Poster #CO14

Identification and Use of Prognostic Variables (PVs) and Treatment Effect Modifiers (TEMs) in Indirect Treatment Comparisons (ITCs) by Systematic Literature Review (SLR): Case Study of Chimeric Antigen Receptor (CAR) T-Cell Therapies

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This case study identified a lack of transparency in the identification of PVs/TEMs and inconsistencies in the way PV/TEMs are incorporated into ITCs. There is a need for guidance to reduce bias in ITC results and increase confidence in decision-making.

Background

- ITCs estimate relative effects of treatments in the absence of head-to-head clinical trials.
- There are limited head-to-head clinical studies comparing chimeric antigen receptor (CAR) T-cell therapies for the treatment of cancers.
- Several assumptions are used in ITCs, including the assumption of transitivity/similarity, stating that all included trials must be comparable in all important factors (i.e., prognostic variables, treatment-effect modifiers, and patient characteristics), other than the intervention.[1]
- Prior reviews have identified that there is limited guidance on the selection process of prognostic factors and treatment-effect modifiers, for the purpose of an ITC.[2]

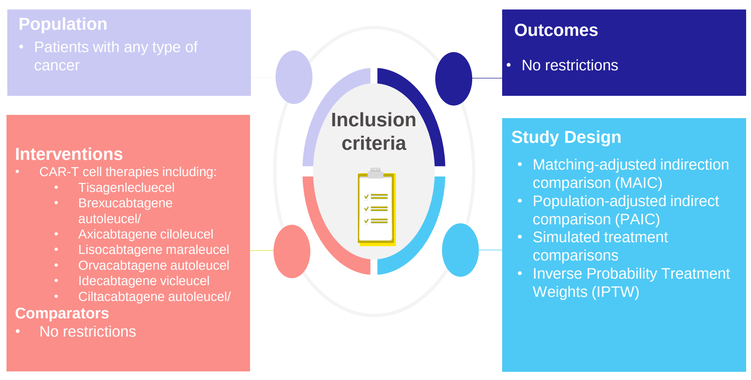
Objective

- To analyze the approach for identifying, and selecting, prognostic variables and treatment-effect modifiers considered in ITCs, using CAR-T cell therapies as a case study.

Methods

- An SLR was conducted across key databases (Embase, MEDLINE, CDSR) to identify ITCs including CAR T-cell therapies.
- Data on the indication, intervention, identification, PVs/TEMs, and sensitivity analyses were extracted and summarized. Abstracts were considered if no associated full-text articles were identified.

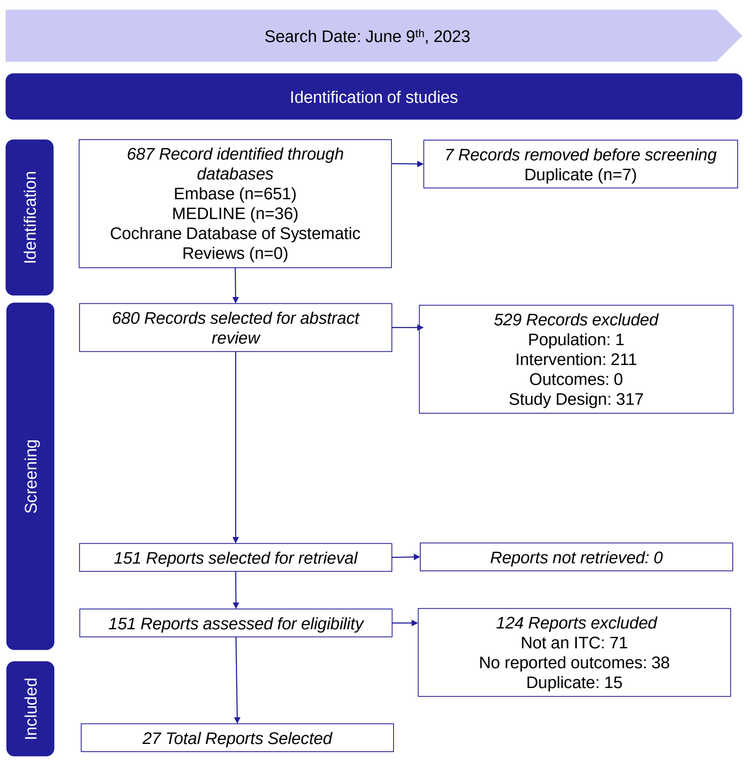
Figure 1: PICOS framework



Results

- From the database searches, 687 records were identified, of which 151 were screened at the full-text stage. A total of 27 publications (16 full-text; 11 abstracts), representing 32 indirect treatment comparisons were included in the analysis (Figure 2).

