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Uncertainty in appraisals of CAR-T products

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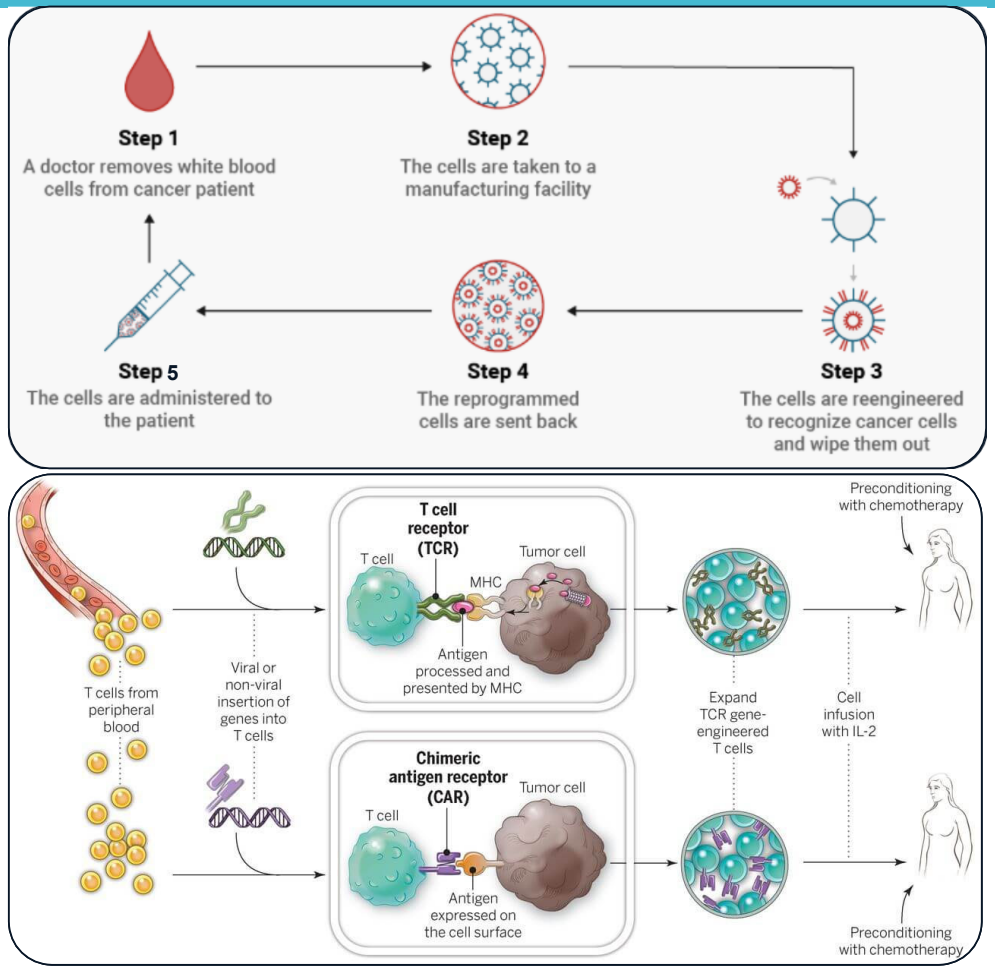
Therapy background

Chimeric antigen receptor T-cell (CAR-T) therapies are innovative treatments, with the potential to revolutionise oncology by providing long-term survival outcomes in diseases where such outcomes were not thought possible

- CAR-T therapies involve extracting peripheral T-cells and genetically modifying them before transplanting them back into the patient
- One-time treatment
- CAR-Ts are currently only available for haematological cancers, but there is hope they will soon be available for solid tumours
- Some experts believe that CAR-T therapies represent the next era of immuno-oncology[1,2]



1. Feinberg BA, Fillman J, Simonici J and Nabhan C. CAR-T Cells: The Next Era in Immuno-Oncology. *AJMC*. 2017; 23(2):SP48-SP52.
2. Labanieh L, Majzner RG and Mackall CL. Programming CAR-T cells to kill cancer. *Nat Biomed Eng*. 2018; 2(6):377-91.

