# Axicabtagene ciloleucel for treating relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy

Public observer slides, no confidential information

**Technology appraisal committee C [1 November 2022]**

**Chair:** Stephen O'Brien

**Lead team:** Matt Stevenson, John Hampson, Ugochi Nwulu

**Evidence assessment group:** Aberdeen HTA

**Technical team:** Catie Parker, Alex Filby, Ross Dent

**Company:** Kite, a Gilead company

# Background on diffuse large B-cell lymphoma

An aggressive type of cancer of the lymphatic system

## Causes

- Multifactorial; risk factors include body mass index, weakened immune system, exposure to carcinogens and genetics

## Epidemiology

- About 5,200 people diagnosed in the UK each year
- More common in people over age 60

## Diagnosis and classification

- Most people diagnosed with advanced stage disease (3 or 4)

## Symptoms and prognosis

- Swollen lymph nodes, night sweats, fever, weight loss and itching
- Emotional burden that can be made worse by relapsed or refractory disease
- People with relapsed or refractory disease have lower chance of later disease response

# Axicabtagene ciloleucel (Yescarta, Kite)

**Table 1** Technology details

| | |
|---|---|
| **Marketing authorisation** | • European license: for treating 'adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy'<br>• GB license extension expected [redacted] |
| **Mechanism of action** | Autologous CAR T-cell product that recognises and eliminates all CD19-expressing target cells, including B-cell malignancies and normal B-cells |
| **Administration** | • **Production**: patient T-cells are extracted via leukapheresis and activated with IL-2 and an anti-CD3 mAb, then transduced with the anti-CD19 CAR transgene-containing γ-retroviral vector<br>• **Infusion**: Bag of axi-cel for IV infusion has target dose of 2 x $10^6$ CAR-positive viable T-cells per kg of body weight<br>• **Additional medication**: Lymphodepleting chemotherapy (cyclophosphamide and fludarabine). Premedication with paracetamol and diphenhydramine recommended |
| **Price** | • List price including shipping, engineering and generation of CAR T-cells: £280,451<br>• Patient access scheme discount available |

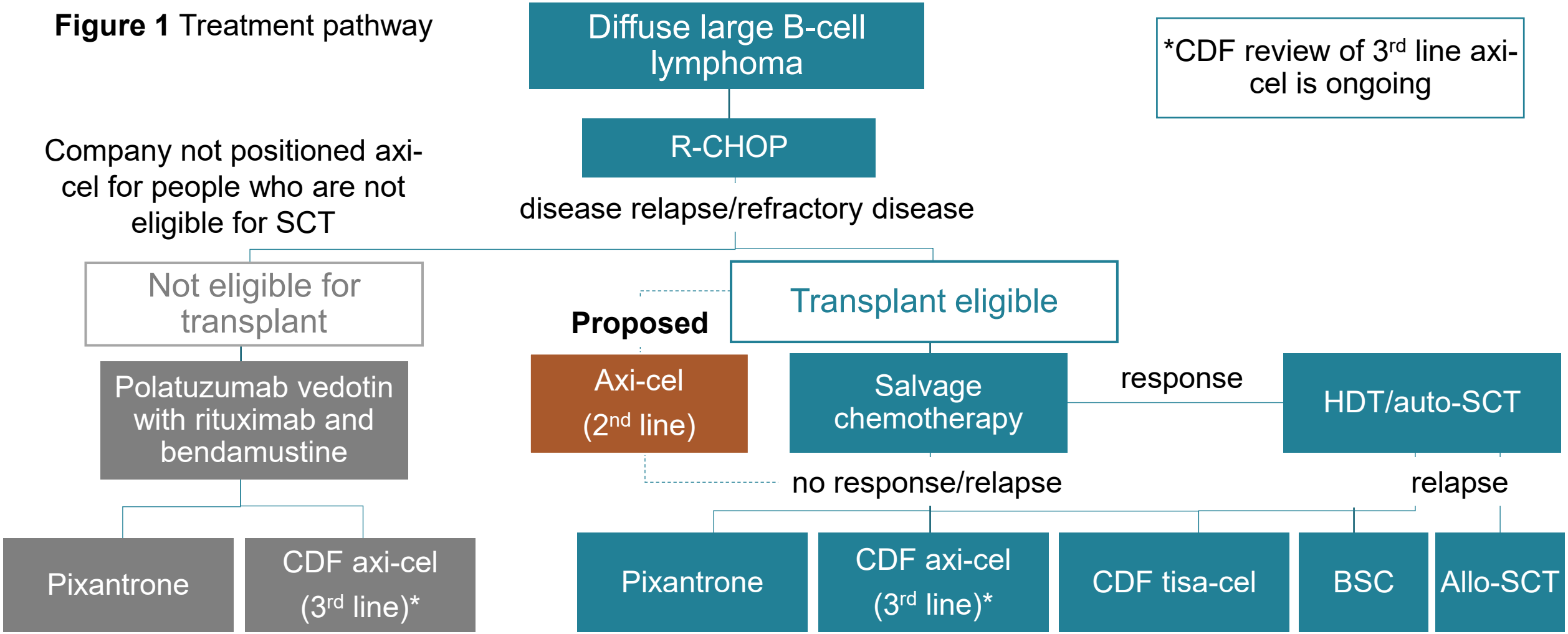
Population in appraisal is narrower 'Adults with primary refractory or early relapse (≤ 12 months) DLBCL **who are intended for transplant**'

Abbreviations: CAR T, chimeric antigen receptor T; CD3, cluster of differentiation 3; CD19, cluster of differentiation 19; CHMP, Committee for Medicinal Products for Human use; DLBCL, diffuse large B-cell lymphoma; IL-2, interleukin 2; kg, kilogram; mAb, monoclonal antibody

# Treatment pathway

## Proposed as 2nd line treatment for people who are transplant eligible

**Figure 1** Treatment pathway




Abbreviations: allo-SCT, allogenic stem cell transplant; auto-SCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; BSC, best supportive care; CDF, Cancer Drugs Fund; HDT, high dose therapy

# Patient perspectives

## Disease has large burden and current treatment has many side effects

**Symptoms:** lumps in the neck, armpit or groin; chest or abdominal pain; bone pain; coughing or breathlessness

**Impact on daily life:**

- Patients spend a lot of time in hospitals which can impact their ability to work and socialise. This can also cause financial worry
- Mental health effected by insomnia and anxiety
- Many patients need carers

**Current treatment:**

- High-dose chemotherapy with auto stem cell transplant is effective, but can be intense with very severe side effects
- Other chemotherapy regimens can work but also have side effects
- Unmet need for relapsed DLBCL

**Axi-cel:**

- Many possible side effects: CRS, infections, ICANS, confusion and weight loss
- Despite side effects, one patient felt their health and quality of life returned to pre-diagnosis levels after axi-cel

[I felt] so weak after R-CHOP, I didn't know how my body or my mind was going to cope