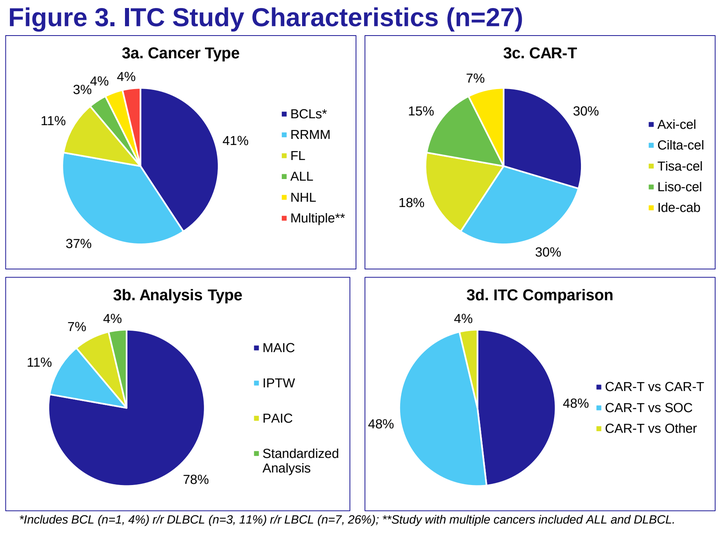
Figure 2. PRISMA Flow Chart



Results

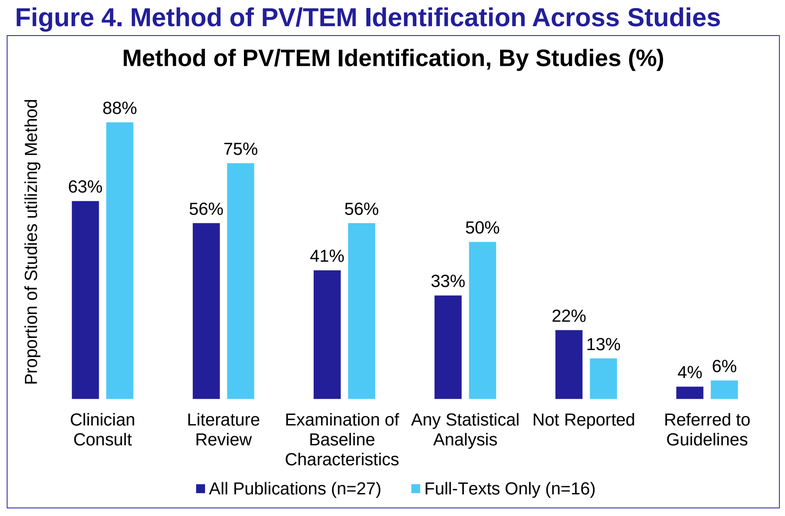
- Of the 27 publications, B-cell lymphomas (41%) and relapsed refractory multiple myeloma (37%), were the most represented cancers in the included ITCs (Figure 3a), MAICs were the most frequently utilized analysis technique (Figure 3b). A similar proportion of studies compared one CAR-T to another CAR-T, and CAR-T to standard of care (Figure 3d).
- Clinician consult and literature review were the most common methods for identification of PV/TEM; guideline reference (n=1) (Figure 4).

Figure 3. ITC Study Characteristics (n=27)



