NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Lisocabtagene maraleucel for treating relapsed or refractory large B-cell lymphoma after first-line chemoimmunotherapy when a stem cell transplant is suitable

1 Recommendations

1.1 Lisocabtagene maraleucel (liso-cel) is recommended as an option for treating large B-cell lymphoma that is refractory to, or has relapsed within 12 months after, first-line chemoimmunotherapy in adults with:

- diffuse large B-cell lymphoma
- high-grade B-cell lymphoma
- primary mediastinal large B-cell lymphoma, or
- follicular lymphoma grade 3B.

Liso-cel is recommended only if:

- an autologous stem cell transplant would be considered suitable, and
- the company provides it according to the commercial arrangement (see section 2).

1.2 Healthcare professionals should not use a person's age as a proxy measure for fitness when determining whether an autologous stem cell transplant would be suitable.

1.3 This recommendation is not intended to affect treatment with liso-cel that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without

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change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

Why the committee made these recommendations

For this evaluation, the company asked for liso-cel to be considered only for people who can have an autologous stem cell transplant. This does not include everyone who it is licensed for. People can have a stem cell transplant if their healthcare professional thinks they are fit enough to have it.

Standard care for relapsed or refractory large B-cell lymphoma after first-line chemoimmunotherapy when a stem cell transplant is suitable is salvage chemotherapy, high-dose chemotherapy and stem cell transplantation.

Clinical trial evidence shows that liso-cel increases how long people have before they need another line of treatment, or their condition gets worse, compared with standard care. Evidence for how long people live after treatment with liso-cel is uncertain.

There are uncertainties in the assumptions used in the economic model. But there are also some benefits of liso-cel that are not captured in the modelling. These include the potential for people to have liso-cel as an outpatient treatment. The cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, liso-cel is recommended.

Because age is a protected characteristic under the Equality Act 2010, it should not be used as a measure of fitness when deciding whether an autologous stem cell transplant is suitable.

2 Information about lisocabtagene maraleucel

Marketing authorisation indication

2.1 Lisocabtagene maraleucel (liso-cel; Breyanzi, Bristol-Myers Squibb) is indicated for ‘the treatment of adult patients with diffuse large B-cell

lymphoma (DLBCL), high grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) and follicular lymphoma grade 3B (FL3B), who relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for liso-cel.

Price

2.3 The list price for a single infusion, including shipping, engineering and generation of CAR-T cells is £297,000 (company submission, May 2024).

2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes liso-cel available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence submitted by Bristol-Myers Squibb, a review of this submission by the external assessment group (EAG) and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition

3.1 Large B-cell lymphoma is an aggressive type of non-Hodgkin lymphoma. There are different subtypes of large B-cell lymphoma, including those considered within this evaluation:

- diffuse large B-cell lymphoma (DLBCL)
- high-grade B-cell lymphoma (HGBCL)
- primary mediastinal B-cell lymphoma (PMBCL)

- follicular lymphoma grade 3B (FL3B).

DLBCL is the most common type. The disease characteristics and treatment pathways of each of these subtypes are considered similar at second line. People with large B-cell lymphoma can have swollen lymph nodes, night sweats, fever, weight loss and itching. The patient expert explained that large B-cell lymphoma has a large impact on daily life. Also, people may need the support of a carer because of physical weakness and fatigue. They also described the significant mental health challenges that people may have from:

- worry about the effects of the condition
- the impact it has on friends and family
- worry about not being able to tolerate the substantial side effects of current treatment options.

The committee recognised that relapsed or refractory large B-cell lymphoma after first-line chemoimmunotherapy has a large disease burden.

Clinical management

Treatment options

3.2 DLBCL, PMBCL, HGBCL and FL3B are generally managed using the same clinical pathway in NHS clinical practice. But some treatments are only reimbursed for specific large B-cell lymphoma types. People with untreated large B-cell lymphoma may be offered rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP). In 2023, NICE recommended polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin and prednisolone (R-CHP) for untreated DLBCL. For large B-cell lymphoma that is relapsed or refractory to initial treatment, clinicians may offer salvage chemotherapy. If the condition responds after salvage chemotherapy, people may be offered high-dose

chemotherapy and, for those able to have it, a stem cell transplant. Transplant suitability is based on the person's tolerance of intensive treatment and is usually only offered to people under 70 years. The clinical experts said that high-dose chemotherapy is associated with high toxicity and can cause substantial side effects for the people who have it. The patient expert also explained that some people are unable to tolerate the side effects of intensive chemotherapy. The clinical experts noted that people with large B-cell lymphoma that relapses within 12 months or is refractory to initial treatment and who can have an autologous stem cell transplant may be offered axicabtagene ciloleucel (axi-cel; see NICE's technology appraisal guidance on axi-cel for treating relapsed or refractory diffuse large B-cell lymphoma after first-line chemoimmunotherapy, from now TA895). But axi-cel is only available for use at second line through the Cancer Drugs Fund, so this does not represent routine clinical practice. The committee concluded that people with relapsed or refractory large B-cell lymphoma and clinicians would welcome a new treatment option.