Previous chemotherapy made me feel chronically unwell, but CAR-T was a short burst of side effects

NICE



Abbreviations: axi-cel, axicabtagene ciloleucel; CAR T, chimeric antigen receptor T; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; ICANS, immune effector cell-associated neurotoxicity syndrome ; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone

# Clinical perspectives

## Relapsed disease outcomes are poor, axi-cel may improve them

**Submissions from Royal College of Pathologists and 2 clinical experts**

**Current treatment and prognosis:**

- Aim of treatment is to cure disease
- For transplant eligible: 2-3 cycles of intensive salvage chemotherapy then high dose chemotherapy and auto-SCT
- People with disease relapse within 12 months of R-CHOP have estimated 2 year OS of 35% and PFS of less than 20%

**Axi-cel:**

- 2L CAR T therapy for DLBCL is a major shift in current treatment
- Likely improves PFS for disease relapsing within 12 months of R-CHOP. Similar trend for OS, but longer follow up is needed
- Need for intensive care support for about 20% of patients
- High mortality with Covid-19 infection in patients after CAR T therapy

Critical side effects such as CRS or neurotoxicity are seen within days after the infusion of CAR T cells. Most patients recover fully from these



Abbreviations: auto-SCT, autologous stem cell transplant; CAR T, chimeric antigen receptor T; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; OS, overall survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone 2L, 2nd line

# Decision problem

## Company's population is narrower than scope, but other PICO aligned

**Table 2** Population, intervention, comparators and outcomes from the scope

| | Final scope | Company | EAG |
|---|---|---|---|
| **Population** | Adults with relapsed or refractory diffuse large B-cell lymphoma after 1 systemic therapy | Adults with primary refractory or early relapse (≤ 12 months) DLBCL **who are intended for transplant** (aligned with ZUMA-7) | Appropriate |
| **Intervention** | Axicabtagene ciloleucel | Axicabtagene ciloleucel | N/A |
| **Comparators** | Established clinical management without axi-cel including:<br>• salvage chemotherapy +/- RTX and +/- SCT<br>• polatuzumab vedotin with RTX and bendamustine and tafasitamab with lenalidomide (both subject to NICE appraisal) | Re-induction therapy with high dose therapy and auto-SCT | Appropriate |
| **Outcomes** | OS, PFS, response rates, adverse effects of treatment and HRQoL | EFS, OS, PFS, response rates, adverse effects of treatment and HRQoL | Appropriate |

Abbreviations: DLBCL, diffuse large B-cell lymphoma; OS, overall survival; PFS, progression free survival; PICO, population intervention comparators and outcomes; RTX, rituximab SCT, stem cell transplant +/-, with or without

# Key issues

**Table 3** Key issues

| Issue | Resolved? | ICER impact |
|---|---|---|
| **Axi-cel 3rd line crossover adjustment (because it is not routinely commissioned in NHS)**<br>• Is the RPSFTM with full re-censoring the most appropriate cross-over adjustment for overall survival in the standard of care arm? | No – for discussion | Unknown |
| **Axi-cel retreatment costs**<br>• Should costs or benefits be adjusted to account for axi-cel retreatment? | No – for discussion | Large |
| **Overall survival for axi-cel**<br>• Is generalised gamma or log-logistic extrapolation more appropriate? | No – for discussion | Medium |
| **End of life criteria**<br>• Is axi-cel a life extending treatment at the end of life? | No – for discussion | N/A |
| **CAR-T tariff**<br>• What are the most appropriate costs for axi-cel administration in the NHS? | No – for discussion | Large |

Abbreviations: auto-SCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; ICER, incremental cost-effectiveness ratio; RPSFTM, rank preserving structural failure time model; SoC, standard of care

# Other areas of uncertainty

**Table 4** Other areas of uncertainty

| Issue | ICER impact |
|---|---|
| **Autologous stem cell transplant costs**<br>• Company prefer £37,735 from NICE Guideline 52<br>• EAG prefer £17,181.37 from NHS reference costs | Medium |
| **Extrapolation of event free survival**<br>• Uncertain, but not a key driver of the ICER<br>• EAG consider company approach reasonable | Small |
| **Pre-progression utility values**<br>• Company prefer JULIET study values, used in TA567 (tisa-cel 3L DLBCL)<br>• EAG prefer ZUMA-1 values, used in TA559 (axi-cel 3L DLBCL) | Small |
| **Salvage chemotherapy use in standard of care arm**<br>• Company use 100% and EAG prefer [redacted]% from ZUMA-7 | Small |
| **Distribution of post-event treatments**<br>• Company prefers clinical opinion<br>• EAG prefers ZUMA-7 distribution | Small |
| **ZUMA-7 trial design**<br>• Clinical experts noted it did not include chemotherapy bridging, unlike the NHS | Unknown |

Abbreviations: CAR T, chimeric antigen receptor T cell; ICER, incremental cost-effectiveness ratio; RPSFTM, rank preserving structural failure time model

# Clinical effectiveness

NICE National Institute for Health and Care Excellence

# Key clinical trial: ZUMA-7

**Table 5** Clinical trial designs and outcomes

| | ZUMA-7 [ongoing] |
|---|---|
| **Design** | Phase 3, randomised (1:1), open-label, parallel assignment |
| **Population** | Adults with histologically confirmed DLBCL<br>• refractory to frontline treatment or relapsed ≤ 12 months after frontline chemoimmunotherapy<br>• intended to proceed to high-dose therapy and auto-SCT<br>• ECOG PS 0 or 1 |
| **Intervention** | Axi-cel (lymphodepleting chemotherapy then IV axi-cel. Bridging therapy of corticosteroids permitted before chemotherapy for high disease burden) |
| **Comparator** | Standard of care (platinum-based 2nd-line combination chemotherapy followed by high dose therapy and autologous stem cell transplant) |
| **Primary outcome** | Event free survival |
| **Secondary outcomes** | ORR, OS, PFS, DoR |
| **Locations** | US, Canada, Israel, Austria, Belgium, France, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, United Kingdom, and Australia |
| **Used in model?** | Yes |

