high prognostic relevance based on clinical input, due to an insufficient overlap in this characteristic between ZUMA-1 (3% with one prior line, 32% with two prior lines, and 65% with ≥3 prior lines) and L-MIND (50% with one prior line, 43% with two prior lines, 7% with ≥3 prior lines). For the comparison of ZUMA-1 and GO29365, would be also substantial differences between the study populations in lines of prior therapy, age, and best response to last treatment, which would likely result in a large reduction in effective sample size (ESS) after matching.

It is also important to highlight that a MAIC could not factor in the pre-infusion time required in ZUMA-1 (median of 23 days from leukapheresis to axi-cel infusion). The population of interest in a MAIC based on ZUMA-1 mITT population (101/111 leukapheresed patients who received axi-cel infusion) and L MIND/GO29365 ITT population (enrolled patients), and the relative treatment effects would be based on outcomes measured from the point of infusion onwards (ZUMA-1) and start of treatment (L MIND/GO29365).

130. P196: PFS: historical controls for LBCL: “PFS was not reported for the defined historical control cohort. As in existing evaluations, PFS was derived from OS by assuming a constant cumulative HR of 0.65” reference is related to a tisa-cel publication.

Gilead understands that in the absence of PFS time to event outcomes in the comparator arm, an assumption was made that the ratio of PFS to OS in the intervention arm was used as a proxy to derive comparator PFS data. However, Gilead would like to point out that this is an extremely conservative assumption given the comparators are rarely curative (unlike CAR T) and patients on the comparator arm are likely to progress much faster and receive subsequent CAR T in current clinical practice. As a result, we would expect PFS rapidly to approach 0, and costs in the SOC arm to include some newer more costly treatments. Therefore, the ICER presented is conservative at best, and likely much lower in reality. This assumption should be made clear in the report.

131. P199: "The EBMT/EHA handbook suggests that the potential for polatuzumab to serve as a curative treatment is small if it exists at all, but that it may be a good candidate as a bridging therapy prior to CAR T-cell therapy" Expert clinical advice is that some Swiss centers are switching to Pola-BR as a bridging therapy prior to CAR T-cell therapy. Regarding use of Pola-BR as a stand-alone treatment, Pola-BR may provide an option for patients unable to receive CAR T-cell therapy.259" In the modelling, Pola-BR was considered as a comparator to CAR T- cell therapies in an exploratory scenario analysis which does not seem appropriate given the references in the HTA report.
132. P201: Compared to all patients receiving axi-cel in the SBST registry, and patients included in the ZUMA-1 trial, "patients in the KEYTNOTE-107 trial were significantly/much younger, and there were more female patients." There are strong concerns over the applicability of the KEYNOTE-107 trial as a comparable patient cohort to patients receiving axi-cel in PMBCL and a comparison creates a high risk of bias.
133. P202: The unadjusted comparison with different patient populations of studies ZUMA-1, KEYNOTE-107, SBST registry and a Pola-BR mixes study results, creates a high risk of bias and therefore an unreasonable data comparison and results. Similar issue applies to JULIET & Pola-BR data unadjusted comparison.
134. P204: The Pembrolizumab OS extrapolations seem overly optimistic. Pembrolizumab is not curative in this setting, and so it is unclear why OS extrapolation is considered to be equivalent to axi-cel in the economic model (see fig 81). Please could this HTA re-check whether this is an error as it seems clinically implausible given the differences in the trial populations.
135. P216: Economic results for axi-cel for LBCL: HTA report states: "Modelling was informed by naive treatment comparisons and results should be interpreted in view of this limitation."