Proposed positioning

3.3 The company proposed lisocabtagene maraleucel (liso-cel) for a narrower population than its marketing authorisation. It focused on DLBCL, PMBCL, HGBCL and FL3B that were refractory to, or had relapsed within 12 months of, first-line chemoimmunotherapy in adults who could have an autologous stem cell transplant. This was to align with the key clinical trial, TRANSFORM (see section 3.5). The committee would have preferred to evaluate liso-cel for the whole population in the marketing authorisation. But it concluded that it could only evaluate liso-cel for people who can have an autologous stem cell transplant, because that was the evidence presented by the company.

Comparator

3.4 The committee recalled that relapsed or refractory large B-cell lymphoma after first-line chemoimmunotherapy is usually treated with salvage chemotherapy, high-dose chemotherapy and an autologous stem cell transplant (from now, called standard care). The clinical expert submission said that axi-cel was expected to be the main alternative for liso-cel in clinical practice. Both liso-cel and axi-cel are chimeric antigen receptor (CAR) T-cell therapies (also called CAR-T therapies). The clinical experts at the committee meeting also noted that the key difference between liso-cel and axi-cel was the safety profile. There are expected to be substantially lower grade 3 and 4 adverse events for people having treatment with liso-cel. They said that this would be important for the quality of life of people having treatment. They also expected that it will reduce resource use, including length of hospital stay and intensive care use. The committee recalled that axi-cel had not been recommended for routine commissioning at second line, so was not an appropriate comparator in this evaluation. The committee concluded that standard care was the relevant comparator.

Clinical effectiveness

TRANSFORM trial

3.5 The clinical-effectiveness evidence for liso-cel compared with standard care came from TRANSFORM. This was a phase 3 randomised open-label trial. It included adults with primary refractory or early relapsed (within 12 months of first-line treatment) DLBCL, HGBCL, PMBCL, T-cell histiocyte rich B-cell lymphoma (THRBCL) or FL3B eligible for a stem cell transplant. Standard care consisted of 3 cycles of re-induction therapy followed by high-dose chemotherapy and an autologous stem cell transplantation if the condition responded. People in the standard-care arm could cross over to have liso-cel if their condition:

- did not completely or partially respond by 9 weeks after randomisation
- progressed at any time, or

- needed to start a new antineoplastic therapy because of efficacy concerns (absence of complete response) 18 weeks after randomisation.

The primary end point was event-free survival (EFS) defined as:

- the time from randomisation to progressive disease
- failure to have a complete response or partial response by 9 weeks after randomisation, or
- start of a new antineoplastic therapy because of efficacy concerns or death from any cause, whichever happens first.

At the final data cut-off in October 2023, there was a statistically significant benefit for liso-cel compared with standard care for EFS (hazard ratio [HR] 0.38, 95% confidence interval [CI] 0.26 to 0.54). The difference in overall survival (OS) was not statistically significant (HR 0.76, 95% CI 0.48 to 1.19). But the result was confounded by the high proportion (66.3%) of people in the standard-care arm who crossed over to have liso-cel as a subsequent treatment. Median OS could not be estimated for liso-cel or standard care at the final data cut-off. The committee concluded that the results of the trial showed a statistically significant EFS benefit for liso-cel compared with standard care.

Generalisability

3.6 The company noted that TRANSFORM was done specifically in the population of interest (see section 3.3). It allowed people to cross over from the standard-care arm to have subsequent liso-cel, and chemotherapy-based bridging therapy regimens were used. This was in contrast with the ZUMA-7 trial used to inform TA895. ZUMA-7 was a phase 3 randomised trial of axi-cel used after chemoimmunotherapy in adults with primary refractory or early relapse DLBCL who were due to

have a stem cell transplant. Crossovers between treatment arms and chemotherapy bridging were not included in ZUMA-7. So, the company considered that the design of TRANSFORM better reflected NHS clinical practice than that of ZUMA-7. The company did acknowledge that TRANSFORM differed from NHS clinical practice in some respects. Firstly, TRANSFORM was done before several treatments for subsequent use in the pathway were available in routine practice. See NICE's technology appraisal guidance on:

- glofitamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments
- loncastuximab tesirine for treating relapsed or refractory diffuse large B-cell lymphoma and high-grade B-cell lymphoma after 2 or more systemic treatments
- epcoritamab for treating relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments.

