HTA93

Mixture cure models: a new paradigm to model long-term remission (LTR) for Chimeric antigen receptor (CAR) T-cell therapies?

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INTRODUCTION

- CAR-T therapies hold the promise of a cure for some blood cancer patients, but capturing this clinical benefit in clinical trials is not always feasible due to limited follow-up.
- For the purpose of cost-effectiveness-based health technology assessments (HTAs), such benefits need to be modelled to understand the impact over patients' lifetime.
- The purpose of this research is to understand the methods used to model LTR in National Institute for Health and Care Excellence (NICE) technology appraisals (TAs) evaluating CAR-T therapies and their potential impact on reimbursement recommendations in England.

METHODS

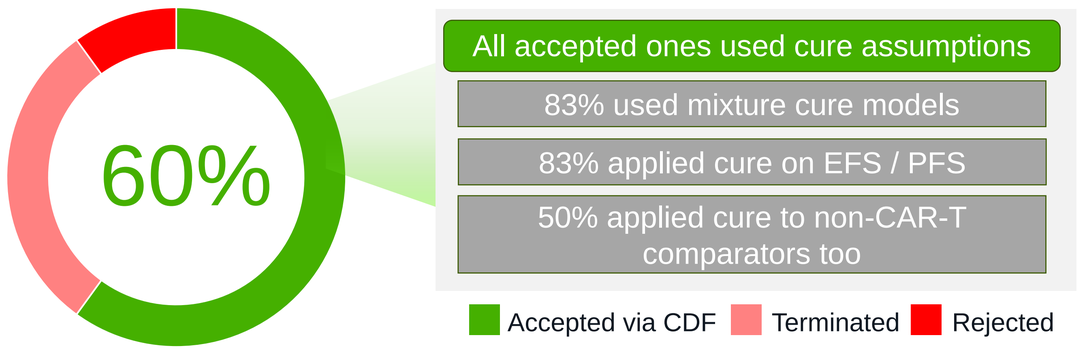
- All NICE TAs for CAR-T therapies were reviewed for approaches to model LTR and appraisal outcomes.
- Details extracted included modelling approach, trial follow-up and NICE critique of the submitted evidence.
- Lisocabtagene maraleucel was excluded from this research as its assessment is currently ongoing.

RESULTS

Overview of NICE recommendations and reimbursement outcomes

- Out of the 10 submissions identified, six were initially recommended for funding via the Cancer Drugs Fund (CDF), one was rejected, and three were terminated by the manufacturer prior to NICE assessment (Figure 1).
- Out of the CAR-Ts which were initially accepted via CDF, three re-assessments have been initiated: two were fully recommended based on substantial longer follow-up, and one appraisal was terminated by the manufacturer once data for re-assessment became available.
- The remaining three reassessments are expected in the upcoming years.

Figure 1: Initial NICE appraisal outcomes of assessed CAR-Ts



Use of mixture cure models (MCM) to model LTR assumptions

- All (6/6) models implemented a cure assumption on overall survival (OS) and 83% (5/6) on event- or progression-free survival. Half (3/6) implemented the cure assumption to non-CAR-T comparators, too.
- In the rejected TA894, the company did not use a MCM due to the outcomes not being mature enough to fit them. Instead, standard parametric models (SPM) were used to extrapolate OS and PFS until Year 5. After that, an SMR-adjusted general population mortality hazard was applied to 25% of patients treated with axi-cel (in line with clinical opinion). Those who were not captured as long-term survivors continued to follow the hazards associated to the parametric models, an assumption which the EAG considered to underestimate the risk of progression of the non-long-term survivors.
- An additional challenge in TA894 was the nature of disease, as the average prognosis for patients with FL is significantly longer than all other diseases explored in adults, with a 5-year overall survival of 82%. These two key factors (not robust long-term data and good prognosis) deviated from the Palmer algorithm[1] for inclusion of MCMs.
- All submissions used a partitioned survival model (PSM). 2/7 used an initial decision tree to account for costs and outcomes related to leukapheresis (before CAR-T infusion) followed by a PSM. In 4 out of 7, costs prior to CAR-T infusion were accounted through a cost multiplier. In TA895, as ZUMA-7 patient outcomes were measured from randomisation, events before CAR-T infusion were captured in the PSM.