This is a major limitation as already stated above related to MCM and MAIC and results in a significant risk of bias. **136.** P217: ICERs Pembrolizumab Keynote-107 patient population vs ZUMA-1 is only comparable for a very small proportion (100% PMBCL patients in KEYNOTE-107 vs 7% PMBCL patients in ZUMA-1), therefore the HTA report likely shows an unfavorable comparison with a high risk of bias and understates likely the incremental QALY for axi-cel vs pembrolizumab considering the usually higher aggressiveness of DLBCL vs PMBCL as stated above.
137. P219: It is acknowledged that the insurer claims data analysis was rejected by the authors of the HTA report draft as this analysis is not directly comparable to cost-effectiveness calculations, which focus on treatment-related costs. Furthermore, the insurer claims data analysis does not distinguish cost differences between CART products. There are no directly attributable disease-related costs reported for axi-cel. Even if the insurer claims data analysis is included as a scenario, axi-cel remains cost-effective. Nevertheless the claims data should be excluded from the axi-cel scenario as these costs probably relate more to tisa-cel rather than axi-cel due to higher proportion of tisa-cel patients in the claims data analysis. Among the 81 patients included in the claims data analysis, 54 (66.7%) were treated with tisa-cel. Please clarify if the insurer claims data was applied in the scenario analysis not only for CAR T but also for the SOC.
138. P221 & P225: The defined CAR T-product price sensitivity -10% to -50% is not displayed in the charts. Given the results confirming cost-effectiveness of axi-cel at the product price in the HTA, a sensitivity analysis it is recommended to test in addition a price sensitivity of +10% to +50% instead -60% to -100%. Please check and update accordingly.
139. P226: Table 60: Annual CART numbers in Swiss registry: Patients treated with axi-cel, tisa-cel & total numbers don't add up and are probably not correct. Please check and update.
140. P226: "Percentages of infusions from slot requests" are not product specific. Please add a comment that these values were derived from total CART rather than specifically from axi-cel or tisa-cel RWE or the pivotal studies. Please use data as per pivotal trial for both products and a scenario analysis could be performed with RWE.
141. P228: Table 61: Epidemiology: Incidence is apparently based on UK data. Please use in the Swiss HTA report Swiss cancer registry data that shows lower incidence vs UK data (a sense check could also be performed by comparing with epidemiology data in GB-A dossiers/IQWIG-Analysis relatively to total population ratio of Germany to Switzerland): Non-Hodgkin lymphoma 1705 https://gco.iarc.fr/today/online-analysis-

table?v=2020&mode=cancer&mode_population=continents&population=900&populations=756&key=asr&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&group_cancer=1& DLBCL incidence 30% 512 https://www.nkrs.ch/assets/files/publications/others/skb_01-2015_survival_non-hodgkin_ch.pdf 1L R-CHOP 88% 450 Friedberg 2011, Tilly 2015 & estimate by Swiss experts 2L (=not cured with 1L) 33% 150 Chaganti 2016, Li 2018, Friedberg 2011 (…)
142. P228: Gilead/Kite does not agree with the estimated epidemiology or projected patient numbers mainly due to lower incidence from Swiss cancer registry and different treatment flow assumptions.
143. P230: HTA report budget impact assumptions and results are not considering shift of CAR T from 3L+ to 2L LBCL & further CAR T product in the Swiss market which are major limitations of the HTA budget impact analysis. These should be considered to inform about more

realistic budget impact analysis for the CAR Ts in this 3L+ HTA. Please update assumptions accordingly. **144.** P231: Pembrolizumab in r/r PMBCL: What does it mean if patients are "fit enough" for pembrolizumab? Pembrolizumab population could be a different population vs CAR T population. A comparison of CAR T vs pembrolizumab creates a high risk of bias. Pembrolizumab should be therefore excluded as a comparator.
145. P231: Table 62: It seems that a linear trend extrapolation of patients eligible for infusion was performed as a base case. It is rather unrealistic to assume that each year in the forecasted years the same linear volume is added (here +12 infused CAR T in LBCL/year). Innovation adoption/uptake curves usually show a logarithmic/softening uptake (Bass innovation diffusion model or double sigmoid-curve, e.g. in Bass 1969, Management Science. 15 (5): 215–227.) rather than a linear innovation adoption pattern. Please update assumptions accordingly.
146. P232: Table 63 & 64: Please double-check calculations of projected cost of CAR T 2023-2027 to avoid errors in the final HTA report.
147. P232: The favorable market share trend for axi-cel was not extrapolated in the HTA but ratios for outer years projections were taken and frozen from 2022 actuals (if these numbers are correct in SBST report – please double check). This seems to be an unfavorable and unrealistic assumption for axi-cel. Please update accordingly.
148. P236: Uncertainty analysis of budget impact: overall materially overstated 3L+ budget impact calculations due to shift of 3L+ CART to 2L not considered in budget impact calculations. Scenario 8: assuming 100% ICU after all CAR T infusions +tocilizumab & sometimes ventilation is a very low probability, therefore unrealistic scenario. Upper-bound should be referenced from clinical/RWD data or expert feedback. SBST registry data reported ICU utilization after CAR T with low occurrence.
149. P236: Uncertainty analysis of budget impact: Scenario 9: Full uptake - assumed number of patients receiving CAR T using author's epidemiological maximum estimates is a very low probability, therefore unrealistic scenario.
150. P236 comparators: The comparator regimen cost per patient is highest for Tafa-Len (CHF190,552), and lowest for GEMOX (CHF20,988). It was assumed that no patient received Tafa-Len in scenario 11, and all patient received GEMOX in scenario 12. In scenario 13, both Tafa-Len and Pola-BR were assumed to be excluded because they can be provided in second-line treatment. There was no cost-effectiveness analysis performed vs Tafa-Len. These are very low probability, therefore unrealistic scenarios. Pola & Tafa should not be considered as comparator to CAR T due to the reasons as already stated above.
151. P237: Table 65: Please double check uncertainty analyses on projected net costs of CAR T vs comparators to avoid errors in the final HTA report.
152. P240: Table 66 Uncertainty analyses on projected net cost of CAR T vs comparators in B-ALL population: CAR T infusion range does not reflect volatility observed in SBST registry for this indication (3 to 8 CAR T/year). At least 8 CAR T+20%=10patients/year should have been analyzed/explored as an upper-bound.
153. P246: Ring 2022 publication is within Swiss healthcare context but focusing probably on 2L LBCL rather than 3L+. Nevertheless, the analysis demonstrates a favorable hospital resource use for CAR T vs SCT.