Appraisals of CAR-T therapies

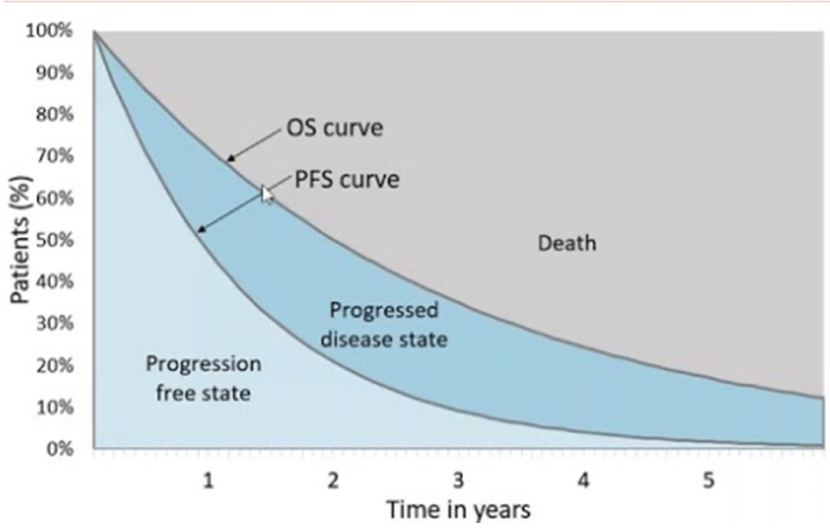
There are three technology appraisals for the first two licensed CAR-T therapies for both NICE and ZIN:

Appraisal	Drug name (brand name)	Sponsor company	NICE appraisal code	NICE decision	ZIN assessments	ZIN decision
Axicabtagene ciloleucel ('axi-cel') for treating diffuse large B-cell lymphoma, mediastinal B-cell lymphoma and follicular lymphoma	Axicabtagene ciloleucel (Yescarta®)	Gilead (acquired Kite Pharma)	TA559	CDF (with discount)	Pharmacotherapeutic Pharmacoeconomic Budget impact	No, unless price reduction
Tisagenlecleucel-T ('Tis-T') for treating relapsed or refractory diffuse large B-cell lymphoma	Tisagenlecleucel-T (Kymriah®)	Novartis	TA567	CDF (with discount)	Pharmacotherapeutic	No
Tisagenlecleucel-T ('Tis-T') for treating relapsed or refractory B-cell acute lymphoblastic leukaemia in patients aged 3–25 years	Tisagenlecleucel-T (Kymriah)	Novartis	TA554	CDF (with discount)	Pharmacotherapeutic Budget impact	Yes

Key: CDF, Cancer Drugs Fund; NICE, National Institute for Health and Care Excellence.

Model structure

- General recommendation: Aim to produce a model that is only as complex as required, whilst still considering all important health and cost differences between the intervention of interest and its comparators
- The key value proposition for CAR-T therapies appears to be lengthened overall survival (OS), with a cure in some proportion of patients
- Standard partitioned survival models were used across all company submissions. Health states considered were progression-free, post-progression and death



Choice of model type

- There is already considerable uncertainty arising from data used
- PartSA is a frequently used and widely accepted model structure
- The use of a PartSA facilitated discussions on the extrapolations without needing to constantly refer to uncertainty introduced by the model structure
- In PartSA, proportions of patients in the health states are directly derived from the PFS and OS curves

Comparator data selection

- Accelerated regulatory approval means clinical trial data to inform the economic model are expected to be limited
  - Phase III randomised data were not available for any of the appraisals
- In lieu of randomised comparative data, non-randomised data are required:
  - Naïve comparisons
  - Matched comparisons
- Need to understand the ‘real-world’ data available
- Carefully consider sample size and imbalances in baseline prognostic factors when selecting comparator data set
  - How well do these and the CAR-T data reflect the relevant patient group in clinical practice?

Treatment effect estimation from non-randomised data

- For Yescarta, the evidence review group (ERG) requested matching-adjusted indirect comparison (MAIC), which the company undertook
  - The ERG then critiqued the results as implausible, so MAIC was considered inappropriate
  - Naïve comparisons were used for decision making
- For TA554 (Kymriah for the paediatric indication) Novartis submitted MAICs to Jeha et al. (2006) and von Stackelberg et al. (2016)
  - The committee preferred naïve comparisons for decision making
- In TA559 (Kymriah for diffuse large B-cell lymphoma [DLBCL]) patient-level data access to SCHOLAR-1 broadened possibilities for matched comparisons
  - Only patients with ECOG 0 or 1 in SCOLAR-1 were retained to better match ZUMA-1 patients

Survival and extrapolation

- Immature data – Extrapolation required
- Type of model for extrapolation
  - ‘Standard’ parametric survival models
  - Mixture cure models (MCM)
    - When does cure occur?
    - What proportion of patients are cured?
    - What are the effects of cure?
    - Can comparator arm patients also be cured (autologous stem-cell transplantation [ASCT])?
  - Spline models
    - How many splines?
    - Where are the splines?
- Clinician input required to help make decisions here