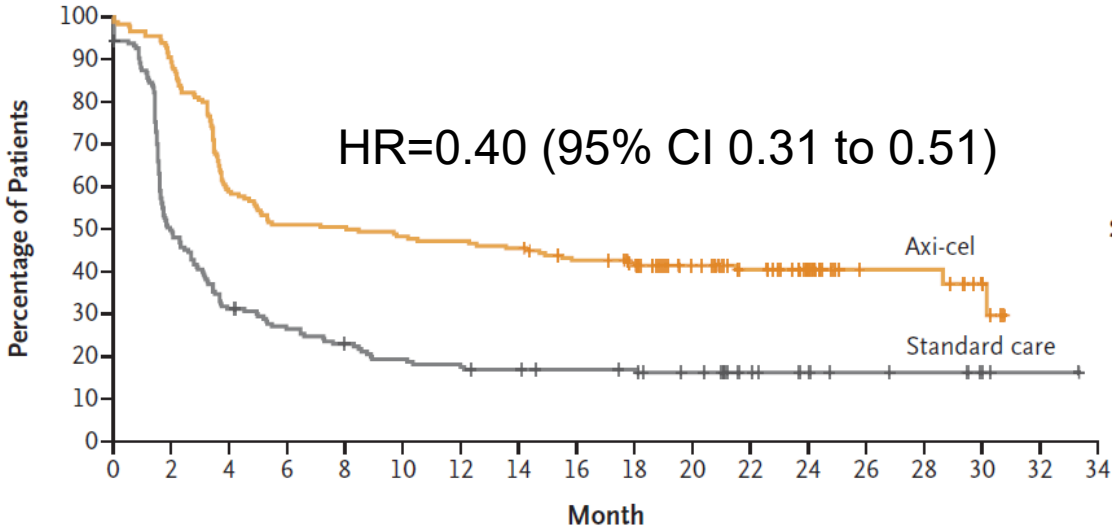


Abbreviations: auto-SCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; DLBCL, diffuse large B-cell lymphoma; DoR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression free survival

# ZUMA-7 results

## Median EFS and PFS were longer in axi-cel arm than SoC arm

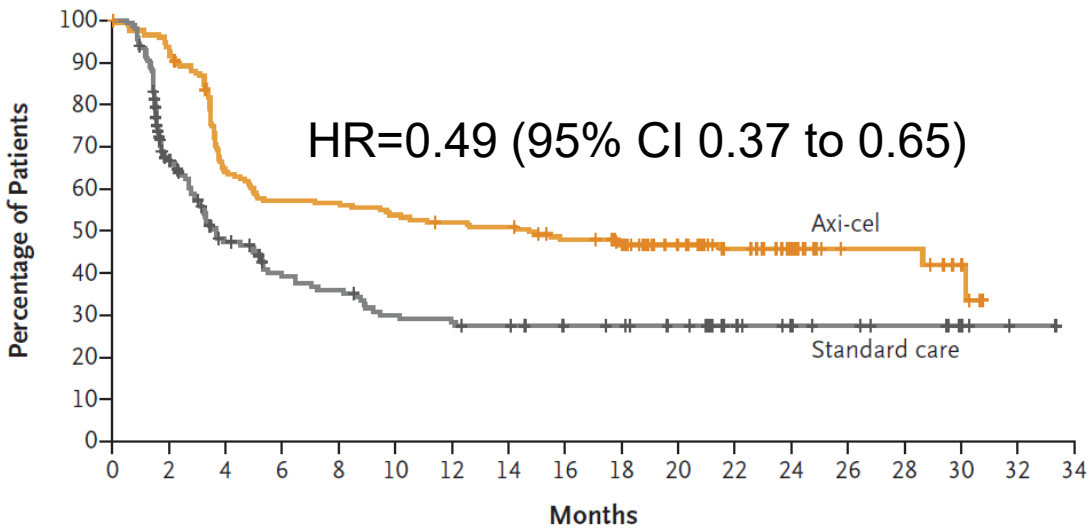
**Figure 2** Event free survival, ZUMA-7 full analysis set




| No. at Risk | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Axi-cel | 180 | 163 | 106 | 92 | 91 | 87 | 85 | 82 | 74 | 67 | 52 | 40 | 26 | 12 | 12 | 6 | | |
| Standard care | 179 | 86 | 54 | 45 | 38 | 32 | 29 | 27 | 25 | 24 | 20 | 12 | 9 | 7 | 6 | 3 | 1 | 0 |

**Event free survival: [central assessment]** time from randomisation to earliest date of disease progression, new lymphoma therapy, death from any cause, or a best response

**Figure 3** Progression free survival, full analysis set




| No. at Risk | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Axi-cel | 180 | 166 | 112 | 100 | 99 | 94 | 90 | 88 | 80 | 73 | 56 | 43 | 28 | 12 | 12 | 6 | | |
| Standard care | 179 | 94 | 61 | 47 | 43 | 35 | 33 | 31 | 28 | 27 | 24 | 15 | 11 | 9 | 7 | 4 | 1 | 0 |

**Progression free survival: [investigator assessment]** time from randomisation to disease progression or death from any cause

Figures are pre-FDA update: 4 people initially censored were confirmed to have died during study. Figures include those participants as censored.

**NICE**

Abbreviations: axi-cel, axicabtagene ciloleucel; CI, confidence interval; EFS, event free survival; HR, hazard ratio; PFS, progression free survival; SoC, standard of care

# ZUMA-7 results

## A larger proportion of people had disease response on axi-cel than SoC

**Table 6** Disease response, full analysis set

| | Axi-cel (N = 180) | SOC (N = 179) |
|---|---|---|
| Objective responders (CR + PR), n (%) [95% CI] | 150 (83%) [redacted] | 90 (50%) [redacted] |
| Difference in ORR (95% CI) | [redacted] | |
| Stratified CMH test p-value | [redacted] | |
| **Best objective response** | | |
| Complete response, n (%) [95% CI] | 117 (65%) [redacted] | 58 (32%) [redacted] |
| Partial response, n (%) [95% CI] | 33 (18%) [redacted] | 32 (18%) [redacted] |
| Stable disease, n (%) [95% CI] | 5 (3%) [redacted] | 33 (18%) [redacted] |
| Progressive disease, n (%) [95% CI] | 21 (12%) [redacted] | 38 (21%) [redacted] |

NICE

Abbreviations: axi-cel, axicabtagene ciloleucel; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CR, complete response; ORR, objective response rate; PR, partial response

