Recommendation No. 11/2021

of 5 February 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 diffuse large B-cell lymphoma (ICD-10 C83, C85) with tisagenlecleucel".

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 diffuse large B-cell lymphoma (ICD-10 C83, C85) with tisagenlecleucel" under the terms proposed so far.

Explanation for recommendation

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

It should first be emphasised that this recommendation refers to CAR-T contained 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 being evaluated for the indication of diffuse large B-cell lymphoma (DLBCL), which is the most common group of lymphomas of all lymphoid malignancies, and the target population is patients (trade secret)

With regard to the therapy in question, it should be pointed out that the clinical evaluation showed an effect of a probability of 3-year survival of 36% (JULIET study). In addition, median OS at the level of 8.3 months (JULIET study) and 22.2 months (A2101J study), as well as response rates (ORR) ranging from 52% to 54%, were achieved. However, the strength of the inference of treatment efficacy is weakened by the quality of the scientific evidence presented (single-arm phase II studies, without a control group and without randomisation).

Furthermore, with respect to the last year's evaluation of the therapy in question under emergency access to medicinal technology procedure, doubts remain as to the scientific evidence for the effectiveness of the proposed technology. As indicated above, the results are from single-arm studies (JULIET, A2101J) without a randomized control group, and this type of studies (i.e. randomized controlled trials) sets the standard for scientific evidence in evaluating clinical effectiveness (thus, there is no way to estimate the exact magnitude of effects in the form of benefits of tisagenlecleucel compared to salvage chemotherapy). In addition, the level of uncertainty is affected by the short follow-up period in the trials, and data from the JULIET study for the longest follow-up period (median 40.3 months) are only available as conference abstracts and only for selected endpoints.

No studies were found that would directly compare Kymriah (tisagenlecleucel, TIS) with the selected comparator, i.e. salvage chemotherapy, in the indication in question. Therefore, the clinical analysis was based on a qualitative summary of the results of the studies for tisagenlecleucel (JULIET and A2101J) as well as the comparator (CORAL studies) and (company secret) Moreover, the analyses submitted do not take into account all comparators, that is the possibility of using pixantrone.

Health effects regarding safety were also highlighted. According to the results of the JULIET study, adverse events occurred in all patients analysed (111 patients), with 89% of them likely related to treatment. Grade 3 and 4 adverse events occurred in 89% of the patients.

The concerns raised in Opinion No. 5/2020 also remain valid in the scope of the following fragment: "the requested medicinal product was conditionally registered, meaning that an obligation to conduct additional studies was imposed on the responsible party. Among other things, 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 studies concern further evaluation of the efficacy and safety of Kymriah in patients with ALL and DLBCL where publication of results is scheduled for 2022-2023."

(trade secret)

The evaluation also took into account the results of a budget impact analysis, which showed that the inclusion of Kymriah in the reimbursement scheme in the indication analysed would entail (trade secret)

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

Out of 9 reimbursement recommendations identified, 4 recommendations are positive conditionally (due to uncertainties concerning the scientific evidence and cost of therapy), 3 are positive (from countries with GDP higher than Poland), and 2 are negative, with one of them being a conditionally negative recommendation (these decisions mainly indicate uncertainties regarding higher efficacy of tisagenlecleucel over standard therapy and the need to reduce the price of therapy).

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

Non-Hodgkin's lymphomas (NHLs) are tumours of the lymphatic, haematopoietic, and related tissues. The hallmark of NHL is clonal proliferation of lymphoid cells corresponding to different stages of differentiation of

normal B cells, T cells, or natural killer (NK) cells. Diffuse large B-cell lymphomas (DLBCL) is a group of lymphoid neoplasms that originate from mature peripheral B lymphocytes from proliferative centres.

The etiology of most DLBCLs remains unclear. There are many factors with a proven causal relationship to the disease, including environmental, infectious, immunologic, and iatrogenic ones.

Diffuse large B-cell lymphomas are the most common group of lymphomas among all lymphoid malignancies (approx. 35%), including aggressive lymphomas (approx. 80%). In Europe, the incidence of DLBCL is estimated to be about a dozen cases per 100,000 of the general population per year and increases with age, from 2/100,000 at age 20-24, to 45/100,000 at age 60-64, to 112/100,000 at age 80-84.

According to KRN data, in 2018, diffuse non-Hodgkin's lymphomas (ICD-10: C83) affected 1541 people (crude incidence rate of 4.27/100,000 in men and 3.77/100,000 in women), while other and unspecified forms of non-Hodgkin's lymphoma (ICD-10: C85) were diagnosed in 881 patients (crude incidence rate of 2.43/100,000 in men and 2.16/100,000 in women).