154. P249: “Evidence gaps”: Please mention shift of CAR T from 3L to 2L LBCL due to clinically and statistically meaningful significant benefit of e.g. axi-cel vs standard-of-care instead of concluding “low-quality”-evidence or evidence-gaps in a small population without meaningful treatment alternatives before CART availability. 3L+LBCL population will become

less relevant for CAR-T in the future due to 2L CAR T already approved, reimbursed, and recommended in guidelines. **155.** P249: Limitations of the included trials: These are already very small populations (in particular 3L+ PMBCL & B-ALL). Demanding further granularity as stated in the HTA report may contradict patient access to sub-populations of LBCL and it is unlikely that new trials are setup for very small populations. It is important to mention in this context that it requires substantial investments to perform clinical trials in CAR T cell therapy.
156. P250: It was criticized that patients who don’t undergo the infusion lead to a bias in favor of CAR T. In this context it is important to highlight that patients who do not undergo infusion died in most cases due to aggressive disease/progression while CAR T product costs are only charged after successful infusion.
157. P250: N<10 seems to be arbitrary study exclusion criteria. Please provide a rationale why n<10 was chosen.
158. P252ff.: Comparison to existing HTA reports: It is not clear why some existing country HTA reports (Canada, UK, the Netherlands) were prioritized over others (Germany, Australia, and France) in the “comparison to existing HTA reports”-section. What is the rationale?
159. P254: INESSS and Zorginstituut Netherlands compared tisa-cel in DLBCL also to SCHOLAR-1 while this HTA report draft states that results are not comparable with SCHOLAR-1. It is not clear why SCHOLAR-1 was not used, but CORAL (which is a subset of SCHOLAR-1). Axi-cel was compared to SCHOLAR-1 and not to CORAL in the HTAs mentioned except for CADTH HTA.
160. P255: Important/relevant updated conclusion regarding UK NICE HTA for tisa-cel in DLBCL (29.11.2023) to consider in the HTA report: "NICE is unable to make a recommendation on tisagenlecleucel (Kymriah) for treating relapsed or refractory diffuse large B-cell lymphoma in adults after 2 or more systemic therapies. This is because Novartis did not provide a complete evidence submission.” https://www.nice.org.uk/guidance/ta933
161. P256: Gilead/Kite acknowledges HTA report summary regarding that overall international HTAs recognized the presence of a significant unmet need in the treatment of LBCL in those who had previously failed 2 lines of therapy prior to CAR T availability.
162. P257/258: Gilead/Kite acknowledges the HTA report summary regarding that International HTAs acknowledged the clinical benefit of axi-cel and concluded that the adverse effects were acceptable given their treatability, the introduction of risk-reducing measures, and the severity of the disease. Furthermore, in updated submissions with long-term data (60 months OS data), there was less uncertainty about the effects of axi-cel on OS and economic results. Economic outcomes in the HTA report draft were found to be more favorable than those reported in previous HTAs. The most recent assessments by NICE and the Zorginstituut Nederland, have also showed more favorable outcomes in comparison to the earlier assessment.
163. P259: “Exploratory analyses suggested higher ICERs for axi-cel for r/r LBCL and tisa-cel for r/r DLBCL relative to more contemporary alternatives” the suggested “more contemporary alternatives” are as stated above for multiple reasons not appropriate comparators. The exploratory analyses are therefore not relevant to inform future reimbursement decisions for CAR Ts in this HTA.
164. P259: Please clarify if the ICER of CHF 88346 for axi-cel in LBCL includes the unfavorable unadjusted comparison to Pembrolizumab in PMBCL despite not comparable patient populations & OS/PFS curves of ZUMA-1 vs KEYNOTE-107 study. Please report & clarify ICER for axi-cel in 3L+DLBCL if it is different to 3L+LBCL. If axi-cel & tisa-cel are both compared in 3L+DLBCL vs CORAL, this HTA report could conclude in summary that axi-cel is dominant vs tisa-cel in 3L+DLBCL given it produces more QALYS at a lower cost (ICER of CHF 88346 for axi-cel vs CHF 129840 for tisa-cel). Please could this HTA consider assessing in an extended dominance framework.