# ZUMA-7 results

## SoC overall survival was adjusted to remove 3L CAR T-cell therapy

**Figure 4** Overall survival, unadjusted ZUMA-7 full analysis set

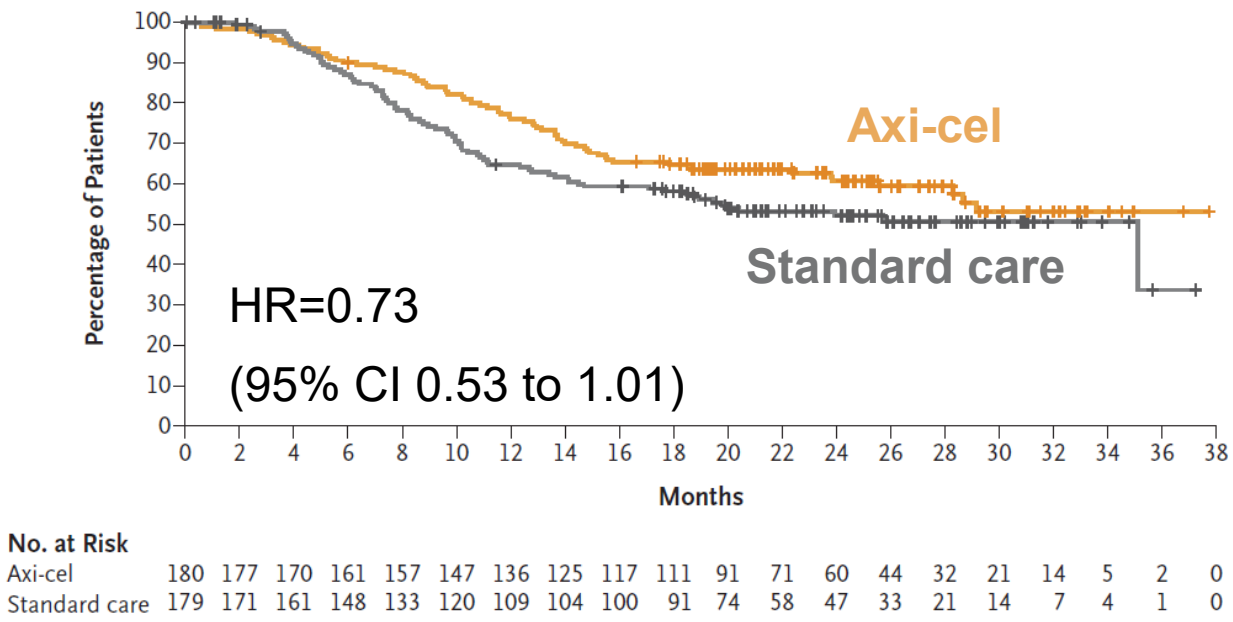
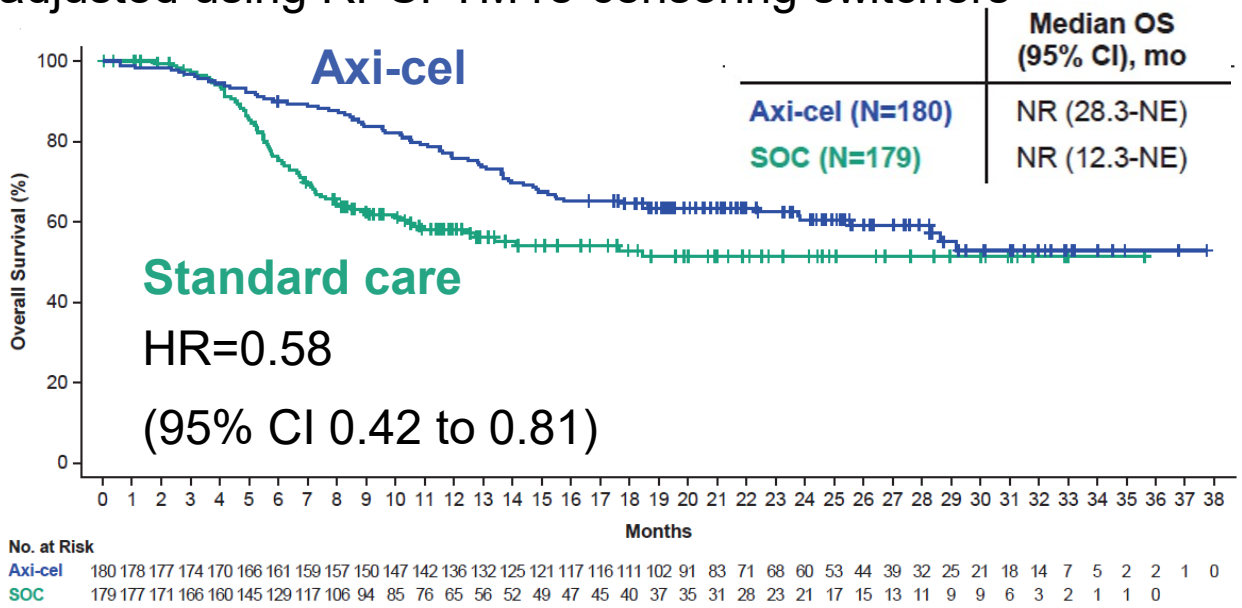



**Figure 5** Overall survival, ZUMA-7 full analysis set adjusted using RPSFTM re-censoring switchers*




*adjustment used in model is RPSFTM with full censoring

Crossover not permitted, but those on SoC could have subsequent cellular immunotherapy outside trial protocol, **56% of SoC had subsequent CAR T-cell therapy.** It is not routinely commissioned in NHS (only available in CDF)

Figures are pre-FDA update: 4 people initially censored were confirmed to have died during study. Figures include those participants as censored.

**NICE**

Abbreviations: axi-cel, axicabtagene ciloleucel; CAR T cell, chimeric antigen receptor T cell; CI, confidence interval; HR, hazard ratio; mo, month; NE, not estimable; OS, overall survival; RPSFTM, rank preserving structural failure time model; SoC, standard of care; 3L, 3rd line

# ZUMA-7 selected adverse events

## Adverse events occurred in both the axi-cel and SoC arms

**Table 7** Selected treatment-emergent adverse events occurring in at least 10% of patients, safety analysis set

| | Axi-cel (N = 170) | | SoC (N = 168) | |
|---|---|---|---|---|
| **Preferred term** | **Any grade** | **Grade ≥ 3** | **Any grade** | **Grade ≥ 3** |
| **Any treatment-related TEAE, n (%)** | [redacted] | [redacted] | [redacted] | [redacted] |
| Neutropenia | [redacted] | [redacted] | [redacted] | [redacted] |
| Decreased platelet count | [redacted] | [redacted] | [redacted] | [redacted] |
| Decreased appetite | [redacted] | [redacted] | [redacted] | [redacted] |
| Sinus tachycardia | [redacted] | [redacted] | [redacted] | [redacted] |
| White blood cell count decreased | [redacted] | [redacted] | [redacted] | [redacted] |
| Febrile neutropenia | [redacted] | [redacted] | [redacted] | [redacted] |
| Tremor | [redacted] | [redacted] | [redacted] | [redacted] |
| Confusional state | [redacted] | [redacted] | [redacted] | [redacted] |
| Encephalopathy | [redacted] | [redacted] | [redacted] | [redacted] |
| Hypogammaglobulinaemia | [redacted] | [redacted] | [redacted] | [redacted] |

**NICE**

Abbreviations: axi-cel, axicabtagene ciloleucel; SoC, standard of care; TEAE, treatment emergent adverse event