The prognosis of patients with DLBCL depends primarily on the stage of the disease and prognostic factors. The rate of complete response (CR) in Ann Arbor stage I-II patients is nearly 100% and 5-year survival is at over 85%. At Ann Arbor stage III-IV, the CR rate is approximately 75% and 5-year survival is at the level of 50-60%. Most recurrences occur in the first 3 years of the disease, with only 10% occurring more than 5 years after the end of treatment. Intensive salvage therapy assisted with auto-HSCT is feasible in no more than 50% of patients with recurrence and leads to a cure only in a small percentage (approx. 10%) of them. In patients in whom intensive salvage therapy and auto-HSCT cannot be applied due to age, poor general condition, or concomitant diseases, the prognosis is decidedly poor, with a median life expectancy of less than a few months.

Alternative health technology

Taking into account clinical guidelines and technologies currently financed from public funds, salvage chemotherapy (excluding pixantrone) 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).

Given that pixantrone is a reimbursed therapy used for the indication analysed and recommended by clinical practice guidelines, it should also be a comparator for Kymriah.

Description of the benefit named in the application

Kymriah is registered as an advanced therapy product, based on an opinion of the Committee for Advanced Therapies (CAT) operating within the framework of EMA. In addition, Kymriah is classified to 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 assessment 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 is adult patients with recurrent or refractory diffuse large B-cell lymphoma (DLBCL) (trade secret)

No studies were found that would directly compare Kymriah (tisagenlecleucel, TIS) with salvage chemotherapy for the indication in question.

Clinical analysis included:

- two single-arm primary studies on the use of Kymriah in patients with diffuse large B-cell lymphoma (DLBCL):
    - JULIET study, a multicentre phase II clinical trial involving 167 patients (Schuster 2018 publication, Schuster 2018a conference poster and conference abstracts: Schuster 2019a, Schuster 2019b, Andreadis 2019);
    - A2101J study, a phase IIa observational case-series study (description of 23 case series, Schuster 2017 publication).
- single-arm study on the use of salvage chemotherapy:
    - randomised CORAL trial, taking into account the results from two publications on the extended phases of the trial, i.e. Van den Neste 2017 (CORAL extension study 1, which included 75 patients who experienced a recurrence after ASCT) and Van den Neste 2016 (CORAL extension study 2, which included 203 patients who did not undergo a planned ASCT and who were candidates for a third-line treatment regimen). Regimens tailored to the recommendations of each participating country and centre were used as salvage therapy (e.g. ICE, DHAP, gemcitabine-containing regimen, CHOP) with or without rituximab;

The analysis presents a qualitative summary of the results for tisagenlecleucel (JULIET and A2101J) and the comparator (extended phases of the CORAL study).

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

In addition, the analysis included:

- PIX301 (Pettengell 2012), Eyre 2016 and Sancho 2020 studies, evaluating the efficacy of pixantrone treatment for the indication analysed. PIX301 is a randomised international, multi-centre, open-label phase III clinical trial, while Eyre 2016 and Sancho 2020 are retrospective multi-centre observational studies.

The analysis evaluated, among other things, the following endpoints:

- overall response rate (ORR)
- overall survival (OS),
- progression-free survival (PFS),
- event-free survival (ESF),
- Quality of life.

The reliability of the included single-arm studies was assessed using the criteria of the NICE scale. The JULIET study was rated at 7 out of 8 points, while the A2101J study was rated at 6 out of 8 points.

Efficacy

<u>Qualitative summary of results from trials for tisagenlecleucel and salvage therapy</u>

Probability of overall survival:

- tisagenlecleucel (TIS)
    - 48.2% after 12 months,
    - 40.4% after 2 years,
    - 36.2% after 3 years – JULIET study
- salvage chemotherapy

- 30.4% after 12 months,
- 15.7%. after 2 years (among patients who were not eligible for ASCT) – CORAL study.

Median overall survival (OS):

- tisagenlecleucel (TIS)
  - 11.1 months – JULIET study
  - 8.3 months (ITT population) – JULIET study
  - 22.2 months – A2101J study
- salvage chemotherapy
  - 5.8 months – CORAL study.

Overall response rate (ORR):

- tisagenlecleucel (TIS)
  - 52 - 54%:
    - CR: 38.3% - 40%, PR: 12-14% – JULIET study
    - CR: 43% – A2101J study
- salvage chemotherapy
  - 44% - 47.6%:
    - CR: 32-33%, PR: 12-14.5% – CORAL study.

