Recommendation No. 7/2021

of 30 January 2021

of the President of the Agency for Health Technology Assessment and Tariff System

on the assessment of Kymriah (tisagenlecleucel) under the drug programme: "Treatment of B-cell acute lymphoblastic leukaemia with tisagenlecleucel (ICD-10 C91.0)".

The President of the Agency does not recommend the reimbursement of the medicinal product Kymriah (tisagenlecleucel) within the framework of the drug programme: "Treatment of B-cell acute lymphoblastic leukaemia with tisagenlecleucel (ICD-10 C91.0)" on the terms proposed to date.

Explanation for recommendation

The President of the Agency, taking into account the position of the Transparency Council, the criteria in accordance with the health technology assessment, i.e. the magnitude of the achieved effect on health, cost-effectiveness and the projected impact on the payer's budget, as well as the significance of the health problem and the uncertainty of the estimates, considers it unjustified to finance the applied technology from public funds under the conditions proposed so far.

It should first be emphasised that this recommendation refers to CAR-T in the medicinal product Kymriah used in the indication evaluated and does not refer to other CAR-T therapies.

It was taken into account that the drug is evaluated in the indication of B-cell acute lymphoblastic leukaemia (B-ALL), which is the most common form of leukaemia in children, accounting for approximately 75-80% of diagnoses and in Poland it is diagnosed annually in approximately 35 per 1 million children. It was considered that the disease affects a limited population and its prognosis is inauspicious.

Regarding the therapy in question, it should be pointed out that the clinical evaluation showed an effect in terms of the probability of 24-month survival, which, depending on the publication, ranged from 45.7% (95%CI: 25.5; 63.8) - ENSIGN trial to 66.2% (95%CI: 52.9; 76.5) - ELIANA trial. The studies also evaluated other endpoints that could give indirect information about efficacy, such as the probability of event-free survival or the probability of overall remission rate (ORR/CR).

However, the strength of the inference of treatment efficacy is weakened by the quality of the presented scientific evidence (single-arm, phase II studies, without a control group and without randomisation) and the fact that 2 of the 3 studies are available only as conference abstracts. Furthermore, with regard to the evaluation of the therapy in question under the emergency access to medicinal technology procedure carried out last year, doubts remain regarding the scientific evidence for the efficacy of the technology applied for, as the results in full-text form come from a single single-arm Phase II clinical trial codenamed ELIANA. Such studies have low reliability as they lack a randomised control group, which is the type of trial (randomised controlled trial) that sets the standard for scientific evidence in assessing clinical effectiveness (thus, it is not possible to estimate the exact magnitude of benefit of tisagenlecleucel compared with salvage chemotherapy). In addition, the level of uncertainty is increased by the small sample size, as only 92 participants were included, 75 of whom received tisagenlecleucel infusion. That population was the one subjected to the efficacy analysis. Another limitation is the short observation period (trade secret), medium-term data are available in the form of conference abstracts. The median time from drug administration to data cut-off point within the 2018 Maude full-text publication was 13.1 months.

No studies were found directly comparing the medicinal product Kymriah (tisagenlecleucel, TIS) with the comparator indicated by the applicant, i.e. blinatumomab (BLIN) in the applied indication. The comparison with blinatumomab was presented in an indirect trial, so it was probably possible to design a randomised comparative trial with a control group. Blinatumomab is recommended in guidelines (NCI, NCCN, ESMO) as a therapeutic option in the evaluated indication.

The clinical analysis included the aforementioned (trade secret) In addition, the submitted analyses do not take into account all comparators, i.e. the applicability of salvage chemotherapy regimens and inotuzumab ozogamicin.

Health effects regarding safety were also highlighted. According to the results of the ELIANA trial, adverse events occurred in all patients analysed, with 95% of them likely related to the treatment. Grade 3 and 4 adverse events occurred in 88% of patients.

Events of special interest of grade 3 and 4 that occurred during the first 8 weeks after infusion were cytokine release syndrome (46% of patients), cytopenias that did not resolve by day 28 (32%), infections (24%), neutropenic fever (35%), neurological events (13%) and tumour lysis syndrome (4%). In addition, it was pointed out that in the ELIANA trial, 47% of patients were admitted to an intensive care unit. The cited data come from the accessible 2018 Maude full-text publication, where the median time from drug administration to data cut-off point was 13.1 months, so the safety over a longer follow-up period is not fully understood. This is confirmed by the obligation imposed by EMA on the responsible entity to conduct and submit studies based on data from the register in order to further characterise the safety of the product.