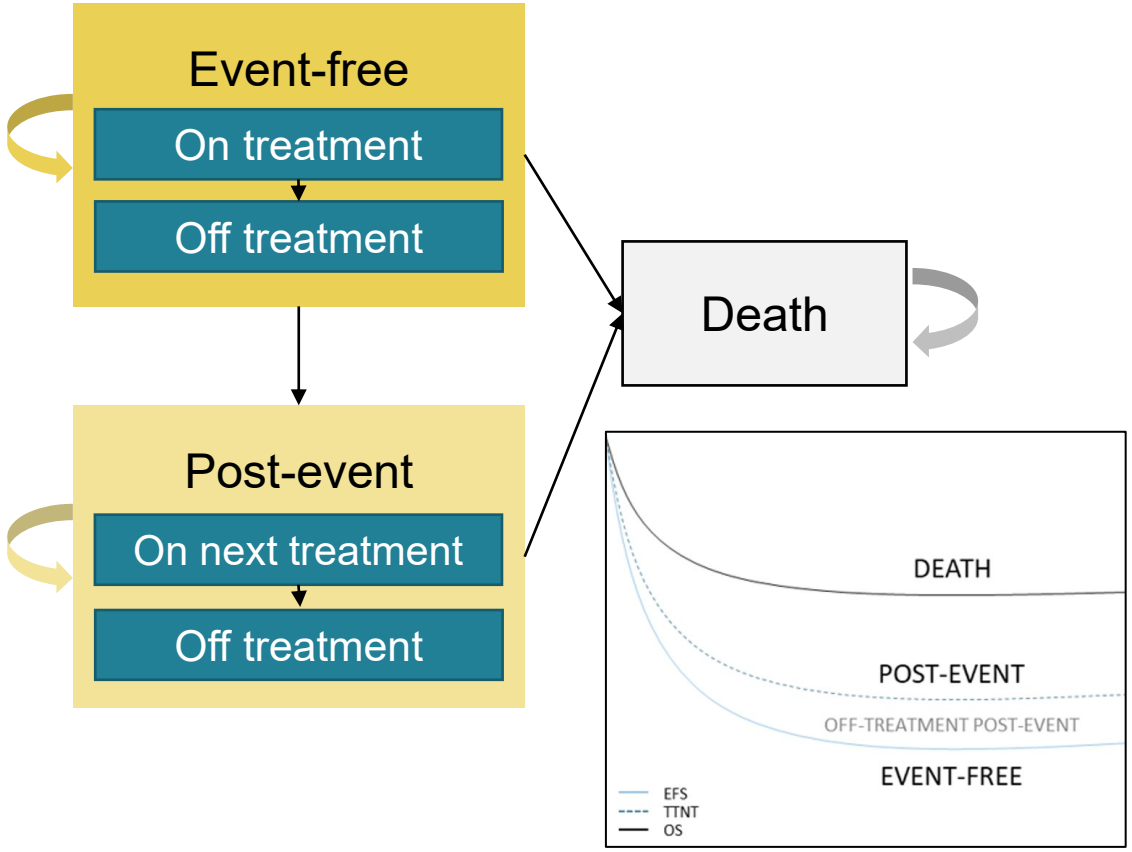
# Cost effectiveness

NICE National Institute for Health and Care Excellence

# Company's model overview

## Partitioned survival model similar to previous CAR T models

**Figure 6** Partitioned survival model structure




Abbreviations: EFS, event-free survival; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year; SoC, standard of care; 3L, 3rd line

Technology affects **costs** by:

- Higher acquisition costs of axi-cel
- Slightly higher costs for axi-cel adverse events
- Small reduction in 3L treatment costs (no axi-cel 3L)

Technology affects **QALYs** by:

- Increasing 'statistically' cured proportion, which increases EFS and higher utility for longer
- Increasing proportion alive in post-event state, accruing more life year gains post-event

Assumptions with greatest **ICER** effect:

- Extrapolation for EFS and OS
- Cross-over adjustment for OS in SoC arm
- Axi-cel re-treatment costs

**EAG comments**

- Model limited at estimating costs and QALYs with subsequent lines of treatment post-event
- On balance satisfied that modelling approach is appropriate

# How company incorporated evidence into model

## ZUMA-7 informed most clinical model inputs

**Table 8** Model inputs and evidence sources

| Input | Assumption and evidence source |
|---|---|
| **Baseline characteristics** | ZUMA-7 |
| **Intervention efficacy** | ZUMA-7 full analysis set (data cut 18 March 2021)<br>• EFS, OS and TTNT for axi-cel use mixture cure model |
| **Comparator** | ZUMA-7 standard of care<br>• platinum-containing salvage chemotherapy, assuming 50% each R-ICE and R-GDP, followed by high dose therapy and autologous stem cell transplant |
| **Comparator efficacy** | ZUMA-7 full analysis set (data cut 18 March 2021). Adjusted using RPSFTM with full re-censoring |
| **Cure timepoint** | 5 years |
| **Utilities** | ZUMA-7 EQ-5D-5L crosswalked to EQ-5D-3L values for pre-event states. Utilities from previous NICE appraisals applied for post-event states |
| **Costs** | NHS Reference Costs, PSSRU, BNF, eMIT and literature |

Abbreviations: axi-cel, axicabtagene ciloleucel; BNF, British National Formulary; EFS, event free survival; eMIT, Drugs and pharmaceutical electronic market information tool; EQ-5D, EuroQol 5 dimensions; OS, overall survival; PFS, progression free survival; R-ICE, rixutimab, ifosfamide, carboplatin etoposide; R-GDP, rituximab, gemcitabine, dexamethasone,e cisplatin; ; RPSFTM, rank preserving structural failure time model; TTNT, time to next treatment

# Key issue: Axi-cel 3rd line and cross-over adjustment

## RPSFTM with full re-censoring is preferred method to remove 3L CAR-T

### Background

- In ZUMA-7, 56% of SoC had 3rd line CAR T-cell therapy
- In England, CAR T-cell therapy is only available 3rd line on the CDF, not routine commissioning

### NICE

Should not consider axi-cel 3rd line because it is only recommended in the CDF so is not established practice

### Company

- Cross-over analysis to adjust SoC overall survival to remove benefits from 3rd line CAR-T therapy
  - RPSFT model with full re-censoring, post-FDA analysis HR = [redacted]
- Explored (in backup): 1. RPSFTM no re-censoring; 2. RPSFTM re-censoring switchers only; 3. IPCW, robust SE, wide intervals; 4. IPCW, robust SE, 2-day intervals

### EAG comments

- RPSFT model with full re-censoring remains the most appropriate cross-over model for SoC
- Uncertainty in SoC survival estimates until 3rd line axi-cel CDF review decision published

**NICE** Is the RPSFTM with full re-censoring the most appropriate cross-over adjustment for overall survival in the SoC arm?