Interpharma

Comment
Als Verband der innovativen Arzneimittelhersteller konzentriert sich Interpharma in dieser Stellungnahme auf übergeordnete Aspekte und geht nicht im Detail auf die Wirksamkeit und Sicherheit der CAR T Zelltherapie ein. Dies wird den jeweiligen Unternehmungen überlassen, die eigenständige Stellungnahmen einreichen werden. Generell möchten wir festhalten, dass die Fristen für das Stakeholderfeedback beim vorliegenden, sehr umfangreichen Bericht, zu knapp bemessen sind. In diesem HTA werden zwei CAR-T-Zell-Therapien untersucht, die in Anhang 1 der Krankenversicherungs-Leistungsverordnung als "in Evaluation" aufgeführt sind. Dieses HTA ist Teil der Gesamtevaluation dieser beiden CAR T-Zell-Therapien gemäss dem Evaluationskonzept. Der Schwerpunkt des HTA-Programms des BAG liegt auf der Desinvestition, während CAR T-Zell-Therapien neue hochinnovative Produkte sind, die nicht mit den Desinvestitionsbemühungen vereinbar sind. Das Desinvestment kann für Patienten, die von einer Behandlung mit CAR-T-Zelltherapien profitieren, diskriminierend sein. Zudem hinterfragen wir den Nutzen eines HTA zu den CAR T Therapien, da in der sich schnell ändernden Therapielandschaft in diesem Bereich davon auszugehen ist, dass einige Erkenntnisse zum Zeitpunkt der Publikation des HTA-Berichts bereits wieder veraltet sind. Des Weiteren halten wir folgende Punkte fest: **Policy** Im Rahmen der wirtschaftlichen Beurteilung wurden als Ergebnisse Life Years (LY), Quality-Adjusted Life Years (QALYs) und die Incremental Cost-Effectiveness Ratio (ICER) verwendet. Für die damit verbundenen **Schwellenwerte** zur Beurteilung der Kosteneffektivität **fehlen in der Schweiz gesellschaftlich und politisch breit abgestützte Rahmenbedingungen** als Grundlage. Bei CAR T handelt es sich um eine **hochkomplexe und individualisierte Therapie** bei der sich die verschiedenen Wirkstoffe deutlich voneinander unterscheiden. Beim nun vorliegenden Bericht handelt es sich um ein Multi-HTA, in dem mehrere Wirkstoffe in einem Bericht zusammengefasst werden. Dieses Vorgehen **setzt konsistente und vergleichbare Studiendaten zu den einzelnen Interventionen und Vergleichstherapien voraus**, was im Fall der CAR T Zelltherapie **nicht gegeben** ist. In anderen Ländern wurde jedes CAR T Produkt jeweils konsequent separat beurteilt. **Experteneinbezug** Wir möchten festhalten, dass obwohl der Einbezug von Experten begrüsst wird, **die Auswahlkriterien, die Liste der befragten Experten** (Name Fachrichtung) **und die gestellten Fragen/Fragebogen und die Antworten als Teil der Methodik offengelegt** werden muss. Im vorliegenden Bericht wird auf den Experteneinbezug zur Beurteilung verschiedener Aspekte verwiesen. In Kapitel 8.2.5 wird beispielsweise darauf hingewiesen, dass drei Experten befragt wurden, zwei aus dem Fachbereich «Onkologie» und ein Experte aus dem Fachbereich «Pädiatrische Onkologie», weitere Informationen zu den Experten werden nicht aufgeführt. Die CAR T Therapie ist hochkomplex und muss gemäss Swissmedic Zulassung an einem «*von der Zulassungsinhaberin qualifizierten Behandlungszentrum angewendet werden*». Zudem muss die Therapie «*unter der Leitung und Aufsicht eines Arztes begonnen und durchgeführt werden, der Erfahrung in der Behandlung von hämatologischen Malignomen besitzt (…)*»1 erfolgen.

1 Auszug aus der Fachinformation zu Kymriah®, vergleichbare Anforderungen finden sich in der Fachinformation von Yescarta®.