In the absence of full-text publications for 2 of the 3 studies, the concerns set out in Opinion No. 6/2020 remain valid as follows: "the medicinal product applied for has been registered conditionally, which means that an obligation has been placed on the responsible party to conduct 5 additional studies. Among others, the applicant should conduct and submit a trial based on disease registry data in patients with acute lymphoblastic leukaemia (ALL) and

diffuse large B-cell lymphoma (DLBCL). The remaining trial concerns further evaluation of the efficacy and safety of Kymriah in patients with ALL and DLBCL where publication of results is scheduled for 2022-2023."

The agency additionally found a full-text publication that was not included in the applicant's review. The aim of this publication was to assess the safety of tisagenlecleucel therapy by analysing the Eudravigilance database with a focus on the paediatric population. The analysis included data from 2017 to 2020. There were 364 individual case safety reports (ICSRs) of TIS therapy, of which 117 are related to the paediatric population (92 reports (80.7%) related to patients with acute lymphoblastic leukaemia. More than a third of reports (41/117) suggested the failure of tisagenlecleucel therapy.

(trade secret)

However, after analysing the assumptions made in the economic model, the Agency has serious reservations about the obtained value of the incremental cost-efficiency ratio. One of the concerns is that a higher rate of patients who eventually received an infusion of the drug was included in the analyses than in the trial. It is important to note that due to the complexity of the preparation and subsequent administration of Kymriah, a proportion of patients ultimately do not receive treatment (according to the ELIANA trial , this applies to 18% of the patient population). In addition, other factors that affect the uncertainty of the estimates are the assumptions made regarding the time horizon, which is not supported by the length of the follow-up period in the presented publications, the lack of consideration of the cost of treating patients who experience treatment failure and the cost of potential therapies used to sustain CAR-T cell activity; the determination of overall survival and event-free survival in the blinatumomab arm on the basis of data for tisagenlecleucel using parametric curves, which affects the uncertainty of estimates; lack of data on the long-term effects of CAR-T therapy (data on survival above 5 years were derived from non-CAR-T therapy literature data); extrapolation of data on the effectiveness of therapy to the period of 88 years on the basis of studies for which the longest median observation period was 32.3 months; failure to take into account decreased usefulness for adverse events other than cytokine release syndrome; failure to include chemotherapy and inotuzumab ozogamicin as comparators.

Changes in the above assumptions result in a change in the incremental cost-effectiveness ratio from a value below the break-even point to a value above the break-even point. This makes it necessary to approach the presented values with caution.

The fact that the Agency considers that the expenditure from the payer's budget appears to be underestimated was also taken into account. Considering the size of the target population determined on the basis of the data of the National Health Fund (trade secret)

The negative recommendation is also supported by the proposed therapy price, (trade secret)

In addition, it should be emphasised that the studies on Kymriah do not include a patient group <3 years of age, so inference about the efficacy and safety of treatment in this population is very limited.

Out of the 7 identified reimbursement recommendations, 4 recommendations are positive conditionally (due to doubts concerning scientific evidence and costs of therapy) and 3 are positive (all of them come from countries with GDP higher than Poland). However, it should be pointed out that (trade secret)

Taking into account a number of uncertainties related to the estimation of the effects of Kymriah in relation to the currently used treatment, as well as a number of limitations of the submitted analyses affecting their reliability, the need for further monitoring and evaluation of data of the assessed health technology remains justified.

In view of the significance of the health problem and the preliminary results of the trial, the President of the Agency indicates the possible legitimacy of including the therapy in question in the reimbursement; however, in the opinion of the President of the Agency, the proposed reimbursement (trade secret) and financial (trade secret) conditions would have to be significantly changed

Subject of the application

The order of the Minister of Health concerns the assessment of the appropriateness of public financing of a medicinal product:

- Kymriah, tisagenlecleucel, dispersion for infusion, 1.2 x 10^6 - 6 x 10^8 cells, 1, bag, EAN: 05909991384388 - proposed selling price net PLN (trade secret).

Proposed payment and dispensing category: free of charge, the drug is to be used under a drug programme as part of a new limit group. (trade secret)

Health problem

According to the ICD-10 classification of diagnoses, lymphoblastic leukaemia falls under the code C91.0.