This meant that few people in TRANSFORM had these subsequent treatments; most had subsequent chemotherapy. So, the company thought that OS in the liso-cel arm was potentially underestimated relative to NHS clinical practice because these subsequent treatments are more effective than chemotherapy. Secondly, people in TRANSFORM had leukapheresis before being randomised to either liso-cel or standard care. Also, liso-cel manufacturing was done for people in both arms to enable rapid liso-cel infusion after crossover (see section 3.5). The clinical experts explained that, in NHS clinical practice, people cannot have apheresis at second line in anticipation of needing a subsequent CAR-T therapy. So, there is a greater delay between progression on standard care at second line and the subsequent CAR-T therapy in NHS clinical practice compared with in TRANSFORM. The clinical experts said that the design of TRANSFORM to allow people to cross over to liso-cel quickly was

beneficial for the people in the trial. It also favoured the standard-care arm. The company also noted that, by having apheresis before randomisation in TRANSFORM, people may have had improved T-cell fitness compared with people who have apheresis after progression on standard care in clinical practice. So, the company thought that OS in the standard-care arm was overestimated relative to NHS clinical practice. The clinical experts estimated that outcomes may improve by about 10% for people who have had apheresis before needing subsequent CAR-T therapy compared with having apheresis at third line, as in clinical practice. In addition to the generalisability issues noted by the company, the EAG was also concerned that:

- drop out between leukapheresis and infusion in the liso-cel arm of TRANSFORM was lower than expected in clinical practice
- the proportion of people having bridging therapy in TRANSFORM was lower than in NHS practice
- more people were expected to have had polatuzumab vedotin with R-CHP at first line in clinical practice than did in TRANSFORM.

The clinical experts noted that drop out between leukapheresis and infusion had improved in clinical practice over the last 5 years. But they were still concerned that some people will not live long enough between T-cell collection and reinfusion. They also commented that the availability of polatuzumab vedotin with R-CHP was expected to reduce the population size at second line because of its higher efficacy than R-CHOP. But they did not expect any biological differences or impact on efficacy at second line for people who had had polatuzumab vedotin with R-CHP compared with R-CHOP. The committee acknowledged the issues of generalisability to NHS practice, and that this increased uncertainty in the clinical- and cost-effectiveness results. But it concluded that TRANSFORM provided the best available evidence for liso-cel compared with standard care.

Economic model

Model structure

3.7 The company provided a partitioned survival model to estimate the cost effectiveness of liso-cel compared with standard care. The model had 3 health states: event-free, post-event and death. The company justified using EFS to inform the model health states because it was:

- the primary end point in TRANSFORM
- consistent with the model health states used in the economic model to support TA895.

The clinical experts at the committee meeting agreed that EFS was a relevant outcome. They explained that it was standard practice to collect it in clinical trials (such as ZUMA-7) for relapsed or refractory large B-cell lymphoma after first-line chemoimmunotherapy. The EAG was concerned that progression from the event-free state to a post-event health state did not reflect an objective change in health status. It said that the modelled cohort with large B-cell lymphoma that is cured at subsequent treatment lines would not be assigned the health benefits associated with cure. This was because they would remain in the same post-event health state. It also noted that the post-event health state included people who were cured (for example, after subsequent CAR-T therapy) and not cured, so was not a homogenous population. The EAG acknowledged that an economic model based on EFS had been accepted by the committee as part of the axi-cel evaluation. But it said that suitable alternatives may not have been available for consideration then. So, the EAG preferred to use progression-free survival on subsequent treatment (PFS2) to partition the model health states instead of EFS. The company noted that the model based on PFS2 was limited because of discrepancies in follow up between death and disease progression. It explained that, after 36 months, people in TRANSFORM were only followed up for OS. So,

it thought that the PFS2 endpoint could have been underestimated because people were censored from this dataset but known to be alive after the 36-month timepoint. The company was also concerned that the PFS2 model structure assumed that there is no health-related quality of life detriment for people who move from second line to subsequent treatment for any reason. The committee noted the EAG's concerns. But it thought that the pre-PFS2 health state in the EAG's preferred model structure included people having second and third lines of treatment, so was also not homogenous. The committee concluded that the company's model with health states based on EFS was appropriate for decision making.