Survival and extrapolation – NICE appraisals

Company submitted base case models across all appraisals

Appraisal	Curve	Intervention	Comparator
TA559	OS	Weibull MCM based on ZUMA-1 with cure fraction of 50%; implies cure at approximately 2 years	Gompertz standard parametric model based on SCHOLAR-1, with implied long-term survivors of ~15% after approximately 3 years
	PFS	Gompertz standard parametric model based on ZUMA-1 with cure fraction of ~40% at approximately 2 years	No PFS data from SCHOLAR-1; therefore, OS:PFS HR from ZUMA-1 was applied
TA567	OS	Lognormal MCM based on pooled JULIET and Schuster Cure fraction OS: 35.5%; PFS 34.9%	Exponential model based on Eyre (2016)
	PFS		
TA554	OS	Exponential MCM based on pooled ELIANA, ENSIGN and B2101J studies (plateau ~50%)	Lognormal MCM for blinatumomab based on von Stackelberg (2016) Generalised gamma parametric model for salvage chemotherapy based on Jeha (2006)
	EFS	Generalised gamma MCM on pooled ELIANA, ENSIGN and B2101J studies (plateau ~44.7%)	HR applied to OS based on UK ALL study

Key: ALL, acute lymphoblastic leukaemia, EFS, event-free survival; HR, hazard ratio; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival.

Survival and extrapolation – NICE appraisals (2)

Decision-making models across all appraisals

Appraisal	Curve	Intervention	Comparator
TA559	OS	Combination of ERG model (log-logistic then general population upon convergence with PFS) and company base case	Combination of ERG model (ECOG 0–1 subgroup of SCHOLAR-1) and company base case
	PFS	MCM for PFS	Combination of ERG model (convergence with OS) and company base case
TA567	OS	Lognormal MCM based on pooled JULIET and Schuster (Company base case, cure point between 2–5 years)	CORAL data weighted based on SCT rates (ERG analysis)
	PFS		
TA554	OS	Log-logistic MCM	Log-logistic MCM for blinatumomab Lognormal MCM for salvage chemotherapy based on Kuhlen et al.
	EFS	Log-logistic MCM	HR applied to OS based on UK ALL study

Key: ALL, acute lymphoblastic leukaemia, EFS, event-free survival; ERG, evidence review group; HR, hazard ratio; MCM, mixture cure model; OS, overall survival; PFS, progression-free survival; SCT, stem-cell transplant.

Mixture cure models in NICE appraisals

When	• TA559 and TA567: After 2 years of non-progression. The ERG suggested this was later (4–5 years)
Fraction of cure	• TA559 and TA554: Lack of consistency of cure fraction PFS vs OS – Might have to do with retreatment and treatment post progression? • Wide ranges of cure fractions were major driver of cost-effectiveness
Effects of cured period	• For all appraisals, companies claimed age-matched general population mortality after 2 years • This was not accepted. Patients have higher mortality risks than general population. Low impact on cost-effectiveness
Comparator cure	• TA559 and TA567: No cure in comparator arm was not accepted as ASCT can induce long-term survival

Treatment costs

- Retreatment allowed in CAR-T clinical trials
  - Will this also happen in clinical practice?
  - Affects survival outcomes in trial
  - Costs of retreatment considered in modelling?
- All treatment costs are upfront
  - High risk compared with other drug therapies
  - Not possible to ‘stop treatment’ if not effective and have only part of the costs

Adverse events

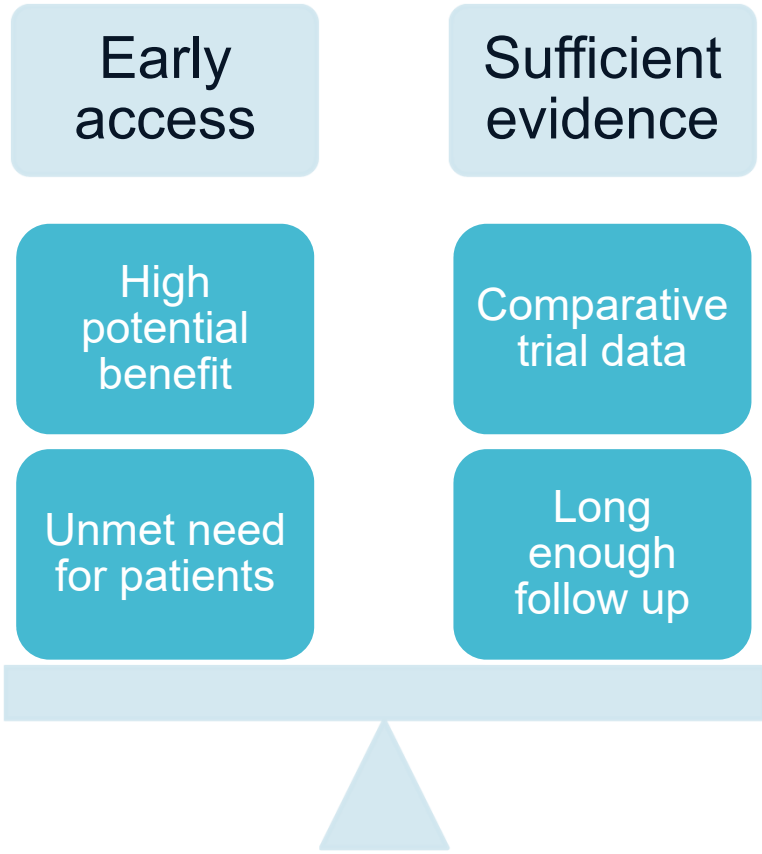
- Discussions about costs of adverse events (AEs)
  - Cytokine release syndrome
  - B-cell aplasia
- Both are severe and extremely costly to treat
  - Fear of underestimating costs
- Conclusion: While AE costs can be high, and utility effects substantial, by their nature they need to be resolved
  - AE assumptions were not key drivers of cost-effectiveness results in these CAR-T cost-effectiveness models