The development of B-cell acute lymphoblastic leukaemia (B-ALL) occurs as a result of neoplastic transformation of the lymphocyte precursor cell. B-ALL is characterised by clonal proliferation, impaired maturation and accumulation of lymphoblasts in the bone marrow, peripheral blood and other organs. ALL can spread to the lymph nodes, spleen, liver, central nervous system (CNS) and other organs. Without treatment, the acute progression of the disease is very rapid.

The incidence of new cases of ALL is 2/100,000 people per year, of which 20-25% are adults. The peak incidence occurs in children between 2 and 5 years of age, reaching 6.2 cases/100,000 population per year in the USA. After the age of 20, the incidence rate decreases to <1/100,000 and remains at this level in the middle-aged population. In the age group >60 years, the rate increases, reaching 2.4 /100 000 for those >80 years. According to US data, the average age of a patient diagnosed with ALL is 14 years. 60% of ALL cases are detected in people aged <20 years, 24% in those aged ≥45 years, 11% in those aged ≥65 years. ALL remains rare in older people, although there is an increase in incidence in this age group, with the proportion of patients aged ≥55 years (17%) similar to that of patients aged 21-54 years (22%).

ALL is the most common form of leukaemia in children - accounting for around 75-80% of diagnoses. In Poland, leukaemia is diagnosed every year in approximately 35/million children. In other European countries the rate is around 44/million children. Compared to the general population, a significantly higher predisposition to leukaemia is found in children with various chromosome syndromes, most notably trisomy of chromosome 21. (Down syndrome), in ataxia, telangiectasia, Fanconi aplastic anaemia.

Acute Lymphoblastic Leukemia (ALL) is one of the most aggressive proliferative diseases with a survival time of a few to a dozen weeks without adequate treatment. ALL is highly sensitive to chemotherapy and complete remission (CR) is achieved in approximately 90% of patients. Almost half of the patients develop a relapse, which is unambiguously associated with a poor prognosis. Therefore, early identification of risk factors for relapse and the use of appropriate intensive treatment, including allogeneic haematopoietic stem cell transplantation (alloHSCT) in justified cases, are important.

Treatment of ALL/LBL is radical and conducted with the intention of curing the patient. The choice of therapeutic regimen is mainly determined by the presence or absence of the BCR-ABL1/t(9;22) fusion gene and the age of the patient.

Alternative health technology

Taking into account clinical guidelines and technologies currently financed from public funds, the drug Blincyto (blinatumomab) was indicated as a comparator for the proposed technology.

At the same time, it was highlighted that there is currently no fully adequate comparator for a therapy based on the use of tisagenlecleucel (Kymriah).

Description of the benefit named in the application

Kymriah has been registered as an advanced therapy product based on the opinion of the EMA's Committee for Advanced Therapies (CAT). In addition, Kymriah has been included in the group of Gene-Therapy Medicines (GTMPs). Gene therapy with the Kymriah drug is based on genetic modification of T lymphocytes taken from the patient.

According to the Summary of Product Characteristics (SmPC), Kymriah is recommended for the treatment of:

- Paediatric and young adult patients up to and including 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.
- Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy. The indication applied for is included in the registration indication.

Evaluation of efficacy (clinical and practical) and safety

This evaluation consists of collecting data on the health consequences (efficacy and safety) of a new therapy for a given health problem and other therapies that are currently publicly funded and represent alternative treatments available for the particular health problem. Subsequently, this evaluation involves determining the reliability of the collected data and comparing the efficacy and safety results of the new therapy against therapies that are already available for the treatment of the health problem in question.

Based on the above, the evaluation of efficacy and safety provides an answer to the question of the measure of health outcome (in terms of both efficacy and safety) to be expected for the new therapy compared to other therapeutic options considered.

The target population in the application consists of children, adolescents and young adults up to the age of 25 years with B-cell acute lymphoblastic leukaemia (ALL) refractory to therapy; who are in relapse after transplantation or in second or subsequent relapse.

No studies were found directly comparing Kymriah (tisagenlecleucel, TIS) with the chosen comparator, i.e. blinatumomab (BLIN) in the applied indication.