Abbreviations: axi-cel, axicabtagene ciloleucel; CAR T, chimeric antigen receptor T cell; CDF, Cancer Drugs Fund; FDA, Food and Drug Administration; HR, hazard ratio; IPCW, inverse probability of censoring weighting; RPSFTM, rank preserving structural failure time model; SE, standard error; SoC, standard of care; 3L, 3rd line

# Key issue: Axi-cel retreatment

## Benefits, but not costs, of retreatment are included in company model

### Background

- [redacted] patients [redacted] in ZUMA-7 had axi-cel retreatment. Of these, [redacted] had a confirmed response to axi-cel but most were of short duration ([redacted] to [redacted] months), 1 had response of [redacted] months

### Company

- Impact of keeping retreated patients in base case efficacy is expected to be small
- Scenario including retreatment costs increases ICER by about £3,000 compared with base case
- Lack of retreatment in UK, so base case excludes retreatment costs and no effect adjustment

### EAG comments

- Recognise that axi-cel re-treatment is unlikely in UK practice but concerned that including retreatment benefits while excluding costs may bias in favour of axi-cel

### NHS England

- NHS E would not commission retreatment
- Might be some benefit to retreatment, understand EAG's position to align benefits and costs.
- Key issue: magnitude of benefit. Committee should consider this if ICERs exclude retreatment costs

**NICE** Should costs or benefits be adjusted to account for axi-cel retreatment?



Abbreviations: axi-cel, axicabtagene ciloleucel; EAG, external assessment group; ICER, incremental cost-effectiveness ratio

# Key issue: Extrapolation of overall survival for axi-cel

## Company and EAG disagree about appropriate extrapolation

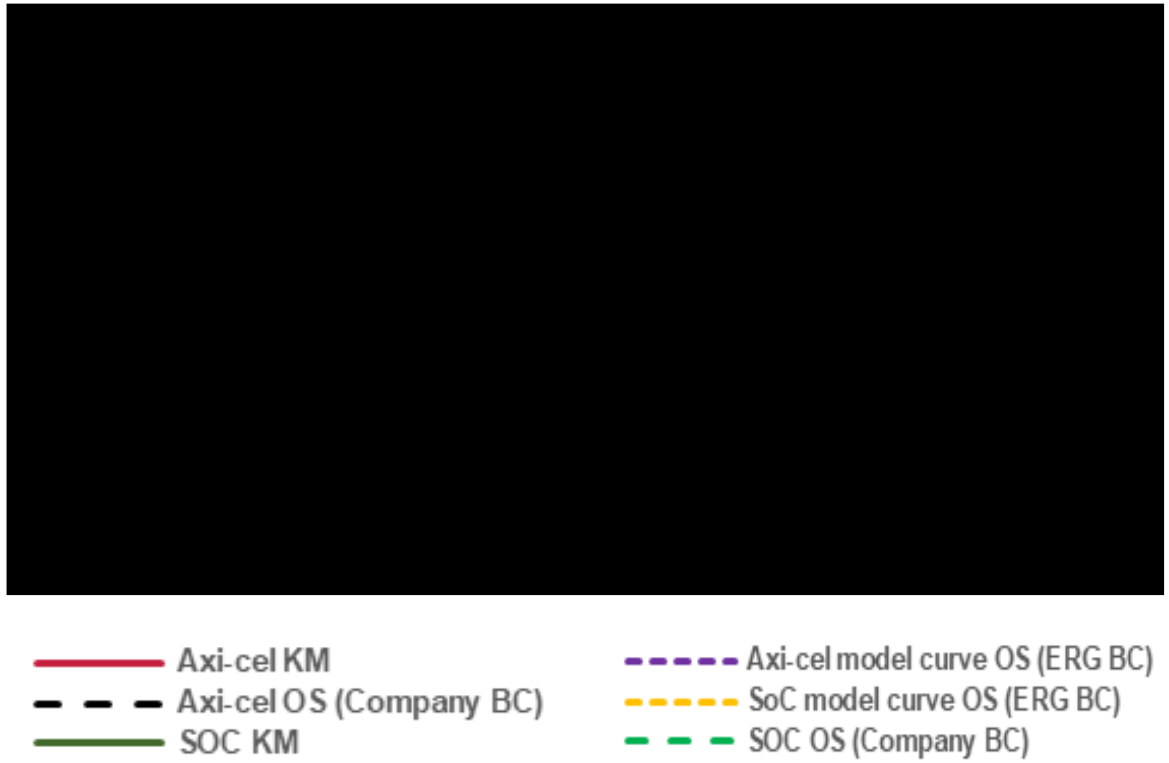
### Company

- Generalised gamma mixture cure model for axi-cel most plausible
- Naive comparison of observed ZUMA-1 (R/R DLBCL patients treated 3L+ with axi-cel) and ZUMA-7 shows about 10% improvement in 2-year OS
  - generalised gamma 5-year OS prediction aligns (ZUMA-1 [redacted]% and ZUMA-7 [redacted]%)
  - EAG estimate not aligned with clinical expectation

### EAG comments

- Appropriate to compare ZUMA-1 and ZUMA-7, but magnitude of difference uncertain
- Both models plausible, but conservative log-logistic more appropriate
- Full comparison, next slide

**Figure 7** Mixture cure models for OS




Abbreviations: axi-cel, axicabtagene ciloleucel; DLBCL, diffuse large B-cell lymphoma; EAG, external assessment group; MCM, mixture cure model; OS, overall survival; R/R relapsed or refractory; SoC, standard of care

# Key issue: Extrapolation of overall survival for axi-cel

**Table 9** Comparison of company and EAG preferred axi-cel overall survival extrapolations

| | Company | EAG preferred | ZUMA-1 (3L + axi-cel) |
|---|---|---|---|
| Mixture cure model used | Generalised gamma | Log-logistic | -- |
| Modelled cure fraction | [redacted] | [redacted] | -- |
| AIC | 702.1 | 700.00 | -- |
| BIC | 714.9 | 709.6 | -- |
| Modelled median OS | [redacted] | [redacted] | NR |
| Mean life years gained (discounted) | [redacted] | [redacted] | -- |
| 2-year OS | [redacted] | [redacted] | 50.5% (2-yr OS rate) |
| 5-year OS | [redacted] | [redacted] | 42.6% (5-yr OS rate) |
| 10-year OS | [redacted] | [redacted] | NR |

Is the generalised gamma or log-logistic extrapolation more appropriate?

Abbreviations: AIC, Akaike information criterion; axi-cel, axicabtagene ciloleucel; BIC, Bayesian information criterion; MCM, mixture cure model; NR, not reached; OS, overall survival; 3L, 3rd line

# Key issue: End of life criteria

## Life extension likely met, short life expectancy more uncertain

**Company**

- Primary refractory or early relapse DLBCL intended for transplant has poor prognosis and survival not expected beyond 2 years
- 2-year survival rate is more appropriate than mean/median survival estimates because a small proportion of people may survive for a long time → precedent of using median from TA567, tisagenlecleucel

**Table 10** Comparison of survival estimates

| | | Company (years) | | EAG (years) | |
|---|---|---|---|---|---|
| Population | 2-year survival rate | Median OS | Mean LYs* | Median OS | Mean LYs* |
| Axi-cel | 61% (ZUMA-7) | [redacted] | [redacted] | [redacted] | [redacted] |
| SoC RPSFTM full re-censoring | [redacted]% | [redacted] | [redacted] | [redacted] | [redacted] |
| SoC no adjustment (includes 3L CAR-T) | 52% (ZUMA-7) | [redacted] | [redacted] | [redacted] | [redacted] |

**EAG comments**

- Life-extending criterion met but short life expectancy more uncertain, especially whether the median or the mean is more appropriate

*Discounted
†Post FDA analysis (4 people censored confirmed to have died during study)

Is axi-cel a life extending treatment at the end of life?