Event-free survival (EFS), progression-free survival (PFS), time to response (TTR), duration of response (DoR), and quality of life were evaluated only in the studies for tisagenlecleucel.

(trade secret)

In the JULIET study, (trade secret).

Patient outcomes indicated a gradual improvement in the quality of life for patients who showed a response to treatment.

(trade secret)

Safety

Kymriah (tisagenlecleucel)

No treatment-related deaths were reported in the JULIET study (median follow-up period 19.3 months). Adverse events occurred in all patients analysed (111 patients), with 89% of them likely related to treatment.

Grade 3 and 4 adverse events occurred in 89% of patients, while in 63% of patients, they were suspected to be related to the treatment. Serious adverse events occurred in 65% of patients and were suspected to be related to treatment in 47% of patients.

Adverse events of special interest occurred in 80% of patients during the first 8 weeks of the follow-up period, including grade 3 and 4 adverse events in 33% and 24% of patients, respectively. The most common events of special interest that occurred during the first 8 weeks after infusion were cytokine release syndrome (58% of patients), cytopenias that did not resolve by day 28 (44%), infections (34%), neurologic events (21%), and neutropenic fever (15%).

The most common adverse events of any grade in the JULIET study were cytokine release syndrome, which occurred in 58% of patients, anaemia (48%), fever (35%), decreased neutrophil count (34%), decreased platelet count (33%), and diarrhoea (32%). In the JULIET study, 50 patients eligible for tisagenlecleucel treatment did not receive the drug. The most common reasons for withdrawal were death and physician decision (9.7% each). In addition, 4 patients of the 165 eligible for tisagenlecleucel-based therapy did not receive treatment before the data cut-off.

The most common adverse events in the A2101J study (median follow-up time - 28.6 months) suspected to be related to tisagenlecleucel therapy were cytokine release syndrome, which occurred in 57% of patients (16 persons), and neurotoxicity, which occurred in 39% of patients (11 persons). The A2101J study only reported that

cytokine release syndrome was not the cause of death in any of the patients studied. In contrast, the most common reason for loss of patients was an insufficient number of T cells to produce CTL019 cells (21.7%) and rapid disease progression (13%).

Salvage chemotherapy

The safety profile of the therapies used, including death rates, was not analysed in detail as part of the extended phases of the CORAL study.
In the CORAL study, 82 patients in the R-ICE group (40%) and 64 (33%) in the R-DHAP group were lost from treatment after three cycles of induction. During the consolidation phase, 7 patients (6%) in the R-ICE arm and 6 (5%) in the R-DHAP arm were lost.

Additional safety information

The safety assessment for Kymriah 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 multi-centre registration clinical trials.

Diffuse large B-cell lymphoma (DLBCL)

The adverse reactions listed below were observed in 115 patients who received Kymriah by infusion during a single, multi-centre, international, global study, i.e. the ongoing CCTL019C2201 registration clinical trial (JULIET).

The most common non-haematologic adverse reactions were cytokine release syndrome (57%), infection (58%), fever (35%), diarrhea (31%), nausea (29%), fatigue (27%), and hypotension (25%).

The most common haematologic adverse reactions were decreased lymphocyte count (100%), decreased white blood cell count (99%), decreased haemoglobin (99%), decreased neutrophil count (97%), and decreased platelet count (95%).

Grade 3 and 4 adverse events were reported in 88% of patients. The most common grade 3 and 4 non-haematologic adverse reactions were infection (34%) and cytokine release syndrome (23%). The most common (>25%) abnormalities in grade 3 and 4 haematologic laboratory test results were: decreased lymphocyte count (95%), decreased neutrophil count (82%), decreased white blood cell count (78%), decreased haemoglobin (59%), and decreased platelet count (56%). Grade 3 and and 4 adverse events were more frequently observed within the first 8 weeks after infusion (82%) compared to over 8 weeks after infusion (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.

Kymriah is on the EMA list for medicinal products subject to additional monitoring.

Limitations

The major limitation to the reliability of the analysis presented here is the lack of randomised trials directly comparing the technology covered by the application with the selected comparator (salvage chemotherapy) in the population in question.