Addressing uncertainty

- Explore different scenarios (e.g. for extrapolation)
  - None is perfect
  - Explore what is the option that best reflects what happens in clinical practice
- Use clinician input (expert elicitation) to identify the most plausible scenario(s)

Balance early access versus sufficient evidence

- NICE was willing to make positive (CDF) recommendations on the basis of limited and non-randomised comparator data
- ZIN required good quality evidence of a survival benefit of at least 3 months



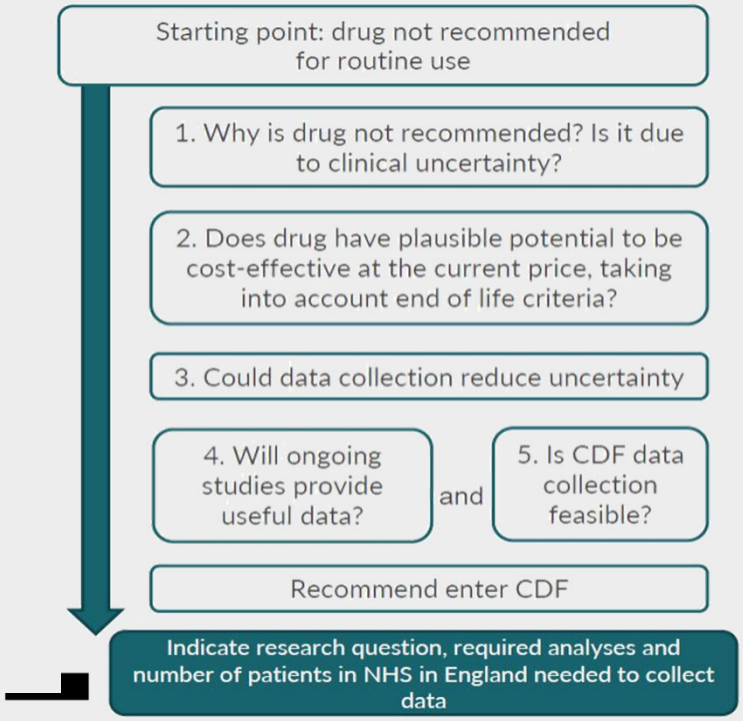
Financial solutions

- Annuity payments?
- Performance-based payments?
- Discount
- NICE: CDF – preliminary acceptance with further evidence gathering and discount

CDF process and access

NICE committees are the gatekeeper for CDF access

Figure 1[1]



- **Figure 1 illustrates the process** committees use to determine whether a CDF recommendation is appropriate
- Entry into the CDF <u>then</u> requires a managed access agreement (MAA) with NHSE
- The MAA comprises two parts
  1) Data collection arrangement – which describes the arrangements and responsibilities for further data collection
  2) Commercial access agreement (confidential) – which provides details on discounts to drug price

CAR-T therapies may be appropriate for the CDF because of high cost combined with uncertainty regarding their effectiveness in real-world practice, particularly due to short-term follow-up combined with long-term claims about survival and uncertainty in AE rates, costs and long-term consequences:

NHSE viewed these CAR-T therapies as ideal candidates for the CDF

1. NICE. https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/cancer-drugs-fund

Chronic versus curative treatment

- If a pharma company has the choice between developing a chronic and a curative therapy for a condition:
  - What decision do we want the company to take?
  - Do we provide the right incentives/rewards?

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Questions?

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