Gerade bei hochkomplexen Therapien ist es zentral, dass die befragten Experten die von Swissmedic im Rahmen der Zulassung definierten Voraussetzungen für die Anwendung der Therapie erfüllen.

Methodik
Damit HTAs ein nützliches Ergebnis liefern, müssen sie nach **wissenschaftlich festgelegten und standardisierten Methoden** durchgeführt werden. Die Transparenz und der Zugang zu den verwendeten Methoden/Modellen muss dabei über alle Schritte hinweg gewährleistet sein.

Für die gesundheitsökonomische Betrachtung wurden Studien aus Ländern eingeschlossen, in denen sich das Gesundheitssystem grundsätzlich von dem in der Schweiz unterscheidet (z.B. China), daher sollten solche Studien bzw. Daten nicht berücksichtigt werden.

Vertrauliche Daten
Die Stellungnahmen der Zulassungsinhaber zum vorliegenden HTA-Bericht werden jeweils auf der Website des BAG publiziert. Dies verunmöglicht es den Zulassungsinhabern vertrauliche Daten und Preise in ihrer Stellungnahme aufzuführen. Es muss daher eine Möglichkeit geschaffen werden, dass diese Daten im Rahmen des Stakeholderfeedbacks zum Bericht einbezogen werden können, ohne dass die Vertraulichkeit gefährdet wird.

Novartis

Comment
Es bestehen weiterhin grundsätzliche Bedenken bezüglich des beabsichtigten HTAs, welche wir nachfolgend erläutern. Wir verweisen gleichzeitig auch auf die Stellungnahme von Interpharma vom 06. Februar 2024. Wie bereits in der Stellungnahme zum HTA Protokoll angemerkt, **fehlen klare Rahmenbedingungen sowie transparente Prozessstrukturen für eine Durchführung des HTA bei innovativen Medikamenten. Insbesondere fehlt ein politisch und gesellschaftlich getragener Schwellenwert der bezüglich Kosteneffizienz herbeigezogen werden kann.** Zudem bleibt auch beim abschliessenden Bericht das genaue Ziel des HTA unklar (Verweis Stellungnahme vom 23. Februar 2023 zum Kommentar zur Forschungsfrage). Dem vorliegenden HTA-Bericht kann entnommen werden, dass dieser erstellt wurde, um die verfügbare Evidenz zur Wirksamkeit und Sicherheit von den CAR-T-Zell-Therapien im Vergleich zur Standardbehandlung zu evaluieren. Zusätzlich sollen die Kosten, die Kosteneffizienz und der Budget Impact der CAR-T-Zell-Therapien und zusätzlich ethische, rechtliche, soziale und organisatorische Fragen im Zusammenhang mit ihrer Anwendung untersucht werden. Aufgrund der fehlenden Rahmenbedingungen sowie das Fehlen eines politisch und gesellschaftlich getragenen Schwellenwerts der bezüglich Kosteneffizienz herbeigezogen werden kann, sind die Ergebnisse einer solchen Auswertung schwierig zu kontextualisieren und somit limitiert aussagekräftig.

Als zu klärendes legales Grundproblem stellt sich weiterhin die Frage, wie im HTA die effektiven Nettopreise der betroffenen Präparate mit vertraulichen Preismodellen berücksichtigt werden können. Sensitivitätsanalysen können hinsichtlich vorhandener Schwellenwerte Hinweise liefern, sind im vorligenden HTA Bericht allerdings rein spekulativer Natur. Insbesondere die Spanne einer Preisreduktion von 0-100% verstärkt den spekulativen Charakter einer solchen Auswertung.

Die CAR-T Zelltherapien sind nicht alle gleich
Der HTA Bericht analysiert die beiden Therapien Kymriah® und Yescarta® in einem HTA Bericht. Dies steht im Gegensatz zu systematisch durchgeführten HTA Prozessen anderer ausländischer Institute, die die jeweiligen Therapien individuell bewerten.

Gerne verweisen wir hier auf unsere Stellungnahme vom 23. Februar 2023 zu den Unterschieden der CAR-T Zelltherapien.

Die Zulassungsstudien der CAR-T Zelltherapien weisen Unterschiede bezüglich der eingeschlossenen Patientenpopulationen auf, was die Vergleichbarkeit der Studiendaten und - Resultate stark limitiert. **Die Durchführung und Analyse von Multi-HTAs (mehrere verschiedene Wirkstoffe in einem HTA) erfordert konsistente und vergleichbare Studiendaten zu den individuellen Interventionen und Vergleichstherapien. Diese Voraussetzung ist im vorliegenden HTA nicht gegeben**. In anderen Ländern wurde jedes CAR-T Produkt jeweils konsequent separat beurteilt.