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;
- (trade secret)
- the only sources on the efficacy of the drug technologies discussed were single-arm clinical trials (for both Kymriah and the alternative intervention);
- (trade secret)
- the qualitative summary of results from studies for tisagenlecleucel (JULIET, A2101J) and for salvage therapy (CORAL study) has some limitations due to the heterogeneity of the included trials;
- failure to include in the analysis all alternative technologies available and reimbursed in the indication evaluated (i.e. pixantron);
- some results in the JULIET study were presented only as conference abstracts;

- an assessment of the effect of the therapies examined on quality of life was performed only in the registration study for TIS (JULIET);
- conference abstracts on quality of life only analysed changes in quality of life for patients who responded to treatment, making it impossible to assess the impact of tisagenlecleucel on quality of life for all patients, regardless of treatment success;
- the lack of a complete assessment of the comparator safety profile in the included studies precludes a reliable comparison of the evaluated intervention with salvage therapy in this regard.

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 (46years) from the perspective of a public payer – the entity required to fund the services from public funds, i.e. the National Health Fund (NFZ)

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

- drugs – the intervention in question and chemotherapy drugs,
- haematopoietic cell transplantation and the cost of follow-up treatment as well as the monitoring of patients after transplantation;
- treatment of adverse events,
- diagnosis and treatment monitoring.

The cost of potential therapies used to sustain CAR-T cell activity was not included in the analysis.

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 salvage chemotherapy comparison was: (trade secret).

(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)

- the percentages of patients who will actually undergo HSCT after Kymriah or salvage chemotherapy may differ from those assumed in the analysis;
- the chemotherapy regimens whose efficacy was considered in the comparator arm do not overlap with the regimens for which costs were estimated;
- the estimated programme cost for the technology in question was based on (trade secret);
- the model did not take into account the impact of adverse events, other than those leading to an admission to an intensive care unit, on quality of life during the course of treatment;
- it was assumed that the performance of HSCT, both allo- and auto-HSCT, was associated with an annual decrease in usefulness of -0.30. The above assumption may have the effect of lowering QALYs on the comparator side due to more frequent transplantations in this patient group;
- sensitivity analyses for most parameters tested alternative values set arbitrarily, without providing any justification for them;
- inconsistencies between the data given in the economic analysis and the data in the submitted model;
- a change was noted in the cost of bendamustine, oxaliplatin, rituximab and epirubicin compared to those adopted in the applicant's analysis;
- failure to include in the analysis all alternative technologies available and reimbursed in the indication evaluated (i.e. pixantron);

Own calculations of the Agency

Own calculations were made to update the applicant's calculations with respect to the cost-effectiveness threshold of PLN 155,514/QALY and current prices of drugs used in drug and chemotherapy programmes (Communication of the Drug Management Department of 31 December 2020).

The value of ICUR estimated with the above assumptions was (trade secret)

With the ICUR value estimated in own calculations, the designated threshold value of the drug net selling price at which the cost of an additional quality-adjusted life year is equal to the threshold amount referred to in Art. 12 point 13 and Art. 19 sec. 2 point 7 of the Act, after taking into account the updated value of the threshold, is (trade secret)

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.

Own calculations of the Agency

The value of the official selling price of Kymriah at which the cost of its use is not higher than the cost of the comparator (salvage chemotherapy – R-IVE regimen) 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 the 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 (NFZ).

Direct medical costs were taken into account, in accordance with the CUA.

The applicant 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;
- analyses are based on the content of the drug programme (trade secret);
- not all available alternative technologies have been taken into account.

Own calculations of the Agency

Own calculations were made taking into account (trade secret) and current prices of drugs used in drug and chemotherapy programmes (Communication of the Drug Management Department of 31 December 2020).

After incorporating the above assumptions into the applicant's model, the total incremental expenses (trade secret), which does not significantly affect the results and conclusions of the analysis.

Comments on the proposed risk-sharing scheme

(trade secret)

Comments on the drug programme

In accordance with the information provided in the reimbursement application, the applicant is seeking funding for the drug under the new drug programme "Treatment of diffuse large B-cell lymphoma (ICD-10 C83, C85) with tisagenlecleucel"

(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

Three clinical recommendations related to the indication named in the application were identified, issued by:

- Polskie Towarzystwo Onkologii Klinicznej (Polish Society of Clinical Oncology) (PTOK 2020);
- National Comprehensive Cancer Network (NCCN 2020);
- European Society for Medical Oncology (ESMO 2015/2020).

In the guidelines describing the management of diffuse large B-cell lymphoma, CAR-T therapy is recommended by the American NCCN and European ESMO (recommendations adapted in view of the SARS-COV-2 pandemic). CAR-T therapy is not mentioned in the 2020 Polish PTOK guidelines.

