Use of Single-arm Trials in Health Technology Assessment Reviews of Axicabtagene Ciloleucel

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Background

- With their unique mechanism of action and potential to offer lifelong benefits after a single treatment, gene therapies have been increasingly introduced and approved in global markets.
- Single-arm trials are commonly used to evaluate gene therapies given their novelty and ability to target life-threatening or rare diseases.
- In the absence of relative treatment efficacy directly available from single-arm trials, alternative approaches are available that use external controls to support reimbursement submissions for gene therapies worldwide.

Objectives

- The objective of this study was to assess and compare the use of single-arm trials, approach to generating comparative evidence, and recommendations by various health technology assessment (HTA) agencies for gene therapies.

Methods

- Axicabtagene ciloleucel (axi-cel)—one of the first FDA-approved chimeric antigen receptor T-cell (CAR-T) therapies—was selected for review given that newer gene therapies have not been fully submitted or reviewed by HTA agencies as of June 2023.
- For the same reason, recent submissions to major HTA agencies were identified for the first indication that received regulatory agency approval for axi-cel—adult patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL). This allows a fair comparison to be based on sufficient evaluations by multiple HTA agencies compared with subsequently approved indications.
- Two independent investigators conducted full-text screening of clinical evidence reports and reimbursement guidance documents. Information on trial design, external comparator data, indirect treatment comparison methods, and HTA critiques/decisions was extracted.

Table 1. Reimbursement Submissions and Assessments for Axi-cel in Adult R/R DLBCL

Assessment Agency	Recommendation Decision (Month/Year)	Key Critiques	Key Reasons for Recommendation
ICER Institute for Clinical and Economic Review	Not applicable (March 2018) [1]	• Not applicable	• Demonstrates clinical benefit in terms of gains in quality-adjusted life years and OS over chemotherapy • Cost-effective
Norwegian Medicines Agency	Not reported (published June 2018, updated November 2020) [2]	• Unresolved imbalance in patients' characteristics between trials through PS adjustment, given lack of direct comparison • Large uncertainty around long-term outcomes, due to small sample size and short follow-up	• Curative potential given the current unmet needs • Acceptance of using SCHOLAR-1 as the historical control for the comparator
NICE National Institute for Health and Care Excellence	Initial recommendation under CDF (January 2019) [3] Updated for routine use (February 2023) [3]	• Indirect adjustments substantially reduced the sample size and led to increasing uncertainty • Heterogeneity exists between study populations	• Life-extending treatment at the end of life • Cost-effective • Regardless of the data limitations, SCHOLAR-1 dataset was appropriate for decision-making
cadth Canada's Drug and Health Technology Agency	Reimburse with condition (August 2019) [4]	• Definition of RR, CR, and OS are different between Zuma-1 and SCHOLAR-1 studies • Heterogeneity exists between study populations	• Effective alternative treatment that may prolong remission and/or survival for patients
Healthcare Improvement Scotland | Scottish Medicines Consortium	Accepted under end of life and ultra-orphan evaluation process (September 2019) [5]	• Heterogeneity exits between and within trials • Assumptions are needed to derive PFS, given the lack of data	• Greater uncertainty in economic evaluation can be accepted, given that axi-cel is an ultra-orphan medicine
Australian Government Medical Services Advisory Committee	Supported by public funding (January 2020) [6]	• Heterogeneity exists between study populations • The magnitude and durability of the benefit was difficult to estimate reliably, given the quality of the evidence	• Superior efficacy compared with standard of care and has a consistent and well-characterized safety profile

Abbreviations: CADTH = Canadian Agency for Drugs and Technologies in Health; CDF = Cancer Drug Fund; CR = complete response; ICER = Institute for Clinical and Economic Review; NICE = National Institute for Health and Care Excellence; OS = overall survival; PFS = progression-free survival; PS = propensity score; RR = response rate