OS for liso-cel

3.8 The company said that plateaus were seen in the OS data from TRANSFORM, suggesting that some people had long-term remission and survival. So, it fitted mixture cure models to each treatment arm to model the long-term OS outcomes. The company used the log-normal curve in its base-case analysis for liso-cel OS because it had:

- the best statistical fit
- a good visual fit to the observed data
- a cure fraction (60.8%) that aligned with the estimate of one of its clinical experts.

The EAG thought that the TRANSFORM OS data was less mature than the EFS and PFS2 data. This meant that it was less likely that the true cure fraction was estimated accurately. It also noted that the OS follow up from TRANSFORM was less mature and had a smaller sample size than ZUMA-7. So, it thought that ZUMA-7 was a more reliable source than TRANSFORM for estimating the long-term efficacy of liso-cel, despite being for a different treatment. The EAG thought that the company's preferred log-normal curve for liso-cel OS was too

optimistic. This was because the cure fraction was higher than estimated by models fitted to PFS2 data, and because it did not expect cure to happen after the PFS2 outcome. The EAG also noted that the company's predicted long-term survival outcomes for liso-cel were higher than the long-term survival accepted for axi-cel in TA895. The EAG preferred to use SurvInt to model liso-cel OS. SurvInt is a freely available R Shiny tool that uses user-specified population survival at key time points to produce parametric extrapolations. Its inputs into SurvInt included:

- a survival estimate at 11.05 months from TRANSFORM
- a survival input at 4 years from ZUMA-7
- a cure fraction of 50%, chosen for consistency with the cure fractions estimated from the TRANSFORM PFS2 data, and extrapolations from ZUMA-7
- a log-logistic model.

The company said that the EAG's use of ZUMA-7 data to inform the efficacy of liso-cel was not appropriate. It thought that the study design of TRANSFORM better reflected NHS clinical practice (see section 3.6). It noted that differences in the survival outcomes between TRANSFORM and ZUMA-7 could be explained by differences in the trial designs. It also noted that both trials were expected to underestimate long-term OS because of the recent availability of novel subsequent treatments in clinical practice (see section 3.6). The company commented that liso-cel and axi-cel are different treatments with different manufacturing processes, and that TRANSFORM provided relevant data for liso-cel in the population of interest. The company also recalled the issue of censoring in the PFS2 data from TRANSFORM (see section 3.7). It said that this likely influenced the difference in cure rates between the OS and PFS2 models. The company was also concerned with the use of SurvInt to extrapolate

survival in its preferred analyses. It said that the SurvInt approach ignored most of the observed trial data for liso-cel, and arbitrarily used 2 survival inputs to inform extrapolations. It also noted that the cure fraction was arbitrarily chosen. But the cure fractions predicted by its mixture cure models were based on the observed data, and produced from an approach aligned to NICE's technical support document on survival analysis for economic evaluations alongside clinical trials and NICE's technical support document on flexible methods for survival analysis. The clinical experts thought that longer-term OS estimates were likely to be similar between liso-cel and axi-cel. They also commented that the OS estimates for liso-cel (based on the company's mixture cure models) at 5, 10 and 15 years were reasonable. The committee commented on the usefulness of the SurvInt tool for exploring the sensitivity of extrapolated outcomes. But it was concerned that the tool did not use most of the observed data for liso-cel, and it was uncertain of the tool's reliability for use in decision making. The committee concluded that the company's mixture cure OS model was acceptable for liso-cel, but there was remaining uncertainty on long-term survival.

OS for standard care

3.9 The company's clinical experts thought that all the survival curves produced using mixture cure models for standard care overestimated long-term survival compared with clinical practice. The company explained that OS estimates for standard care may be higher than expected in NHS clinical practice because of the design of TRANSFORM (see section 3.6). It used the log-normal curve in its base-case analysis because it had the best statistical fit and it estimated the lowest cure fraction (50.7%). It noted that this approach was biased in favour of the standard-care arm because the curve likely overestimated survival for people having standard care. The EAG agreed that survival was likely overestimated by all the company's mixture cure models because of

immaturity of the data. The EAG preferred to use a log-logistic curve from SurvInt to estimate standard-care OS in the absence of a suitable alternative. Its inputs to SurvInt included:

- survival estimates at 6.59 and 17.76 months from TRANSFORM
- a cure fraction of 35%, chosen for consistency with the cure fractions estimated from the TRANSFORM PFS2 data.

The EAG acknowledged that its SurvInt model underestimated the tail of the Kaplan–Meier curve from TRANSFORM. But it thought that this was appropriate given that TRANSFORM was expected to overestimate survival compared with NHS clinical practice (see section 3.6). The company was concerned with the EAG's use of the SurvInt approach (see section 3.8). The committee recalled its concerns with the SurvInt approach and concluded that the company's mixture cure OS model for standard care was the most appropriate.