Bereits in der vorherigen Stellungnahme zum HTA-Protokoll hatten wir angemerkt, die Untersuchungsfrage auf spezifische Patientenpopulation und CAR-T Produkt zu limitieren und getrennte HTA Untersuchungen durchzuführen. Der Anmerkung wurde nicht Rechnung getragen.

HTA-Prozess
Der Einbezug von Experten wird an verschiedenen Stellen im Protokoll erwähnt. Grundsätzlich begrüsst Novartis den Einbezug von Experten, **allerdings sollten die Auswahlkriterien der Experten, deren Auflistung (Name und Fachrichtung) sowie die ausgehändigten Dokumente (z.B. Fragebogen und Auswahl der Alternativtherapien) im Rahmen des Protokolls ausgewiesen werden, um die Prozesstransparenz sowie die Validität des HTAs zu erhöhen. Dieser Anforderung wurde in dem abschliessenden HTA Bericht nicht nachgekommen.**
In der Stellungnahme zum HTA Protokoll wurde bereits angemerkt, dass weitere Stakeholder in den HTA Prozess einzubeziehen sind. Die Zulassungsinhaberinnen sind wichtige Akteure bei der Herstellung der patientenindividuellen CAR-T Zelltherapie. Gerne hätte sich auch Novartis dem BAG für einen kollaborativen Austausch zur Verfügung gestellt.

Aufgrund der in der Stellungnahme geteilten Ausführungen war aus unserer Sicht eine Revision des HTA Protokolls dringend notwendig. Dies wurde aus unserer Sicht nicht umfassend durchgeführt.
Generell stellt sich die Frage, ob aufgrund der fehlenden Klarheit hinsichtlich Zielvorgabe, die Durchführung des HTA der bereits etablierten CAR-T Zelltherapien einen Sinn ergibt.
Eine gänzliche Streichung / Desinvestition einer dringend gebrauchten, innovativen
Therapie aus dem Schweizer Versorgungskontext wäre mit dem Grundgedanken des KVG, den Schweizer Patienten einen einheitlichen Zugang zu den neusten Medikamenten zu gewähren, nicht vereinbar und ist auch rein ethisch äusserst fragwürdig.

Swiss Society of Hematology (SSH)

Comment
General comments on the HTA report Chimeric Antigen Receptor (CAR) T-cell therapy revolutionized the treatment of major B-cell malignancies, namely B-cell Acute Lymphoblastic Leukemia (B-ALL) in children and young adults and Diffuse Large B-Cell Lymphoma (DLBCL) in adults. Almost 7 years since their original approval by the FDA, thousands of patients including children received CAR T cell therapy, the favorable risk/benefit profile of which is clearly demonstrated. **Efficacy** DLBCL is the major indication for CAR T cells worldwide and is therefore the disease in which most experience was acquired. Initially approved based on single-arm, non-comparative phase 2 studies with relatively short follow-up, the efficacy of CAR T cells in DLBCL is now supported by long term analyses and comparative data. Long term follow-up of the ZUMA-1 and JULIET pivotal clinical trials who lead to axicabtagene ciloleucel (axicel) and tisagenlecleucel (tisacel) approval in 3rd line show long term (more than 5 years) progression free survival (PFS) in about one third of treated patients. Importantly, a real-world series reported by the US-consortium at the last ASH meeting showed 5-year outcomes very similar to the ones of the pivotal clinical trials, and this despite the fact that a significant proportion of patients treated in the real-life setting did not fulfill the strict criteria of the clinical trials. Collectively the long-term results obtained both in clinical trials and real life indicate that CAR T cells, even when administered in third line, can represent a curative option for DLBCL patients. After their original approval in third line, CAR T cells have now been tested in well conducted, multicenter, randomized phase 3 clinical trials assessing their potential use in second line in comparison with salvage chemotherapy and high dose chemotherapy followed by autologous stem cell transplantation (HD-ASCT). These studies demonstrated that second line treatment with axicel improved PFS and overall survival (OS) when compared with salvage chemotherapy and HD-ASCT. To note, the OS benefit associated with CAR T cell use was demonstrated even though more than half of the patients in the HD-ASCT group received subsequent off-protocol third line CAR T cell therapy because of lack of response or disease progression. A similar trial performed with tisacel failed to show a positive impact of tisacel treatment over HD-ASCT. Based on these results, axicel treatment in second line became a new standard of care for patient with refractory or early relapsing DLBCL. The need to have access to two different products, axicel and tisacel, for DLBCL is debatable. A propensity score matched analysis performed by the French colleagues on a large cohort of patients showed significantly improved PFS and OS in axicel treated patients compared to tisacel treated ones. However, axicel treatment was clearly associated with higher rates of toxicities. These and other retrospective results oriented most centers to privilege the use of axicel over tisacel in fit patients and to limit the use of tisacel to frail patients judged not eligible for axicel treatment because of toxicities. It is therefore of potential interest having access to both products at the national level if we want to increase the eligible population that can potentially benefit of such treatment. The increased use of lisocel (a product not part of this consultation) might solve this issue given its excellent toxicity and efficacy profile. B-ALL was the first indication for which CAR T cells were approved in 2017. Since then, several hundreds of children and young adults with r/r B-ALL received tisacel. More recently brexucel (a product not part of this consultation) was approved for adults with this disease. Although the experience in B-ALL is still limited compared to DLBCL, results in the real-word setting are comparable with those of the pivotal clinical trials. In particular, the response rate is very high although the duration of response might be hampered by limited persistence of CAR T cells or the appearance of CD19-negative relapses under selective pressure. Therefore, in both pediatric and adult B-ALL, the role of allogeneic hematopoietic stem cell transplantation in the context of CAR T treatment is still under investigation and transplant may be critical for the achievement and maintenance of long-term remissions. **Safety**