The review included:

- three single-arm primary studies on the use of Kymriah in patients with acute lymphoblastic leukaemia (ALL):
    - ELIANA - B2202 (full-text publications: Maude 2018, Laetsch 2019; abstracts: Dietz 2017, Grupp 2018, Grupp 2019) - A pivotal trial for the evaluated intervention, which is a phase II trial that evaluates the efficacy and safety of tisagenlecleucel in children

and young adults with relapsed/refractory B-cell acute lymphoblastic leukemia (pB-ALL) (ongoing trial);

- ENSIGN - B2205J (abstract and conf. poster: Maude 2016, Maude 2018a) - Phase II trial that evaluates the efficacy and safety of tisagenlecleucel in children and young adults with relapsed/refractory pB-ALL (trial completed);
- Pedi CART19 - B2101J (abstracts: Maude 2016a, Levine 2016) - a phase I/IIa trial that evaluates the safety, tolerability and feasibility of administering tisagenlecleucel in patients with CD19-positive haematological malignancies. This trial also aimed to evaluate and adjust the dosage of TIS.

- two single-arm studies on the use of blinatumomab (BLIN):
  - MT103-205 (full-text publications: von Stackelberg 2016, Gore 2018) - a pivotal trial for blinotumomab, representing a phase I/II trial that determines dosing (phase I) and evaluates its clinical efficacy in children with relapsed/refractory pB-ALL (phase II);
  - RIALTO (abstracts: Locatelli 2018, Locatelli 2019/2020) - expanded access trial, presented as additional/complementary in the applicant's analysis.

The analysis presents a qualitative summary of the results of single-arm studies included for tisagenlecleucel (ELIANA, ENSIGN + Pedi CART19) and blinatumomab (MT 103-205, RIALTO).

At the same time, the basis of the analysis for the comparison of the clinical effectiveness of TIS vs BLIN are the results developed by (trade secret)

The reliability of the included single-arm studies was assessed using the criteria of the NICE scale. The ELIANA, ENSIGN and Pedi-CART19 studies were rated 7/8, 5/8 and 4/8 by NICE respectively.

Efficacy

Qualitative summary of results from trials for tisagenlecleucel vs blinatumomab

Probability of 24-month survival:

- tisagenlecleucel (TIS)
  - 66.2% (95%CI: 52.9; 76.5) - ELIANA trial
  - 45.7% (95%CI: 25.5; 63.8) - ENSIGN trial
  - (company secret) - Pedi-CART trial
- blinatumomab (BLIN)
  - 25.9% (95%CI: 16.7; 40.3) - MT 103-205 trial.

(trade secret)

Median of relapse-free survival (RFS):

- tisagenlecleucel (TIS)
  - NR (95% CI: 12.1; not reached) - ELIANA trial
  - NR (95% CI: 5.9; not reached) - ENSIGN trial
  - (company secret) - Pedi-CART trial
- blinatumomab (BLIN)
  - 4.4 months (95% CI: 2.3; 7.6) - MT 103-205 trial (concerning patients who achieved CR after 2 cycles of BLIN treatment);
  - 8.5 months (95% CI: 3.4; not reached) - RIALTO trial (concerning patients who achieved CR after 2 cycles of BLIN treatment).

Overall remission rate (ORR/CR):

- tisagenlecleucel (TIS)
    - 82% - ELIANA trial
    - 69% - ENSIGN trial
    - (company secret) - Pedi-CART trial
- blinatumomab (BLIN)
    - 39% - MT 103-205 trial
    - 59% - RIALTO trial.

(trade secret)

In the ELIANA trial, at all follow-up points, there was a higher proportion of patients achieving quality of life at the general population level in all domains studied except social functioning than at baseline. The improvement in mean change in scores for the EQ-5D and PedsQL questionnaires at months 3 to 12 was greater than the minimum clinically meaningful difference of 7-10 points for the EQ-5D questionnaire and 4.36 points for the PedsQL questionnaire. The studies for blinatumomab did not analyse patients' quality of life.

Percentage of patients who underwent allo-HSCT after therapy:

- tisagenlecleucel (TIS):
    - (trade secret)
- blinatumomab (BLIN)
    - (trade secret) - review (trade secret)
    - 37% - MT 103-205 and RIALTO studies.

(trade secret)

Safety

<u>Kymriah (tisagenlecleucel)</u>

In the ELIANA, ENSIGN and Pedi-CART19 studies the median follow-up time was respectively: 24, 19.6 and (trade secret) there were (trade secret) patient deaths, due to disease progression and adverse events.
In the ELIANA trial, the most commonly reported AEs associated with treatment were cytokine release syndrome (CRS) (77.3%, including 25.3% of grade 4) and hypoglobulinaemia (29.3%).
In the ENSIGN trial, the most common AEs (ref. ≥30% of patients), possibly related to tisagenlecleucem therapy were: CRS (90%), vomiting (45%), hypogammaglobulinaemia (41%), nausea (38%), fever (38%), neutropenia with fever occurring within 8 weeks after infusion (31%), increased alanine aminotransferase (35%), leukopenia (31%), decreased appetite (38%), increased aspartate aminotransferase (38%) and hypotension (31%).
In the Pedi-CART19 trial, the most common AEs possibly associated with tisagenlecleuc therapy were CRS (82%), neutropenia with fever (71%), hypotension (38%) and encephalopathy (27%).