Time to next treatment

3.10 Time to next treatment was defined as the time from randomisation to death from any cause, or to the start of new antineoplastic therapy, whichever happened first. The company extrapolated data for time to next treatment from TRANSFORM using mixture cure models to inform the modelling of subsequent treatments. It noted that all the extrapolations for the liso-cel arm had similar estimates of long-term survival. This meant that there was low uncertainty associated with the choice of curve for time to next treatment. The EAG was concerned that the company's extrapolations for time to next treatment were more optimistic than the EFS extrapolations, given they had similar definitions. It thought that EFS was the more mature outcome, and that it was likely to give a more reliable long-term extrapolation. It also noted that the extrapolations of time to next treatment from TRANSFORM were more optimistic than the extrapolations from ZUMA-7 in TA895. So, the EAG preferred to use the

EFS extrapolations from TRANSFORM to model time to next treatment. The committee thought that the dataset for time to next treatment provided the best available evidence for the outcome for time to next treatment. So, it preferred to use the company's extrapolations for time to next treatment in the model.

Model starting age

3.11 The company used the mean age of people in TRANSFORM to inform the starting age at model entry. The company considered the mean age to be confidential, so it cannot be reported here. The EAG preferred to align the model starting age with data provided by NHS England. This suggested that the mean age of people who have had second-line axi-cel since it entered the Cancer Drugs Fund is 59 years. The committee noted that the model starting age had a minimal impact on the cost-effectiveness estimate. It concluded that the company's use of the mean age of people in TRANSFORM was acceptable for the model starting age.

Application of discount rate

3.12 The company applied a weekly cycle length for the first 5 years in its economic model, followed by an annual cycle length. It discounted costs and benefits at a rate of 3.5% per annum in its base-case analyses. The EAG disagreed with the annual application of the discount rate during the weekly cycle period and preferred to use a per cycle discount rate for the first 5 years. The committee noted that application of the discount rate in the first 5 years of the model had a minimal impact on the cost-effectiveness estimate. It concluded that the EAG's application of a per cycle discount was acceptable.

Utility values

Event-free utility value

3.13 Health-state utility values in the company's base-case analyses were estimated using EQ-5D data from TRANSFORM. A value of 0.852 was

estimated for the event-free health state. This value was also used to inform the pre-PFS2 health state in the EAG's preferred model structure (see section 3.7). The EAG thought that the utility value of 0.852 was too optimistic. This was because it was higher than the event-free utility value of 0.785 used in TA895 and similar to the general population utility estimate of 0.853. The EAG preferred to use the utility value of 0.785 from the axi-cel evaluation for the event-free and pre-PFS2 health states. The committee noted that there was a low completion rate for EQ-5D data in TRANSFORM, and that data was not collected after treatment switching. The company explained that there had been challenges completing the data during the COVID-19 pandemic. The committee noted the uncertainty in the EQ-5D data from TRANSFORM. But it thought that TRANSFORM provided the most relevant EQ-5D data for liso-cel in the population of interest. The committee also commented that the total incremental quality-adjusted life years (QALYs) were more conservative when using the TRANSFORM data to inform health-state utility values, than when using data from TA895. It concluded that TRANSFORM was the most appropriate source for the event-free health-state utility value.

Costs

Bridging therapy

3.14 The clinical experts explained that bridging therapy is treatment offered to control large B-cell lymphoma and symptoms between T-cell collection and reinfusion. In TRANSFORM, 63% of people had bridging therapy. The company modelled bridging therapy costs (proportion of people having bridging therapy, and the distribution of the bridging therapy regimens) based on TRANSFORM. Clinical experts consulted by the EAG suggested that the proportion of people having bridging therapy and the distributions would differ from those modelled in the company's base case. So, the EAG preferred to use UK-specific data based on a study by Boyle et al. (2023) to estimate the proportion of people having bridging therapy and the distribution of the bridging therapy regimens. The clinical

experts at the committee meeting noted that bridging therapy is commonly used in NHS clinical practice. The NHS England Cancer Drugs Fund clinical lead said that, of the 255 people who had axi-cel at second line, 96% had had bridging therapy. The committee thought that it was important to align modelled costs and benefits. It preferred to use the TRANSFORM data for costing bridging therapy in its decision making, but it noted the generalisability concerns of this to NHS clinical practice.