Since the early trials, acute toxicities, namely cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), appeared as potentially severe complications of CAR T cell treatment. Better understanding of the risk factors and the physiopathology of these complications as well as increased clinical experience led to the establishment of very detailed classification criteria and standardized treatment algorithms that are now included in well-structured clinical guidelines of major medical societies and are well implemented by treating centers. This is now associated with early interventions for these side effects limiting their impact on the morbidity and mortality as well as on the length of hospital stay.
Long term follow-up is critically important to detect long term complications of CAR T cell treatment. In particular, the FDA raised a warning after the observation of rare patients developing T cell lymphomas (TCL) after CAR T cell therapy probably because of insertional mutagenesis. However, given the high number of patients treated and the very limited number of cases of TCL reported, the favorable risk/benefit profile of CAR T cells holds true, as also stated by the FDA.

Cost-effectiveness
The cost-effectiveness of CAR T cells represents a complex and evolving aspect affected by several country-specific aspects. In particular, the upfront cost of CAR T cell therapy, both in terms of product costs and in terms of supporting measures, is currently a significant factor. However, it is essential to consider the potential long-term cost-effectiveness of a one-time treatment as CAR T cell therapy compared to other immunotherapies, including T-cell engaging therapies such as bispecific antibodies, that have been recently approved for the same indications. The curative potential of other therapies is at present unknown and systematic analyses of real-life data with newer non-CAR T agents is very sparse. Moreover, the need of long-term treatment continuation for the majority of alternative immunotherapies might significantly impact their cost on the long run.
Competition between manufacturers, improved production conditions and increased use should lead to a price reduction over time.
Country specific cost-effectiveness analyses are needed to assess the cost/benefit ratio of CAR T cells as well as of other new treatment modalities.

Conclusion
CAR T cells are considered curative in a subset of heavily pretreated patients without any other curative treatment options. Phase III studies are not feasible and justified in such patients. Phase III trials are ongoing for earlier lines and it is too early for serious and reliable HTA evaluations as data is too immature and because of the lack of real-world studies in this setting.

Swiss Society of Medical Oncology (SSMO)

Comment
General comments on the HTA report **Relevance of this report to SSMO community** Our core medical activity includes research in medical oncology for disease for which no curative therapies are available, as such CAR-T based therapies offer the opportunity to explore a novel powerful mean to tackle many of hematological but also solid tumor challenges (tumor heterogeneity, immunosuppressive microenvironment, non permissive tumor stroma). SAKK created a cell and gene therapy group to push forward these therapies in early phase trials. This is also important as CAR-T approaches will have to be included in the control arm

of many trials to come as soon as CAR-T become a standard treatment. For these reasons SSMO representing medical oncologist in private and public practice should be involved in the discussion relative to this HTA.

Safety aspects
CAR-T cells safety profile is well described at least for CD19 for leucemias and lymphomas and BCMA for multiple myeloma (which is not mentioned in this HTA report and is approved), and management algorithms for CRS and ICANs are clearly established in experienced centers. Insertional mutagenesis is recently described as potential risk of induced T cell leukemia as recently raised by the FDA, but it's important to state that over 30 000 patients treated worldwide, only 20 cases were observed. This is a lower incidence of leucemia when compared to other anti-cancer SOC therapies (chemotherapy, radiotherapy). Novel CAR designs including inducible (syn notch, etc.), switch-off, constructs are currently being tested in humans and will further improve safety profile. All of these aspects should at least be mentioned in the report.