<u>Blinatumomab</u>

In the MT 103-205 trial, 48 (68.6%) deaths occurred during a follow-up period of 24 months. In contrast, in the RIALTO trial, a total of 51 (46.4%) deaths occurred during a follow-up period of 13.1 months (of which 43 deaths were due to disease progression).
In the MT 103-205 trial, 100% of patients had adverse events and 87% of patients had events of a ≥3 grade of severity. In the RIALTO trial, 99% of patients experienced adverse events, 65% of which were ≥3 in severity and 28% of which were ≥4 in severity. The AEs most commonly occurring and probably

related to blinatumomab treatment were injection site reactions (49%), neurological events (20%) and fever (57%).

Additional safety information

The drug safety assessment is based on a total of 194 patients (including children, adolescents and young adults with B-cell ALL and DLBCL) who received Kymriah in two multicentre registration clinical trials.

B-cell ALL

The most common non-haematological adverse reactions were cytokine release syndrome (77%), infection (73%), hypogammaglobulinaemia (53%), fever (42%) and decreased appetite (38%).

The most common haematological adverse reactions were decreased white blood cell count (100%), decreased haemoglobin (100%), decreased neutrophil count (100%), decreased lymphocyte count (100%) and decreased platelet count (97%).

Grade 3 and 4 adverse reactions were reported in 89% of patients. The most common grade 3 and 4 non-haematological adverse reaction was cytokine release syndrome (48%).

The most common Grade 3 and 4 haematological laboratory abnormalities were decreased white blood cell count (97%), decreased lymphocyte count (96%), decreased neutrophil count (95%), decreased platelet count (77%) and decreased haemoglobin (48%).

No additional safety announcements regarding Kymriah that are not contained in the Summary of Product Characteristics were found on the EMA, FDA, URPL websites.

Limitations

The main limitation of the reliability of the presented analysis is the lack of randomised trials directly comparing the applied technology with the selected comparator (blinatumomab) in the applied population.

In addition, the uncertainty of the presented results of the clinical analysis is affected by the following aspects:

- a lack of comparative studies allowing a classical indirect analysis (Bucher's method) by a common reference group for the applied population;
- the only sources on the efficacy of the drug technologies in question in refractory B-ALL were single-arm clinical trials (for both Kymriah and the alternative intervention);
- clinical and methodological heterogeneity of the included studies in both the tisagenlecleucel and blinatumomab arms (different follow-up periods, characteristics of the included patients);
- the quantitative analysis of the studies for the evaluated intervention was performed by taking into account the results of patients who received tisagenlecleucel (FAS population) and not the ITT population. The analysis of results obtained only in the FAS population may be related to the lack of consideration of events occurring before Kymriah infusion in all patients qualified for treatment, and thus translate into an overestimation of the results for the evaluated intervention;
- lack of long term studies on the efficacy of Kymriah. Data from the ELIANA trial (the main trial for the evaluated intervention) for the longest follow-up period (median 24 months) are only available as conference abstracts (Grupp 2019a, Grupp 2019b), while the median follow-up time in the full-text publication is 13 months. (trade secret) The longest reported observation period in the found real-world studies amounted to 30 months. (Leahy 2019);
- the ELIANA and ENSIGN trials included patients with ≥5% blasts in the bone marrow while the main comparator trial, the MT 103-205 trial, included qualified patients with ≥25% blasts. In

addition, 71% of patients in the MT 103-205 trial relapsed within 6 months of previous treatment, which also indicates a poor prognosis in patients with r/r B-ALL. The above parameters may indicate a more advanced state of the disease at baseline in patients treated with blinatumomab in the MT 103-205 trial, which may translate into poorer treatment efficacy results;