Subsequent treatment

3.15 Subsequent treatment costs were applied as a one-off cost based on data for time to next treatment from TRANSFORM. The company calculated that the proportion of events for time to next treatment that were the start of a new treatment was 69.6% in the liso-cel arm and 94.2% in the standard-care arm. These percentages were applied to the relevant extrapolation for time to next treatment (see section 3.10) to calculate the total proportion of people who had at least 1 subsequent treatment. The EAG's clinical experts thought that the proportion of events for time to next treatment that were the start of a new treatment was higher than expected in clinical practice for the standard-care arm. They said that a third of people would have palliative care after an unsuccessful stem cell transplant at second line. So, the EAG assumed that 66% of events for time to next treatment were the start of a new treatment for standard care.

The company modelled the distribution of subsequent treatments from TRANSFORM in its base case but noted that they did not fully reflect current NHS clinical practice (see section 3.6). The EAG preferred to use the estimates from the company's clinical experts, which it said were similar to estimates from the EAG's clinical experts. The company said that the EAG's base case substantially underestimated subsequent treatment costs in the standard-care arm. It also noted that the EAG's approach changed the costs to reflect NHS clinical practice but did not also adjust the efficacy. The EAG explained that its preferred efficacy

estimates already deviated from the trial data (see section 3.8 and section 3.9). So, it did not agree that it had not considered an adjustment to the clinical outcomes as well as the costs of subsequent treatment.

The company noted that it had presented a scenario analysis that used estimates from UK clinical experts to inform the distribution of subsequent treatments. In this scenario analysis, a more optimistic Weibull curve was used for liso-cel OS to model the increase in survival expected from having more effective subsequent treatments in clinical practice. At the same time, a weighted average OS curve for standard care was applied to lower survival to a range expected in NHS clinical practice. The EAG noted that the weighted OS curve partly used data from CORAL. This was unlikely to have included subsequent treatment with bispecific antibodies, so it was also not reflective of current clinical practice. The clinical experts and NHS England Cancer Drugs Fund clinical lead explained that the treatment pathway for large B-cell lymphoma is rapidly changing. The clinical experts commented that it was unusual for a person not to have subsequent treatment at third line if they were able to. They explained that the absolute number of people who go on to have a subsequent treatment after liso-cel was expected to be lower than after standard care because of the reduced risk of relapse. But, of the people that did relapse, they expected a similar proportion of people (up to 80.0%) to go on to have subsequent treatment in both treatment arms. The clinical experts said that most people would be given a bispecific antibody as subsequent treatment after liso-cel in clinical practice. They also noted that, generally, the preference is to use CAR-T therapy after standard care in clinical practice if the person is fit enough. But they explained that use was unlikely to be as high as the 94% of people as reported in TRANSFORM. The committee agreed with the clinical experts' expectations that liso-cel would lower the risk of relapse compared with standard care but that, after relapse, a similar proportion of people would have subsequent treatment in both treatment arms. So, it preferred to set the proportion of events for

time to next treatment that were the start of a new subsequent treatment in the model to be equal for liso-cel and standard care.

The committee concluded that the clinical experts' estimate of up to 80.0% was acceptable to use in the model. This was because it was also between the 69.6% value in the liso-cel arm and the 94.2% value in the standard-care arm from TRANSFORM. It agreed with the company that it was important to align modelled costs and benefits. It recalled its preference for modelling OS based on mixture cure models fitted to the TRANSFORM data (see section 3.8 and section 3.9). But it also noted that the subsequent treatments modelled did not reflect NHS clinical practice. In the absence of a method to reliably adjust the treatment effectiveness, the committee concluded that it preferred to model the proportion in each arm as equal. But it agreed that it would accept the distribution of subsequent treatments based on the data from TRANSFORM. The committee noted that it had remaining concerns for the generalisability of this trial data to NHS clinical practice. It also noted that the resulting impact on the clinical- and cost-effectiveness estimates was uncertain and would be considered in its decision making.

CAR-T cell tariff cost

3.16 A CAR-T cell tariff cost of £41,101, assumed to capture all costs of care from the decision for the person to have CAR-T therapy to 100 days after infusion, was accepted for use in TA895. This tariff cost included the costs associated with managing adverse events happening up to 100 days after infusion (excluding any costs associated with the treatment of hypogammaglobulinemia, that is, intravenous immunoglobulin). The NHS England Cancer Drugs Fund clinical lead explained that NHS England had been working with NHS trusts to determine the tariff cost that applied in NHS practice. They said that a value of £57,080 was agreed, which applied from the start of the new financial year for 2024/25. But they also noted that inflation had uplifted this value. So, a tariff cost of £58,964 was

now applicable for the rest of the 2024/25 financial year and for use in this appraisal. The committee concluded that the updated tariff cost of £58,964 should be applied in the model.

