HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
24 MARCH 2021

The legally binding text is the original French opinion version

tisagenlecleucel
KYMRIAH 1.2 x 10^6 - 6 x 10^8 cells dispersion for infusion

Re-evaluation

Key points

Favourable opinion for maintenance of reimbursement in the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy.

What therapeutic improvement?

Maintenance of therapeutic improvement compared to historic management based on various chemotherapies.

Role in the care pathway?

The choice of treatment is based on a systematic assessment of the main prognostic criteria for the disease. The IPI (International Prognostic Index) is used as a prognostic index for aggressive NHL. This takes into account the patient's age, the ECOG performance score, the lactate dehydrogenase (LDH) level, the disease stage and the extent of extranodal involvement.

The therapeutic options proposed for DLBCL are chemotherapy, immunotherapy with monoclonal antibodies and autologous T lymphocytes with an anti-CD19 chimeric antigen receptor (anti-CD19 CAR-T cells), radiotherapy and haematopoietic stem cell transplantation (primarily used at the time of relapse after salvage therapy).

The first-line treatment of choice is based on R-CHOP induction immunochemotherapy (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone). Almost 2/3 of patients achieve remission after this treatment.

As second-line therapy in patients not responding to this first-line treatment (primary refractory disease) or who relapse following this treatment, the therapeutic approach depends on the patient's eligibility for high-dose chemotherapy with the objective of performing allogeneic haematopoietic stem cell transplantation. The major eligibility criteria for high-dose chemotherapy with autologous haematopoietic stem cell transplantation are: chemosensitive disease, adequate performance status (no major organ dysfunction) and age < 65 to 70 years (although there is no consensus concerning this threshold).

In patients in whom high-dose chemotherapy can be envisaged, "salvage" chemotherapy (generally R-DHAP, R-ICE or R-GDP) should be proposed initially, followed by high-dose chemotherapy (intensification) and autologous haematopoietic stem cell transplantation in the event of a response (chemosensitive patients).

In patients who are not candidates for subsequent high-dose chemotherapy, in particular due to their age and/or comorbidities, adapted chemotherapy protocols may be proposed.

Patients who are not eligible for autologous SCT, in particular due to their age or an inadequate response to salvage chemotherapy, may receive platinum and/or gemcitabine-based immunochemotherapy (in particular R-GemOx or R-DHAP regimens) not followed by conditioning for transplant. None of the immunochemotherapies currently recommended have a marketing authorisation.

From the third line of treatment, in patients in whom autologous SCT has failed or having relapsed following two previous treatment lines, two medicinal products based on CAR-T cells, YESCARTA (axicabtagene ciloleucel) and KYMRIAH (tisagenlecleucel), are currently recommended in patients whose life expectancy is compatible with the treatment timeframes (between apheresis and injection). According to the first real-world data, this timeframe, of around 5 to 7 weeks for French patients, is similar for both medicinal products and requires the use of treatments pending injection. In other cases, no chemotherapy (monotherapy or combination therapy) is considered to be a standard of care and the treatment options are limited. Depending on the clinical situation, the following may be envisaged:

- for relapsed patients (excluding refractory patients): additional intensive chemotherapy with the objective of performing allogeneic haematopoietic stem cell transplantation if the patient is eligible; where applicable an autologous transplant. An allogeneic transplant is generally considered in patients under the age of 70, in the absence of major comorbidities, in the presence of a donor (availability of a graft) and in the event of a complete response (or very good partial response) following the chemotherapy regimen;
- other chemotherapies;
- implementation of palliative care.

Role of the medicinal product in the care pathway

The new data available is not of a nature to modify the role of KYMRIAH (tisagenlecleucel) in the care pathway defined in 2018 by the Transparency Committee.

KYMRIAH (tisagenlecleucel) remains a third or later-line treatment for diffuse large B-cell lymphoma (DLBCL) in patients for whom at least 2 lines of systemic treatment have failed, with a history of autologous transplantation for eligible patients.

In view of the available data (numerous limitations of the indirect comparisons provided and immaturity of real-world data), the role of KYMRIAH (tisagenlecleucel) compared to YESCARTA (axicabtagene ciloleucel) in the shared DLBCL indication cannot be robustly established. The Committee nevertheless highlights that, according to the expert opinions and the first follow-up data, it is possible that clinical responses may be more numerous and more rapid under YESCARTA (axicabtagene ciloleucel) than under KYMRIAH (tisagenlecleucel) but with more frequent acute toxicities, particularly neurological, for the former. However, KYMRIAH (tisagenlecleucel) has a logistical advantage compared to YESCARTA (axicabtagene ciloleucel) due to the possibility of freezing the apheresis product.

Therefore both these medicinal products provide an additional response to the identified medical need in relapsed or refractory DLBCL as third or later-line therapy. The choice of one over the other should be made on the basis of the patient's condition, the availability of production slots, the expected clinical response and the safety profile.

Due to the timeframes for product availability (from determination of patient eligibility for CAR-T cell treatment, leukapheresis, the production of the genetically modified cells and lymphodepleting chemotherapy through to transportation to the patient for reinjection) and the significant short-term toxicity, the general condition and life expectancy of patients eligible for KYMRIAH (tisagenlecleucel) must be compatible with these timeframes.

The Committee also highlights that:

- considering the high frequency of grade ≥ 3 adverse events (90% of patients), with, in particular, cytokine release syndromes, neurological adverse effects and possible hospitalisation in the ICU, as well as the constraints related to the need for a lengthy hospital stay and the potential distance from the patient's home of a qualified centre, it is essential to inform patients about these constraints and the risks,
- KYMRIAH (tisagenlecleucel) should be administered in a healthcare facility specifically qualified in the use of CAR-Tcells,
- the summary of product characteristics (SPC) and the risk management plan (RMP) must be complied with and special monitoring during and after treatment is required.