- in the ELIANA trial, the protocol included, in addition to lymphodepletive chemotherapy, the use of bridging chemotherapy between leukapheresis and CAR-T cell administration to stabilise the patients' clinical status. Bridging chemotherapy was administered to 65 of 75 (84%) patients from the ELIANA trial who received Kymriah (Maude 2018). Considering the complexity of the evaluated intervention, including the administration of bridging chemotherapy, it is difficult to state unequivocally whether the additionally applied procedures may translate into the achieved therapeutic effect;
- (trade secret)
- there is a lack of evidence regarding the clinical effectiveness of Kymriah for the youngest population, the requested indication covers the population of children from birth and only one patient (0.5%) in the trials for Kymriah was younger than two years;
- most of the patients for whom quality of life data were analysed in the ELIANA trial achieved a response to treatment. After the 9th and 12th month of follow-up, no quality of life data were presented for patients who did not respond to treatment. This method of measurement may overestimate the effectiveness of therapy in terms of impact on quality of life.

Proposed risk-sharing scheme

(trade secret)

Economic evaluation, including estimates of cost to health outcomes achieved

Economic evaluation involves estimating and comparing the costs and health outcomes that may be associated with using the new therapy for an individual patient in place of already reimbursed therapies.

The costs of therapy are estimated in the currency of our country, and health outcomes are usually expressed in life-years gained (LYG) or quality-adjusted life years (QALY) as a result of the therapy.

By comparing the cost and outcome values of the new therapy to the costs and outcomes of already reimbursed therapies, one can answer the question of whether the health outcome achieved for an individual patient with the new therapy is associated with a higher cost compared to already reimbursed therapies.

The obtained results of the cost to health outcome ratio are compared with the use of the so-called break-even point, i.e. a result that indicates that given the wealth of our country (expressed in GDP), the maximum cost of the new therapy that is expected to produce a unit of health outcome (1 LYG or 1 QALY) compared to already available therapies should not exceed three times the GDP per capita.

Currently, the break-even point is PLN 155,514 (3 x PLN 51,838).

The cost to health outcome ratio does not estimate or determine the value of life, it only enables its assessment and, among others, on this basis, choose the therapy related to potentially the best outcome.

The cost effectiveness evaluation included a cost utility analysis over a lifetime time horizon (88 years) from the perspective of the public payer - the entity required to fund the benefits from public funds, i.e. the National Health Fund (NHF)

The following types of direct medical costs were included in the analysis:

- the cost of the used drugs: Kymriah (including those related to the manufacture and administration of the product), chemotherapy and blinatumomab;
- the cost of haematopoietic stem cell transplantation and follow-up treatment as well as the monitoring of patients after transplantation,
- the cost of treatment of adverse events, diagnostics and treatment monitoring.

The analysis did not include the cost of treatment for patients who failed both Kymriah and Blincyto therapy. The cost of potential therapies used to sustain CAR-T cell activity was also not included.

Discounting of 5% for costs and 3.5% for health effects was considered.

Given these assumptions, the incremental cost utility ratio (ICUR) for the Kymriah vs Blincyto comparison was: (trade secret)

Considering the above values for ICUR, the threshold net sales price at the current break-even point is (trade secret)

Limitations

The following aspects of the economic model, among others, influenced the uncertainty of the presented results:

- (trade secret)
- failure to take into account the cost of treating patients who suffered treatment failure and the cost of potential therapies used to sustain CAR-T cell activity;
- determination of overall survival and event-free survival in the blinatumomab arm from data for tisagenlecleucel using parametric curves, which affects the uncertainty of the estimates;
- lack of data on the long-term effects of CAR-T therapy (survival data beyond 5 years are from non-CAR-T literature) (including therapies used after its failure or to maintain CAR-T activity);
- extrapolation of treatment efficacy data over a period of 88 years based on studies for which the longest median follow-up period was 32.3 months;
- failure to take into account the decrease in usefulness in the presence of adverse events other than cytokine release syndrome;
- failure to consider chemotherapy and inotuzumab ozogamicin as comparators.

Agency's own calculations

An update of the applicant's calculations with respect to the cost-effectiveness threshold of PLN 155,514 was carried out (conclusions and estimation results related to the current threshold are presented above).

Indication whether the circumstances referred to in Art. 13 sec. of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs intended for particular nutritional uses and medical devices (Journal of Laws 2020, item 357 as amended);

If the applicant's clinical analysis does not include randomised clinical trials proving the superiority of the drug over health technologies already reimbursed in a particular indication, the official sales price of the drug must be calculated in such a way that the cost of use of the drug whose reimbursement is applied for is not higher than the cost of health technology with the most favourable ratio of obtained health outcome to the cost of obtaining them.