Access and regulatory aspects
Many programs are ongoing worldwide and science is advancing very fast thanks to regulatory agencies offering clear guidance of requirements to translate academic CARs to early phase trials. Due to very long IND approval times granted by Swissmedic for phase I trials and since Switzerland is lagging behind US, Australia, UK, China and other countries, it would be interesting to suggest the possibility to offer novel CAR-Ts already tested in the clinic elsewhere (with evidence of safety and efficacy) to Swiss patients with compassionate access. This aspect is not taken into account in the current HTA version.

Economical and efficacy aspects
The HTA report concludes by stating a "Very low" certainty comparative evidence about efficacy and safety of tisa-cel and axi-cel compared to the current SOC for B-ALL, DLBCL and PMBCL due to the majority of the evidence base being single-arm. Indeed, that's exactly why the FDA created the "breakthrough designation" for these unprecendented clinical results in such refractory tumor indications. As such we shouldn't agree on this very strong statement suggesting that the selected studies were insufficient to inform about CART superiority as compared to SOC. Many patients especially in refractory LAL-B would have had a fatal outcome without CAR-T cells, since all available SOC had previously failed. The poor outcome of conventional therapies for patients with LAL-B is documented in the SCHOLAR-1 study. This study on a patient-level analysis of outcomes of refractory DLBCL from 2 large randomized trials and 2 academic databases demonstrated poor outcomes in patients with refractory DLBCL, supporting a need for more effective therapies for these patients. The key findings were: For patients with refractory DLBCL, the objective response rate was 26% (complete response rate, 7%) to the next line of therapy, and the median overall survival was 6.3 months. Twenty percent of patients were alive at 2 years. (Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 studyM. Crump et al. Blood (2017) 130 (16): 1800–1808.)
The HTA report introduces the concept of "ICERs" (incremental cost effectiveness ratio) comparing: tisa-cel (novartis' Kymriah 4-1BB based CD19 targeting CAR-T) vs blinatumomab, axi-cel vs tisa-cel for r/r DLBCL, relative to historical salvage chemotherapy control. Swiss clinical practice based on comparative trials cannot be applied for these types of therapies where oftentimes no comparative arm was included. The report doesn't acknowledge the fact that this patient population can be cured with CAR-T cells and no other treatment. The median survival duration only partially captures this reality.
The report did a thorough work on evaluating price tags for general management of patients with CAR-Ts versus other therapies (blinatumomab, POLA-R, Gemox, Allo SCT etc.) from leukapheresis, to IVIG, Tocilizumab etc. as per Swiss DRG and TARMED, on top of the commercial CAR-Ts costs (p138-164). We should acknowledge that these considerations including ICER will not be relevant any more in the coming years as the manufacturing conditions (closed systems and automated processes), short expansion protocols (now as short as 24h as opposed to 2 to 3 weeks currently), use on genome non-integrating CAR constructs (such as RNA based CARs, less expensive that lentivirally transduced CARs, the arrival of in vivo engineered CARs with lipid nanoparticles (LNPs)), allogenic CAR-T cell products (allowing to treat multiple recipients form cell product out a single leukapheresis healthy donor), the

arrival of alternative immune engineered cells (NK CAR, gamma delta CARs, CAR macrophages) should also be taken into account. This HTA reports lacks input from the translational oncology research community to shed light on where the global field of cell and gene therapy (including Tumor infiltrating lymphocytes-TILs) is heading.
Overall, this HTA report's conclusion suggests issues with various aspects: ethical issues such as "waiting times, issues with patient referrals, and cost coverage prior to treatment". Based on the various consideration above, all of these should be nuanced in the report. In conclusion, CAR-Ts fast evolving technology will clearly allow shortly a reduction in overall costs of production and supply chain, this is not taken into account in the HTA. The current anti CD19 CAR-T cell products are prototypes poised to offer powerful therapeutics products in cancer but also auto immune diseases in the near future.
Additional points we wish to stress upon:
 CD19 CAR-T cell therapy are poised to move to other indications in earlier relapses lines of therapy for all CD19 positive lymphoma such as mantle cell, and follicular for example.
 For DLBCL, CARTs are headed to replace autologous SCTs down the line.
Finally, there should be an initiative to stimulate the development of academic CARs even more in Switzerland.