Abbreviations: auto-SCT, autologous stem cell transplant; DLBCL, diffuse large B-cell lymphoma; EAG, external assessment group; FDA, Food and Drug Administration; OS, overall survival; yrs, years; 3L, 3rd line

# Key issue: CAR-T tariff (1/5)

NHSE concerned modelled costs did not reflect practice, provided tariff

## Background

- There are administration, monitoring and adverse events treatment costs for CAR T-cell therapy
- **Company** included administration costs: [redacted]
- **NHSE** advised committee during ID1685 meeting about CAR-T tariff: **£96,016**

## NHS England

- Provided a revised tariff: **£65,415**
  - Based on review of 6 trusts but not micro-costing
  - Adjustments from original:
    - remove overheads
    - length of stay and acuity of care
    - proportion who receive care in ambulatory setting and outside hospital (first 28 days)

**Table 11** Summary of revised NHS England CAR-T tariff

| Resource category | Value (GBP, 2022) | Proportion |
|---|---|---|
| Identification and work-up | £6,514 | 9.96% |
| Leukapheresis | £2,459 | 3.76% |
| Pre-conditioning | £6,935 | 10.6% |
| Inpatient admission up to day 28 | £19,499 | 29.81% |
| Early follow up close to treatment centre up to day 28 | £11,588 | 17.71% |
| Adverse events up to day 28 | £13,070 | 19.98% |
| Follow up post discharge to day 100 | £5,351 | 8.18% |
| **Total** | **£65,415** | **100%** |

Abbreviations: CAR-T, chimeric antigen receptor T; GBP, British pound sterling

# Key issue: CAR-T tariff (2/5)

## Company is concerned about tariff methods and disagrees with using it

### Company

- **Concerned about using NHS tariff in appraisal – it is procedurally unfair and unreasonable**
  - Tariff is a mechanism for NHSE to fund hospitals for CAR-T treatment, not designed for appraisals
  - Initial tariff based on SmPCs, trials, and negotiations to estimate costs [FOIA response]
  - Info from NHSE suggests tariff developed by building on requirements for allogenic transplant, not autologous (which is closer to CAR-T)
- **Tariff may not reflect true cost of treatment**
  - Revised tariff based on original tariff, which included negotiations of unknown factors
  - Original tariff was from 2019, but patient care has improved and may not be captured
  - Unclear why tariff is significantly different from auto-SCT '19/20 HRG £17,181, similar complexity
  - Unclear why Patient Level Information and Costing System (PLICS) not used
  - Unclear how costs applied to CAR-T differ to those used in auto-SCT for leukapheresis
  - Unclear how standard versus complex patient pathways are captured
  - Unexplained wide variation in costs estimates by Trusts
- **Evidence underlying tariff has not been transparently shared**
  - Unclear why there was a 33% reduction to in-patient costs and 171% increase in hotels
  - Variation only captured in simple average, which may not be appropriate
  - Unclear how 30% reduction in overheads was derived



Abbreviations: CAR-T, chimeric antigen receptor T; FOIA, Freedom of Information Act; SmPC, summary of product characteristics

# Key issue: CAR-T tariff (3/5)

## Company is concerned that tariff includes irrelevant costs

### Company

- **Costs in tariff may not be relevant**
  - £6,514 ‘identification and work up’ is unclear. If it reflects second biopsy, it should be excluded because that isn’t required by clinical practice
  - Therapists and counsellors not routinely considered in costing for other treatments. Very unlikely to be a marginal additional cost of CAR-T
  - Unclear how patient drop-out from each stage can be considered
  - £21,573 ‘nursing and medical staff cost’ during treatment is substantial. High levels of care are often not required for people having CAR-T, panel data suggests 27.8% of all CAR-T patients are admitted to ITU
  - £9,586 for clinical supplies and pathology costs is unclear
  - £5,351 cost for Day 28 to Day 100 is significant and unclear. Patient expert in ID1494 stated they had minimal hospital care after discharge



Abbreviations: CAR-T, chimeric antigen receptor T; FOIA, Freedom of Information Act; ITU, Intensive Therapy Unit; SmPC, summary of product characteristics

# Key issue: CAR-T tariff (4/5)

EAG is concerned with tariff, but thinks company may underestimate costs

**EAG comments**

- **Company likely under-estimated costs**
  - Tariff includes higher staffing ratios than company
  - Tariff includes hotel costs, which company does not
- **Concerns about methods of deriving CAR-T tariff**
  - Unclear how trusts estimated expenditure
  - Unclear how expenditure equates to quantities of resource use
  - Revised tariff appears inconsistent with original
  - Unclear if estimates are based on data and experience or are projections
  - Unclear how economies of scale are accounted for
  - Unclear why overheads were removed
- **Considerations for implementation in appraisal**
  - Need to avoid double counting by assessing what is and isn't included

**Table 12** EAG assumptions about CAR-T tariff

| Resource | Included? |
|---|---|
| Leukapheresis | Yes |
| Conditioning chemo (admin) | No |
| Conditioning chemo (drug) | No |
| Bridging chemo (admin) | Yes |
| Bridging chemo (drug) | Yes |
| Axi-cel infusion costs + hospital stay | Yes |
| Hotel costs | Yes |
| AEs (CRS and B-cell aplasia) | No |
| AEs (other) | Yes |
| Hospital health state costs over first 100 days | Yes |
| Subsequent treatment costs over first 100 days | No |

Abbreviations: AE, adverse event; axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T; CRS, cytokine release syndrome; EAG, external assessment group; SoC, standard of care

# Key issue: CAR-T tariff (5/5)

What are the most appropriate costs for axi-cel administration in the NHS?

## EAG explored other scenarios to estimate axi-cel treatment costs

### Background

- Company cost per day of £468.12 from excess bed day cost from malignant lymphoma HRG codes. Elective inpatient reference cost for same codes is £7,528.93, so company derived average LOS of 16.1 days by dividing 1 by the other.
- Mean LOS for axi-cel is [redacted], so company added 2.5 additional days to reference cost. Total admission cost: £[redacted]. Company did not include hotel costs in first 28 days.