Special recommendations

The use of KYMRIAH (tisagenlecleucel) is limited to a small number of centres specifically qualified in the use of CAR-T cells given the complexity of the procedure, as stipulated in the order of 8 August 2019. In this context, the Committee highlights the importance of overall care (in particular including travel and local accommodation near healthcare facilities, where required), as reported by patient and user associations.

The Committee highlights the importance of ensuring patients, and their carers if applicable, having access to appropriate information on the complexity of the CAR-T procedure, the constraints related to prolonged hospitalisation and the risks to patients.

The Committee would like to see all stakeholders mobilised to provide responses to the remaining uncertainties at the next re-evaluation. To this end, the Committee calls for the participation of all qualified centres in the DESCAR-T registry in order to obtain exhaustive, high-quality observational data.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ Diffuse large B-cell lymphoma (DLBCL) is an aggressive non-Hodgkin lymphoma with an unfavourable prognosis in the event of multiple relapses and disease refractory to at least two treatment lines, as reported by patient and user associations.

◗ KYMRIAH (tisagenlecleucel) is a curative treatment for relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy.

◗ The new data available is not of a nature to modify the Committee's previous conclusions. The efficacy/adverse effects ratio of KYMRIAH (tisagenlecleucel) remains high in the short term only and is still to be determined in the longer term, particularly in terms of maintenance of clinical remission and achievement of full recovery.

◗ There are few alternatives (see section 05 of the present opinion)

◗ KYMRIAH (tisagenlecleucel) remains a third or later-line treatment, in relapsed or refractory patients, in good general condition, with a life expectancy and disease progression compatible with the waiting time before administration.

Public health impact

Considering:

- the seriousness of the disease, particularly in relapsed or refractory patients after two or more lines of systemic therapy, which is life-threatening in the short term, as reported by patient and user associations,
- its prevalence,
- the inadequately met medical need at this stage of the disease prior to the arrival of CAR-T cell-based medicinal products,
- the partial response to this need, due to:
    - the additional impact on morbidity and mortality in the short term, but which remains to be determined in the long term, particularly in terms of full recoveries;
    - the lack of demonstrated impact on quality of life in the absence of relevant data;
    - the limitations of the indirect comparisons, making precise quantification of the clinical effect difficult, and the limitations of indirect comparisons with YESCARTA (axicabtagene ciloleucel)
    - the transposability to patients at this stage of the disease that is not guaranteed considering the immaturity of the observational data from the French DESCAR-T registry;
    - the long timeframe between eligibility of patients and reinjection of CAR-T cells, estimated to be 5 to 7 weeks based on real-world data, and persistent uncertainties with respect to the clinical consequences, in particular in terms of efficacy, of the different phases in the procedure (from eligibility to administration);
- the absence of an improvement in the care pathway of patients (as the dossier currently stands) due to:
    - hospitalisations, including in the ICU (particularly during the first 10 days following infusion or in the event of the onset of early signs or symptoms of cytokine release syndrome and/or neurological effects), whereas the third and later-line treatment of lymphoma can be administered in an outpatient context in a day hospital,
    - hospitalisation of patients far from their homes,
    - the need to remain close to this hospital for monitoring for at least 4 weeks following infusion,

- the impact on the organisation of care, despite the logistical advantage of being able to freeze the apheresis product with KYMRIAH (tisagenlecleucel), considering the need for
    - accreditation of hospitals based on precise criteria,
    - coordination between the various departments of centres authorised to treat patients with CAR-T cells (laboratories, internal pharmacy, clinical departments, etc.),

KYMRIAH (tisagenlecleucel) is unlikely to have an impact on public health, on the basis of currently available data.

Considering all these elements, the Committee deems that the clinical benefit of KYMRIAH (tisagenlecleucel) remains <u>substantial</u> in the MA indication.

The Committee issues a favourable opinion for maintenance of inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the "treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy" and at the MA dosages.

Clinical Added Value

Considering:

- **the updated efficacy data in the ITT population of the pivotal JULIET study, which confirms the previously analysed results, particularly in terms of complete response (around 24% of patients included, of whom 16% were still in response with a median follow-up of 40.3 months) and overall survival (median of 8.2 months; survival probability at 40.3 months of 27%), in life-threatening clinical situations in which the treatment options are limited and do not enable remission to be envisaged,**
- **the updated indirect comparison results, which, despite their limitations, suggest a benefit of KYMRIAH (tisagenlecleucel) compared to standard treatments,**
- **the safety profile marked by significant short-term toxicity,**
- **but the initial uncertainties identified, which persist despite the Transparency Committee's requests, particularly with respect to:**
    - **the exact effect size compared to historic management, in the absence of any robust comparison,**
    - **the real-world efficacy of KYMRIAH (tisagenlecleucel) in view of the immaturity of the data in the French DESCAR-T registry (11 active centres, 44 patients treated, median follow-up of 3.3 months since eligibility, numerous missing and unmonitored data), not enabling the results of the pivotal JULIET study to be confirmed at this stage**
    - **maintenance of the clinical efficacy in the medium and long term, particularly concerning achievement of full recovery for patients in lasting remission,**
    - **and the absence of medium and long-term safety data,**

the Committee considers that its previous conclusions are not liable to be modified. On the basis of currently available data, KYMRIAH (tisagenlecleucel) still provides a minor clinical added value (CAV IV) in terms of efficacy compared to the historic management of relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy, based on various chemotherapies.