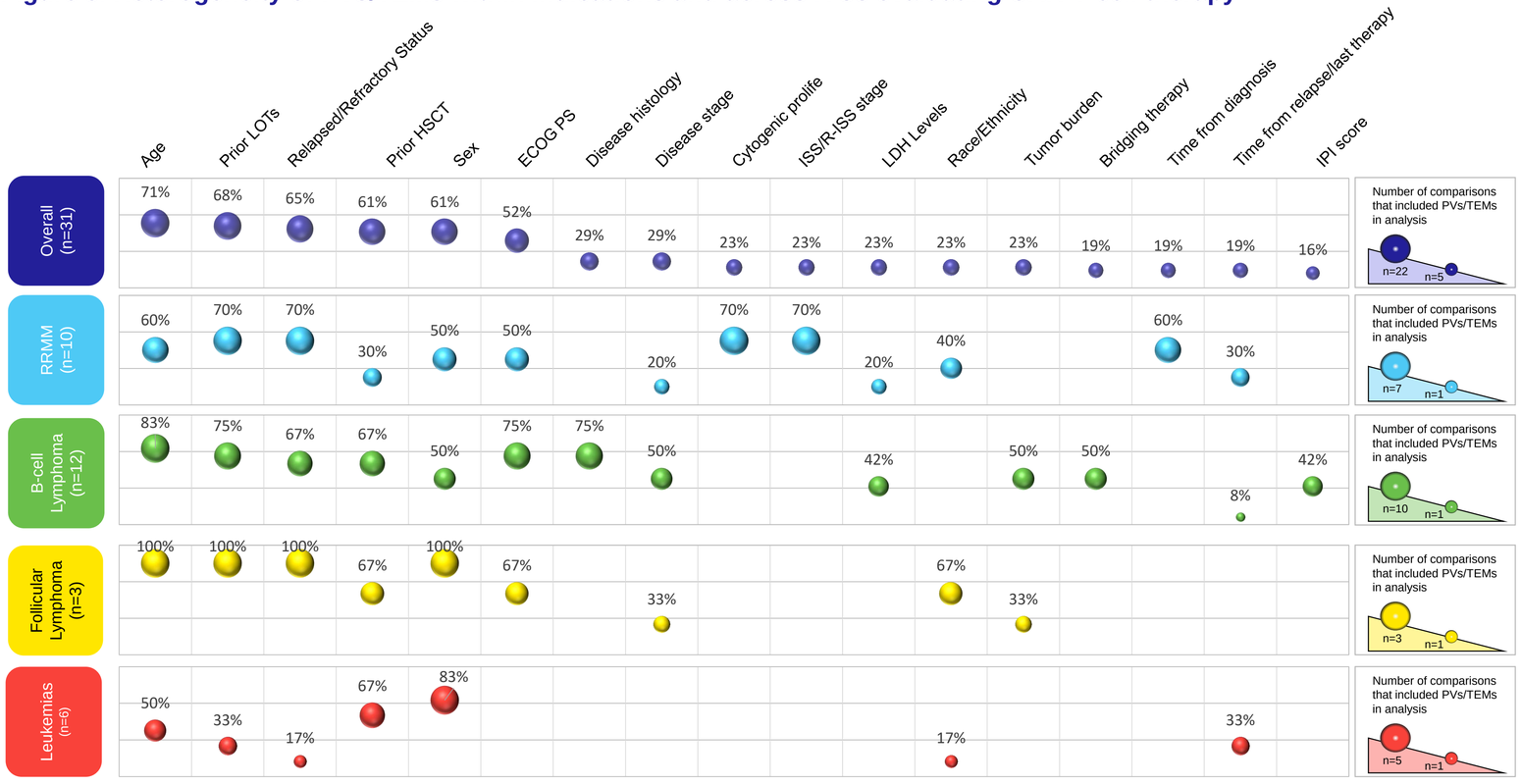
*Includes BCL (n=1, 4%) r/r DLBCL (n=3, 11%) r/r LBCL (n=7, 26%); **Study with multiple cancers included ALL and DLBCL.

Figure 4. Method of PV/TEM Identification Across Studies



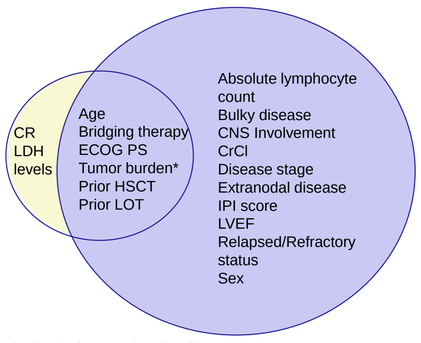
- There was heterogeneity in PVs/TEMs with over 50 different PVs/TEMs reported across the ITCs, with over half of PVs/TEMs (26/51) appearing in ≤ 2 ITCs. PV/TEMs reported in ≥ 5 ITCs are shown in Figure 5.
- In RRMM, 23 different PVs/TEMs were identified across 10 ITCs, with 8 (35%) PVs/TEMs (Age, prior LOTs, relapsed/refractory status, sex, ECOG PS, cytogenetic profile, ISS/R-ISS stage, time from diagnosis) included in ≥ 5 ITCs.
- Of the 12 ITCs in B-cell lymphomas, 51 different PVs/TEMs were identified, with 12 (23%) PVs/TEMs (Age, prior LOTs, relapsed/refractory status, prior HSCT, sex, ECOG PS, disease histology, disease stage, LDH levels, tumor burden, bridging therapy, IPI score) included in ≥ 5 ITCs.