Due to the failure to present RCTs in the clinical analysis, the circumstances of Article 13 of the Reimbursement Act apply.

Agency's own calculations

The value of the net sales price of the medicinal product Kymriah at which the cost of its use is not higher than the cost of the comparator (Blincyto) is: (trade secret)

Assessment of the impact on the healthcare system, including the impact on the budget of the public payer

The health system impact assessment has two major parts.

First, a payer budget impact analysis allows estimating the potential expenses associated with public funding of the new therapy.

Estimates of expenses associated with the new therapy (the "tomorrow" scenario) are compared to how much is currently spent on treating a health problem (the "today" scenario). On this basis, it is possible to assess whether a new therapy will require more resources to treat a given health problem or is associated with savings in the payer's budget.

A budget impact assessment determines whether a payer has adequate resources to fund a particular technology.

The assessment of health system impact in the second part answers the question of how the decision to fund the new therapy may affect the organisation of service delivery (particularly in the context of adjusting to the requirements of delivering the new therapy) and the availability of other healthcare services.

The results of the applicant's budget impact analysis are presented over a four-year horizon. The analysis was conducted from the perspective of the public payer (NHF).

Direct medical costs have been taken into account, in accordance with the CUA i.e:

- the cost of the medical technology applied for,
- the cost of chemotherapy drugs,
- the cost of the comparator (blinatumomab),
- the cost of haematopoietic stem cell transplantation and the cost of follow-up treatment as well as the monitoring of patients after transplantation,
- the cost of treating adverse events,
- cost of diagnostics and monitoring the treatment.

The applicant has estimated the patient population that will use the proposed technology (trade secret).

The results of the applicant's base-line analysis indicate that the inclusion of Kymriah in the reimbursement for the requested indication will result in (trade secret)

Limitations

The uncertainty of the presented results is affected by the following aspects:

- the cost data were taken from the economic analysis, therefore the limitations of the CUA analysis are also limitations of the budget impact analysis;
- (trade secret);
- no justification was provided for the assumptions regarding the level of acquisition of (trade secret) market shares. This parameter was also not tested in the sensitivity analysis;
- not all available alternative technologies have been taken into account.

Agency's own calculations

Own calculations were made taking into account the size of the target population determined on the basis of data of the National Health Fund (trade secret)

Comments on the proposed risk-sharing scheme

(trade secret)

Comments on the drug programme

According to the information provided in the reimbursement application, the applicant seeks funding for the medicine under the new drug programme "Treatment of B-cell acute lymphoblastic leukaemia with tisagenlecleucel (ICD-10 C91.0)".

(trade secret)

Discussion of the solutions proposed in the rationalisation analysis

The rationalisation analysis aims to identify a mechanism whose introduction will result in the release of public funds in an amount corresponding to at least the increase in costs resulting from a positive decision on reimbursement of the health technology named in the application.

A rationalisation analysis is submitted if the budget impact analysis for the entity responsible for funding shows an increase in reimbursement costs.

(trade secret)

Discussion of recommendations issued in other countries in relation to the assessed technology

Five clinical recommendations were presented relating to the indication applied for, from:

- Polish Oncological Society (PTOK 2020);
- National Comprehensive Cancer Network (NCCN 2021, NCCN 2020);
- European Society for Medical Oncology (ESMO 2016);
- The Society for Immunotherapy of Cancer (SITC 2020);
- National Cancer Institute (NCI 2020).

The Polish PTOK 2020 guidelines recommend chemotherapy, immunotherapy or combination therapy for the treatment of refractory and recurrent B-ALL. Immediately after response to salvage chemotherapy and/or immunotherapy, allo-HSCT should be performed as soon as possible. Monoclonal antibodies i.e. rituximab, ozogamycin inotuzumab, blinatumomab should be considered for salvage treatment of refractory/relapsed B-ALL.

The NCCN 2021 and NCCN 2020 guidelines recommend the use of, among others, tisagenlecleucel in patients with B-ALL without the Philadelphia chromosome (Ph-) after a first relapse after HSCT, with the caveat that this applies to patients under 26 years of age with refractory B-ALL or a minimum of 2 relapses. For patients with B-ALL Ph+, tisagenlecleucel is listed as one of the recommended therapies in patients with intolerance or resistance to TKIs or for relapse after HSCT. Tisagenlecleucel is also recommended by the NCCN 2020 guidelines as one of the treatment options for patients with multiple relapses/refractory disease. In addition to tisagenlecleucel therapy for B-ALL Ph- the guidelines also recommend various chemotherapy regimens, blinatumomab and inotuzumab ozogamicin (adults). Blinatumomab and inotuzumab ozogamicin are also recommended for use in patients with B-ALL Ph+.