Adverse-event costs at third line

3.17 The company's original base-case model did not include costs related to managing adverse events at third line. The EAG was concerned that adverse-event costs were included in the CAR-T tariff cost for people having subsequent CAR-T therapy in the standard-care arm, but not for other subsequent therapies in either treatment arm. It commented that this approach biased the cost-effectiveness results in favour of liso-cel. The EAG originally preferred to exclude the costs associated with adverse events (estimated by the company as £10,611) from the CAR-T cell tariff cost when used for subsequent CAR-T therapy. The committee thought that this was appropriate. But, in response to consultation, the company updated its modelling to include the full CAR-T tariff cost, and also to include adverse-event costs for other third-line treatments. These costs were assumed to be a total of £7,310 for each treatment. The EAG highlighted that the costs of treating adverse events after an allogeneic stem cell transplant may be higher than after other third-line treatments. It added that a higher proportion of people may have an allogeneic stem cell transplant after their lymphoma has relapsed on liso-cel rather than standard care. The committee concluded that adverse-event costs should be included for all third-line treatments and accepted the company's assumptions.

Intensive care unit (ICU) costs

3.18 After the first committee meeting, NHS England confirmed that costs associated with ICU admission are not included in the CAR-T or stem cell transplant tariffs. So, the company updated its modelling to include costs for ICU admissions associated with all second- and third-line treatments. The company based the proportion of people who would need to be

admitted to an ICU after treatment with second-line liso-cel or third-line axi-cel on a French real-world evidence study. The study was sponsored by the company and is not yet published. The company based the proportion of people who would need admitting to ICU after a stem cell transplant on data from TRANSFORM. The EAG had concerns about using the real-world evidence study, noting that it was unpublished and there was published trial data available. The EAG presented a scenario analysis that used data from TRANSFORM to model the proportion of people needing ICU admission after second-line liso-cel. The committee noted that the EAG's scenario analysis did not make a big difference to the cost-effectiveness results. It concluded that costs associated with ICU admissions should be included in the model, and that the company's modelling of these costs was acceptable.

Uncaptured benefits

3.19 In its response to consultation on the draft guidance, the company stated that there were uncaptured benefits in the model related to using the CAR-T tariff. It argued that the calculated CAR-T tariff reflects costs associated with using axi-cel at third line. It also argued that the costs associated with liso-cel may be lower compared with axi-cel because of fewer adverse events and a greater potential to administer it in an outpatient setting. To illustrate this, the company presented scenario analyses in which it adjusted the CAR-T tariff:

- It lowered the costs of adverse events with liso-cel based on incidence rates of adverse events in TRANSFORM for liso-cel compared with in ZUMA-1 for axi-cel (see section 3.4).
- It assumed 50% of people had liso-cel as an outpatient, with a further assumption on the proportion of people who would not need to be admitted to hospital following outpatient treatment.

The clinical experts stated that there are different toxicity profiles with

liso-cel and axi-cel, which is supported by both trial and real-world evidence. They advised that the difference between the toxicity profiles is because of the treatments themselves and not just because of the increased experience in managing adverse events associated with CAR-T. They also stated that it could be possible to provide liso-cel in an outpatient setting for around 50% of people. But they said that even people not admitted as inpatients would need to be monitored and stay close to the hospital, with the associated accommodation costs. The committee acknowledged that liso-cel could be given in an outpatient setting for some people, but it thought that the company's scenario analysis was optimistic. It thought that, even if outpatient delivery of liso-cel could be implemented quickly, it would take time for the cost savings to be realised in the NHS. This would happen, for example, through an updated CAR-T tariff cost or a change to bed provision in hospitals. In addition to its scenarios, the company highlighted 2 factors that had not been quantified in the model. These were the effects of outpatient delivery and reduced ICU admissions on quality of life for patients and carers, and on NHS bed capacity outside of ICU. The committee concluded that it was not appropriate to adjust the CAR-T tariff. But it agreed that it would take the potential uncaptured benefits of liso-cel into account in its decision making.

Severity

Severity weighting

3.20 NICE's methods on conditions with a high degree of severity did not apply based on both the company's and the EAG's estimates of the absolute and proportional QALY shortfall. So, a weighting of 1.0 was applied to the QALYs.

Cost-effectiveness estimates

Acceptable ICER

3.21 NICE's manual on health technology evaluations notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the uncertainty in this evaluation, specifically about:

- issues of the generalisability of TRANSFORM to NHS practice, and the impact of this on the clinical- and cost-effectiveness results (see section 3.6), including:
  - the proportion of people having bridging therapy, and the distribution of bridging therapies at second and third lines (see section 3.14)
  - the proportion of people having subsequent therapy, and the distribution of subsequent therapies (see section 3.15)
- long-term OS in people having treatment with liso-cel (see section 3.8)
- the low completion rate for EQ-5D data in TRANSFORM (see section 3.13).