Table 1: Reviewed NICE TAs and acceptance rate

Disease	Prognosis[2-4] (5-year OS)	CAR-T	Initial outcome	Re-assessment outcome	EOL	Trial median follow-up (related to CAR-T)	Approach for LTR	Applied to: (EFS/PFS, OS)	Applied to: (CAR-T only, non-CAR-T)	Model structure	Cure fractions
R/R B-ALL	90%	Tisa-cel *TA554/975[5,6]; Paediatric & young adults <25*	via CDF (2018)	Reimbursed (2024)	✘	ELIANA: 79.4m	MCM	Both	Both	Decision tree + PSM	• OS CAR-T: 42.4% • OS comparator: 9.4-11.4% • EFS CAR-T: 34.6%
	30-40%	Brexu-cel *TA893[7]; Adults over 26*	via CDF (2023)	*Expected in 2028*	✓	ZUMA-3: 26.8m[8]	SPM	Both	Both	PSM	SPM for both EFS/OS followed by adjusted general population mortality from 3 years for CAR-T and comparators
3L+ DLBCL	55%	Axi-cel *TA559/872[9,10]; Adults*	via CDF (2019)	Reimbursed (2023)	✓	ZUMA-1: 60m (minimum; OS)	MCM	OS	CAR-T only	PSM	• OS: ~50%
		Tisa-cel *TA567/933[11,12]; Adults*	via CDF (2019)	Terminated (2023)	✓	JULIET: 14m Schuster: 28.6m	MCM	Both	CAR-T only	Decision tree + PSM	Cure fraction redacted
2L DLBCL	55%	Axi-cel *TA895[13]; Adults*	via CDF (2023)	*Expected in 2028*	✓	ZUMA-7: 24.9m	MCM	Both	Both	PSM	• EFS: CAR-T: 35-39% • EFS: comparator: 14-16% • OS: CAR-T: 24-54% • OS: comparator: 32-49%
R/R MCL	63%	Brexu-cel *TA677[14]; Adults*	via CDF (2021)	*Expected in 2025*	✓	ZUMA-2: 12.3m	MCM	Both	CAR-T only	PSM	Redacted
3L+ FL	85%	Axi-cel *TA894[15]; Adults*	Rejected (2023)	-	✘	ZUMA-5: 18m (minimum)	SPM	Both	CAR-T only	PSM	SPM for both EFS/OS followed by adjusted general population mortality from 5 years for 25% receiving CAR-T
		Tisa-cel *TA842[16]; Adults*	Terminated (2022)	-	-			-	-	-	
4L+ MM	60%	Cita-cel *TA889[17]; Adults*	Terminated (2023)	-	-			-	-	-	
		Ida-cel *TA936[18]; Adults*	Terminated (2023)	-	-			-	-	-	

CONCLUSIONS

- Mixture cure models have emerged as the standard approach to model LTR and have been widely accepted by NICE in CAR-T appraisals
- In line with the Palmer algorithm[1], the key considerations when submitting a mixture cure model to NICE are:
  - Clinical validation is essential for supporting the cure assumption
  - There needs to be sufficient follow-up in the trial and data need to be mature enough to substantiate LTR assumptions
  - Sufficiently mature data is more feasible to collect in diseases which progress more rapidly
- Additionally, successful reimbursement also appears to be correlated with higher unmet need (i.e., paediatric populations or diseases with limited treatment alternatives) and eligibility for end-of-life modifier
- Companies submitting economic models to NICE and to other HTA bodies should take these considerations into account, especially given payer cautiousness around the high upfront costs associated with CAR-Ts vs chronic regimens

ABBREVIATIONS & REFERENCES

Abbreviations: **2L**, second line; **3L+**, third line or later; **4L+**, fourth line on later; **B-ALL**, B-cell acute lymphoblastic leukaemia; **CAR-T**, chimeric antigen receptor T-cell; **CDF**, Cancer Drugs Fund; **DLBCL**, diffuse large B-cell lymphoma; **EAG**, External Assessment Group; **EFS,** event-free survival; **EOL**, end of life; **FL**, follicular lymphoma; **HTA**, health technology assessment; **LTR**, long-term remission; **MCL**, mantle cell lymphoma; **MCM**, mixture cure model; **MM**, multiple myeloma; **NICE**, National Institute for Health and Care Excellence; **OS**, overall survival; **PFS**, progression-free survival; **PSM**, partitioned survival model; **R/R**, relapsed or refractory; **SMR**, standardised mortality ratio; **SPM**, standard parametric model; **TA**, technology appraisal.

References: **1.** Palmer, et al. Value in Health 26.2, 2023. **2.**SEER, 2024. **3.** Cencini, et al. Hematology Reports 16.1, 2024. **4.** Paul, et al. Mayo Clinic Proceedings. Vol. 91. No. 11. Elsevier, 2016. **5.** NICE, 2018 (TA554). **6**. NICE, 2024 (TA975). **7**. NICE, 2023 (TA893). **8.** Shah, et al. Journal of hematology & oncology 15.1, 2022. **9**. NICE, 2019 (TA559). **10**. NICE, 2023 (TA872). **11**. NICE, 2019 (TA567). **12**. NICE, 2023 (TA933). **13**. NICE, 2023 (TA895). **14**. NICE,2021 (TA677). **15**. NICE, 2023 (TA894). **16**. NICE, 2022 (TA842). **17**. NICE, 2023 (TA889). **18**. NICE, 2023 (TA936).

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