Polish PTOK 2020 guidelines in patients with recurrent/refractory DLBCL recommend salvage treatment in the form of subsequent chemotherapy followed by auto-HSCT if a complete response is achieved. The guidelines indicate that patients ineligible for auto-HSCT may be treated with polatuzumab vedotin (especially in combination with bendamustine and rituximab) or, after the failure of at least two lines of treatment, with pixantrone. According to the guidelines, some patients experiencing recurrence after auto-HSCT may be potential candidates for next-line salvage treatment and an allo-HSCT procedure. In patients who have not responded to second-line therapy, participation in clinical research on new molecules is also recommended.

American 2020 NCCN guidelines recommend therapy with modified CAR-T lymphocytes for patients achieving partial response to second-line treatment and for patients with no response or disease progression despite second-line treatment. Chemotherapy from among the recommended regimens in the second and subsequent lines of treatment, participation in clinical trials, palliative radiotherapy of the involved site, or best supportive care (BSC) are also recommended in this line of treatment. Allo-HSCT is also recommended in selected cases.

ESMO 2015 guidelines for at least second-line treatment of DLBCL recommend rituximab-based chemotherapy regimens and, if there is a response, auto-HSCT. Radiation therapy and allo-HSCT are also recommended for patients with refractory disease, early relapse or relapse after auto-HSCT. The guidelines also mention pixantrone but recommend that patients be included in clinical trials for new drugs first. In the 2020 ESMO recommendations, adapted due to the SARS-COV-2 pandemic, with regard to refractory DLBCL lymphoma, experts recommend CAR-T therapy in patients with high priority, that is patients whose condition is immediately life-threatening, clinically unstable, or when the expected benefit of the intervention qualifies it as a priority.

Reimbursement recommendations

The search found 4 positive recommendations (GBA 2020, SMC 2019, HAS 2018, AIFA 2019) emphasising that the real clinical benefit of Kymriah is significant. However, it is worth noting that the recommendations indicate the need to evaluate the efficacy and safety of Kymriah over a longer follow-up period.

Among conditionally positive recommendations (CADTH 2019, NICE 2019, MSAC 2019), the justifications point to an uncertain benefit associated with the use of the proposed therapy due to data from low-quality studies (single-arm study) as well as a lack of long-term safety and efficacy data. The recommendations also address the issue that this therapy is highly expensive, so a positive decision is contingent on a reduction in the price of Kymriah and on the use of measures to reduce the risks associated with funding this therapy.

The Irish HTA Agency (NCPE 2019) issued a conditional negative decision and does not recommend public funding for Kymriah unless the responsible party provides conditions that reduce the value of the therapy's cost-effectiveness ratio in relation to the currently used therapies by reducing the price.

The Netherlands HTA Agency issued a negative decision and does not recommend the inclusion of Kymriah on the list of reimbursable drugs due to the high uncertainty regarding the superiority of tisagenlecleucel over standard treatment in terms of efficacy. However, the recommendation indicates that if new data on the efficacy and safety of the therapy emerge, this may provide the basis for a re-evaluation for inclusion of Kymriah in the reimbursement scheme.

Two of the recommendations found provide drug funding conditions. In Australia (MSAC 2019), the public payer stipulates, among other things, that there will be no payment for tisagenlecleucel in the event of failed infusion and no payment for treatment for patients in whom the infusion of modified lymphocytes was not performed. Italy (AIFA 2019), on the other hand, indicated that the funding for Kymriah will be provided on a "payment at result" basis. The recommendation states that Kymriah is the first medicinal product to be funded under such conditions.

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

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Basis for the recommendation

The recommendation was prepared under an order of the Minister of Health of 25 September 2020 (reference number: PLR.4500.161.2020.21.AP), regarding the preparation of the President's recommendation on the evaluation of Kymriah (tisagenlecleucelum) under the programme: "Treatment of diffuse large B-cell lymphoma (ICD-10 C83, C85) with tisagenlecleucel", 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), having received the Transparency Council Position No. 11/2021 of 1 February 2021 on the evaluation of Kymriah (tisagenlecleucelum) under the program: "Treatment of diffuse large B-cell lymphoma (ICD-10 C83, C85) with tisagenlecleucel".

References

1. Transparency Council Position No. 11/2021 of 1 February 2021 on the evaluation of Kymriah (tisagenlecleucelum) under the programme: "Treatment of diffuse large B-cell lymphoma (ICD-10 C83, C85) with tisagenlecleucel"
2. Report No. OT.4331.38.2020 Application for reimbursement of the medicinal product Kymriah (tisagenlecleucelum) under the programme: "Treatment of diffuse large B-cell lymphoma (ICD-10 C83, C85) with tisagenlecleucel".