**Scenario 1 -** Cost per day from average LOS for DLBCL

- HES data show average LOS of 10.4 days, not 16.1 days.
- Cost per day = £723.94 and axi-cel costs = £[redacted]

**Scenario 2 -** Cost per day based on resource use similar to auto-SCT ward

- Cost per day = £825.17
- Axi-cel costs = £[redacted]

**Scenario 3 -** Resource use increased by factor of 3

- Haematology ward nurse-to-patient ratio 1:6. CAR-T patients may need similar to critical care, 1:2 (x3)
- Cost per day = £2,171.82
- Axi-cel costs =£[redacted]

**EAG scenario 1 + hotel costs**

for [redacted] days (28-[redacted]) for 50%

- Axi-cel costs =: £[redacted]

**EAG scenario 2 + hotel costs**

for [redacted] days for 50% patients

- Axi-cel costs = £[redacted]

**EAG scenario 3 + hotel costs**

for [redacted] days for 50% patients

- Axi-cel costs = £[redacted]



Abbreviations: axi-cel, axicabtagene ciloleucel; CAR-T, chimeric antigen receptor T; DLBCL, diffuse large B-cell lymphoma; EAG, external assessment group; HRG, Healthcare Resource Group; LOS, length of stay

# Other areas of uncertainty

**Table 13** Areas of uncertainty that are not key issues

| Uncertainty | Company | EAG |
|---|---|---|
| **Auto-SCT costs** | • Prefer NG52 costs inflated to **£37,735**<br>• TA567 included follow-up costs: £28,398<br>• Wang 2016 HMRN: £42,000 | • NG52 is not transparent, unable to verify costs<br>• Prefer 19/20 NHS reference costs<br>  • Inflated cost: **£17,181.37** |
| **Event free survival extrapolation** | • All mixture cure models had similar predictions, and base case are axi-cel: log-logistic and SoC: exponential | • Company approach is reasonable<br>• Long term extrapolation is still uncertain |
| **Utility values pre-progression** (EQ-5D not routinely collected post-event in ZUMA-7) | • JULIET: single arm study of tisagenlecleucel for DLBCL<br>  • SF-36 values mapped to EQ-5D, in TA567 | • ZUMA-1: single arm study of axi-cel for refractory LBCL<br>  • pre-progression 5L values crosswalked to 3L, in TA559 |
| **Salvage chemo in SoC arm** | • 100% | • [redacted]% from ZUMA-7 |
| **Distribution of post-event treatments** | • Clinical opinion to reflect NHS practice | • ZUMA-7 to align modelled treatment costs and benefits |



Abbreviations: allo-SCT, allogenic stem cell transplant; auto-SCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; DLBCL, diffuse large B-cell lymphoma; EAG, external assessment group; HMRN, Haematological Malignancy Research Network; SoC, standard of care

# Other areas of uncertainty

**Table 14** Areas of uncertainty that are not key issues

| Uncertainty | Clinical experts |
|---|---|
| **ZUMA-7 trial design – chemotherapy bridging** | • Chemotherapy bridging was not permitted in ZUMA-7 but occurs in the NHS<br>• The lack of option to bridge may have meant investigators did not recruit people with rapidly progressive disease if there were concerns they would not survive between cell collection and reinfusion → may bias in favour of axi-cel, magnitude unknown |



Abbreviations: allo-SCT, allogenic stem cell transplant; auto-SCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; DLBCL, diffuse large B-cell lymphoma; EAG, external assessment group; HMRN, Haematological Malignancy Research Network; SoC, standard of care

# Summary of company and EAG base case inputs

**Table 15** Assumptions and inputs in company and EAG base case

| Assumption/input | Company base case | EAG base case |
|---|---|---|
| Axi-cel mixture cure model OS | Generalised gamma | Log-logistic |
| Axi-cel modelled cure fraction OS | [redacted]% | [redacted]% |
| Cross-over adjustment for standard of care OS | RPSFTM with full re-censoring | RPSFTM with full re-censoring |
| Axi-cel retreatment costs | Excluded | Included |
| Auto-SCT costs | £37,735.95 (inflated from NG52) | £17,181.37 (inflated from 2019/2020 HRG tariff elective SA26A) |
| Distribution of post-event treatments | Clinical expert opinion | ZUMA-7 |
| Utility values source | JULIET | ZUMA-1 (pre-progression) |
| Salvage chemotherapy in SoC | 100% | [redacted]% (ZUMA-7) |

Abbreviations: auto-sct, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; EAG, external assessment group; NG, NICE Guideline; HRG, healthcare resource group; RPSFTM, rank preserving structural failure time model

# Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator discounts

- All analyses, including company base case >£50,000 per QALY gained

Scenarios to be presented include:

- Company and EAG base cases
- Scenarios for all differences between company and EAG base cases
- Original and revised CAR-T tariffs
- Scenarios exploring different resource use assumptions

# Other considerations

## Equality considerations

- Age inequality: 2nd line auto-SCT has ‘cut-off’ age between 65 and 70 years. No age restriction would apply to axi-cel so it could reduce age inequality
- Geographic inequality: challenges for people to travel to CAR-T centres. Will become less significant with more centres

## Innovation

- Clinical experts consider CAR-T therapy to be innovative
- Company noted potential benefits not fully captured in QALY calculation:
    - True benefit of cure is likely underestimated
    - Benefits associated with a single-infusion medicine compared with multiple cycles of immunochemotherapy followed by HDT and auto-SCT



Abbreviations: auto-SCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; HDT, high-dose therapy

# Managed access – including Cancer Drugs Fund

## Criteria for a managed access recommendation

**The committee can make a recommendation with managed access if:**

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

# Cancer Drugs Fund

## ZUMA-7 is ongoing and may resolve some uncertainties

**Table 16** Areas of uncertainty and how they can be addressed

| Uncertainty | How uncertainty can be addressed |
|---|---|
| Axi-cel and SoC overall survival | ZUMA-7 longer term follow-up |
| Axi-cel and SoC event free survival | ZUMA-7 longer term follow-up |
| Cross-over adjustment for SoC overall survival | • Certainty about whether axi-cel will be routinely commissioned 3rd line (ID3890 CDF review)<br>• Model would need to capture 3rd line use, which might be different than trial |
| Axi-cel retreatment costs | Unlikely to be resolved with data collection |
| Auto-SCT costs | Unlikely to be resolved with data collection |
| Distribution of post-event treatments | Unlikely to be resolved with data collection |
| Utility values | Unlikely to be resolved as not routinely collected post-event in ZUMA-7 |
| Salvage chemotherapy use | May be resolved with SACT data collection |

Is axi-cel a candidate for the Cancer Drugs Fund?

NICE

Abbreviations: auto-SCT, autologous stem cell transplant; axi-cel, axicabtagene ciloleucel; CDF, Cancer Drugs Fund; SACT, Systemic Anti-Cancer Therapy dataset; SoC, standard of care

NICE National Institute for Health and Care Excellence

# Thank you.

# Key issue: Cross over adjustment for SoC survival

**Figure** Overall survival adjusted using RPSFTM full re-censoring, **company/EAG base case**

**Figure** Overall survival adjusted using RPSFTM no re-censoring

**Figure** Overall survival adjusted using RPSFTM re-censoring switchers

**Figure** Overall survival adjusted using IPCW, robust SE, wide intervals

**NICE**

**Figure** Overall survival adjusted using IPCW, robust SE, 2-day intervals