Results

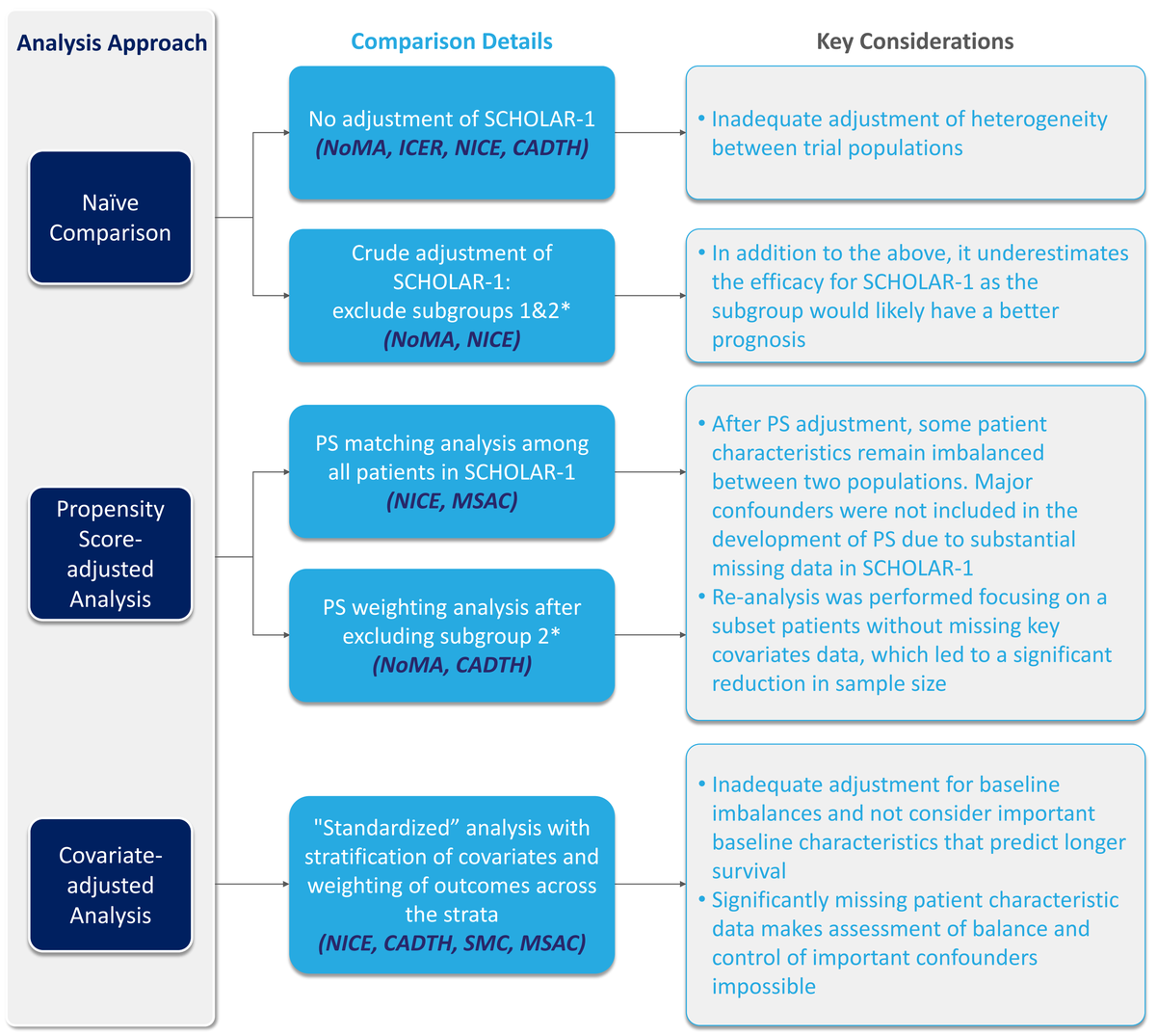
- Six English-based submissions for axi-cel were identified from HTA agencies worldwide, including from the UK, Australia, Norway, Canada, Scotland, and the US (Institute for Clinical and Economic Review was used as a proxy).
- Consistently, ZUMA-1[7] was identified as the only submitted evidence for axi-cel. Salvage chemotherapy was selected as the comparator across evaluations based on SCHOLAR-1 study[8] (**Table 2**).
- Comparative evidence was generated using different methods, including naïve comparison, propensity score analysis (matching, weighting), and covariate-adjusted analysis (**Figure 1**). Key limitations included the inadequate adjustment of confounders due to data limitations and unresolved heterogeneity between patient populations.
- Despite varying levels of criticism on comparator data and comparison methods from HTA reviewers, all agencies made positive recommendations. These were mainly driven by the relative clinical benefits demonstrated through the comparisons, patient unmet needs, quality of comparator evidence, and potential to be cost-effective (**Table 1**).

Table 2. Zuma-1 for Axi-cel and SCHOLAR-1 for Comparators

	Zuma-1 (Axi-cel)	SCHOLAR-1 (Salvage Chemotherapy)
Sample size	mITT population N=101	Survival Analysis Set N = 497
Baseline Characteristics	100% pts with ECOG 0-1 2% primary refractory pts. 85% stage III-IV disease 11% post-refractory SCT pts.	Include 55% pts. with ECOG >=2 20% primary refractory pts. 30% stage III-IV disease 32% post-refractory SCT pts.
Study Design	Phase 1/II, multicenter, single-arm	Pooled study based on two phase III RCTs (CORAL and LY.12) and two cohort studies (MDACC and MAYO)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; mITT = modified intention-to-treat; pts.= patients; RCT = randomized control trial; SCT – stem-cell transplant

Figure 1. Approaches Assessing Comparative Evidence for Axi-cel in Adult R/R DLBCL



Note: * Subgroup 1: patients with ECOG 2–4, subgroup 2: patients with ECOG 2–4 and post-refractory SCT
Abbreviations: CADTH = Canadian Agency for Drugs and Technologies in Health; ECOG = Eastern Cooperative Oncology Group; ICER = Institute for Clinical and Economic Review; MSAC = (Australian) Medicare Services Advisory Committee; NICE = National Institute for Health and Care Excellence; NoMA = Norwegian Medicines Agency; PS = propensity score; SCT = stem cell transplantation; SMC = Scottish Medicines Consortium

Conclusions

- Single-arm, trial-based submissions of axi-cel were well accepted for reimbursement across countries, with the relative treatment effect being addressed through sensible external comparator evidence and comparison approaches.

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