But the committee also noted that:

- relapsed or refractory large B-cell lymphoma after first-line chemoimmunotherapy has a large disease burden (see section 3.1)
- the only treatment option available in routine clinical practice can have substantial side effects for some people (see section 3.2)
- there were some uncaptured benefits in the modelling, including the expected lower rates of adverse events with liso-cel compared with axi-cel, and the potential for outpatient delivery of liso-cel (see section 3.19).

So, the committee concluded that an acceptable ICER would be around £30,000 per QALY gained.

Committee's preferred assumptions

3.22 The exact cost-effectiveness results cannot be reported here because of confidential discounts for liso-cel, comparators and subsequent treatments. After the first committee meeting, the company updated its base case to include the committee's preferred assumptions, which included:

- model health states based on EFS (see section 3.7)
- the company's mixture cure OS model for liso-cel (see section 3.8)
- the company's mixture cure OS model for standard care (see section 3.9)
- the company's extrapolations for time to next treatment to inform time to next treatment in the model (see section 3.10)
- a model starting age based on the mean age of people in TRANSFORM (see section 3.11)
- a per cycle discount rate (see section 3.12)
- the event-free health-state utility value based on TRANSFORM (see section 3.13)
- use of the TRANSFORM data for costing bridging therapy (see section 3.14)
- setting the proportion of people who have subsequent therapy after a time to next treatment event to be equal for liso-cel and standard care, assuming a value of 80% (see section 3.15)
- the distribution of subsequent treatments based on the data from TRANSFORM (see section 3.15)
- the updated CAR-T cell tariff cost of £58,964 (see section 3.16)
- including adverse-event costs for all third-line treatments (see section 3.17).

The company's updated base case also included costs associated with ICU admission, which the committee accepted (see section 3.18). The company also made some minor changes to the adverse-event costs at second line. The committee noted that these changes did not have a large impact on the cost-effectiveness results. The committee agreed that the company's updated base case included all of its preferred assumptions. The resulting ICER was around £30,000 per QALY gained. The committee recalled that it had agreed to take the potential uncaptured benefits of liso-cel into account in its decision making (see section 3.19). When taking these into account, it considered that liso-cel would be a cost-effective use of NHS resources. So, the committee recommended liso-cel for routine use in the NHS for treating relapsed or refractory large B-cell lymphoma after first-line chemoimmunotherapy when a stem cell transplant is suitable.

Other factors

Equality

3.23 At scoping, a stakeholder noted that clinicians consider a person's fitness when deciding whether more intensive cancer treatments are suitable for them. Healthcare professionals have sometimes used a person's age as a proxy for levels of fitness. Age is a protected characteristic under the Equality Act 2010. The committee acknowledged that NICE makes recommendations for technologies within their marketing authorisations. It noted that the company positioned liso-cel only for people for whom a stem cell transplant is suitable, which is usually people under 70 years. The committee noted this limitation but considered the evidence that had been submitted. It noted that it had not seen evidence for liso-cel for treating relapsed or refractory large B-cell lymphoma in people for whom a stem cell transplant is not suitable, who are usually older and less well. The committee acknowledged the need for new treatments in this population and was disappointed the company chose to position liso-cel for the transplant-eligible population only. But it agreed that its

recommendation had to be restricted to the transplant-eligible population, because the evidence it had seen was from this population. The committee concluded that, when determining eligibility for liso-cel based on suitability for autologous stem cell transplant, healthcare professionals should not use age as a proxy measure for fitness. So, NICE has made a recommendation that mitigates the risk of indirect discrimination on the basis of age. Stakeholders also commented that there is a geographic inequality because CAR-T cell therapy is only provided at designated centres. The committee noted that this was an issue related to implementation and could not be addressed through a technology evaluation recommendation.

Conclusion

Recommendation

3.24 The committee concluded that the most plausible ICER based on its preferred assumptions was likely to represent a cost-effective use of NHS resources. So, liso-cel is recommended for treating relapsed or refractory large B-cell lymphoma that is refractory to, or has relapsed within 12 months after, first-line chemoimmunotherapy, when a stem cell transplant is suitable.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft

recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has relapsed or refractory large B-cell lymphoma and the healthcare professional responsible for their care thinks that lisocel is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee C.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Richard Nicholas

Vice-chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Rachel Williams and Kirsty Pitt

Technical leads

Alexandra Filby and Mary Hughes

Technical advisers

Louise Jafferally

Project manager

Ross Dent

Associate director

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