Figure 5. Heterogeneity of PVs/TEMs within indications and across ITCs evaluating CAR-T cell therapy



- Even among studies evaluating the same CAR-T cell therapies for the same indication, heterogeneity in the use of PVs/TEMs was observed (Figure 6).
- Two MAICs[3,4] compared axicabtagene ciltoleucel and lisocabtagene maraleuceli for the treatment of r/r LBCL.
- Maloney et al.[3] identified variables that differed between the two clinical trials for adjustment in the model; Oluwole et al.[4] identified prognostic variables/TEM based on clinical relevance, clinical expertise, and data availability.

Figure 6. Comparison of variables used in Maloney et al. vs Oluwole et al. MAICs



*Tumor burden by the sum of product diameter

Conclusions

- There is a lack of transparency in reporting of how PVs/TEMs are identified in full-text publications, with 13% of publications not reporting any information.
- There is significant heterogeneity in the inclusion of factors across all ITCs and within specific indications. Over half of the PVs/TEMs were included in ≤ 2 ITCs.
- There was heterogeneity in the PV/TEM adjusted in the MAICs evaluating the same CAR-T therapies for the same indication.
- While the inclusion of sensitivity analysis may account for some of the variability in PVs/TEMs, limited information is reported for this type of analysis.
- There is a need for guidance on the identification of PVs/TEMs which would reduce bias in the ITC results and increase confidence in decision-making.

References: [1]Kiefer C, Sturtz S, Bender R. Indirect Comparisons and Network Meta-Analyses. Dtsch Arztebl Int. Nov 20 2015;112(47):803-8. doi:10.3238/arztebl.2015.0803; [2]Freitag A, Gurskyte L, Sarri G. Increasing transparency in indirect treatment comparisons: is selecting effect modifiers the missing part of the puzzle? A review of methodological approaches and critical considerations. J Comp Eff Res. 2023;12(10):e230046. doi:10.57264/cer-2023-0046. [3]Maloney DG, Kuruvilla J, Liu FF, Kostic A, Kim Y, Bonner A, Zhang Y, Fox CP, Cartron G. Matching-adjusted indirect treatment comparison of liso-cel versus axi-cel in relapsed or refractory large B cell lymphoma. J Hematol Oncol. 2021 Sep 8;14(1):140. doi: 10.1186/s13045-021-01144-9. [3]Oluwole OO, Chen JMH, Chan K, Patel AR, Jansen JP, Keeping S, Zheng Y, Snider JT, Locke FL. Matching-adjusted indirect comparison of axi-cel and liso-cel in relapsed or refractory large B-cell lymphoma. Leuk Lymphoma. 2022 Dec;63(13):3052-3062. doi: 10.1080/10428194.2022.2113526.

Abbreviations: ALL, Acute lymphoblastic leukemia; **BCL**, B-cell lymphoma; **CAR**, Chimeric antigen receptor; **CNS**, Central Nervous System; **CR**, Complete Response; **CrCl**, Creatinine Clearance; **ECOG PS**; Eastern cooperative oncology group performance status; **FL**, Follicular lymphoma; **HSCT**, Hematopoietic stem cell transplantation; **IPI**, International prognostic index; **IPTW**, Inverse Probability Treatment Weighting; **ISS**, International staging system; **ITC**, Indirect treatment comparison; **LDH**, Lactase dehydrogenase; **LOT**, Line of therapy; **MAIC**, Matching-adjusted indirect comparison; **NHL**, Non-Hodgkin lymphoma; **PAIC**, population-adjusted indirect comparison; **PICOS**, Population interventions comparators outcomes study-design; **PRISMA**, Preferred reporting items for systematic reviews and meta-analyses; **PV**, prognostic variable; **R-ISS**, Revised ISS; **RRMM**, Relapsed refractory multiple myeloma; **SLR**, Systematic literature review; **SOC**, Standard of care; **TEM**, Treatment-effect modifier.

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