The NCI 2020 guidelines indicate the use of haematopoietic stem cell transplantation (HSCT) as well as chemotherapy with bortezomib for second or subsequent relapse. CAR-T therapy in parallel with a second ablative allo-HSCT is also mentioned in the management of recurrent B-ALL after allo-HSCT.

Whereas, according to the guidelines, the management of refractory ALL includes blinatumomab, ozogamycin inotuzumab (not tested in the pediatric population) and CAR-T therapy.

The SITC 2020 guidelines recommend CAR-T therapy for patients with relapsed ALL after second- and/or third-line therapy. For patients with ALL who have relapsed or become refractory to CAR-T therapy, no consensus has emerged on a recommended single preferred treatment. Potential options may include CAR-T lymphocyte therapy targeted to different antigens, blinatumomab or allo-HSCT (if the patient is eligible).

The 2016 ESMO European guidelines indicate that there is no universal treatment regimen for this patient group and there is a lack of evidence based on randomised trials. Drugs such as blinatumomab, ozogamycin inotuzumab, and CAR-T therapy for patients with refractory or relapsed B-ALL were mentioned as promising new treatments. The guidelines indicate that CAR-T can be taken as part of a clinical trial (ESMO 2016 guidelines were published before Kymriah was registered in Europe).

A search found 7 reimbursement recommendations, including 6 for the use of Kymriah in patients up to 25 years with relapsed refractory B-cell acute lymphoblastic leukaemia and 1 recommendation for patients aged 3 to 25 (CADTH 2019).

Among the positive conditional recommendations i.e. NICE 2018, CADTH 2019, NCPE 2019, the justifications point to the limited evidence on treatment efficacy and safety and the high cost of tisagenlecleucel therapy. These recommendations indicate that a positive decision is subject to a reduction in price and continued data collection for a longer follow-up period on the efficacy and safety of the therapy.

Positive recommendations were issued by HAS 2018, ZIN 2018, SMC 2019 and GBA 2020.

The HAS 2018 recommendation emphasises the need to obtain data for a longer follow-up period, taking into account the uncertainty regarding efficacy, short- and long-term safety, and the complexity of the treatment process. In addition, the necessity to obtain data from clinical trials on the efficacy and safety of therapy in patients <3 years was pointed out. In turn, the ZIN 2018 recommendation notes that the use of tisagenlecleucel in the indication of B-cell acute lymphoblastic leukaemia is in line with current knowledge and clinical practice, but nevertheless draws attention to the high cost of the medicinal product.

According to the information provided by the applicant, the medicinal product Kymriah is funded in (trade secret) EU and EFTA countries (out of 31 indicated). (trade secret)

PRESIDENT

dr n. med. Roman Topór-Mądry

/document signed electronically/

Basis for the recommendation

The recommendation was prepared under an order dated 25 September 2020 of the Minister of Health (reference number: PLR.4500.160.2020.20.AP), regarding the preparation of the President's recommendation on the evaluation of the drug Kymriah, (tisagenlecleucelum) under the programme: "Treatment of B-cell acute lymphoblastic leukaemia with tisagenlecleucel (ICD-10 C91.0)" pursuant to Art. 35 sec. 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs intended for particular nutritional uses and medical devices (Journal of Laws 2020, item 357 as amended), following Transparency Council Position No. 7/2021 of 25 January 2021 on the evaluation of the drug Kymriah, (tisagenlecleucelum) under the programme: "Treatment of B-cell acute lymphoblastic leukaemia with tisagenlecleucel (ICD-10 C91.0)"

References

1. Position of the Transparency Board No. 7/2021 of 25 January 2021 on the evaluation of the drug Kymriah, (tisagenlecleucelum) under the programme: "Treatment of B-cell acute lymphoblastic leukaemia with tisagenlecleucel (ICD-10 C91.0)"
2. Report No. OT.4331.40.2020 Application for reimbursement of the medicinal product Kymriah (tisagenlecleucelum) under the programme: "Treatment of B-cell acute lymphoblastic leukaemia with tisagenlecleucel (ICD-10 C91.0)"