OPINION ON MEDICINAL PRODUCTS

tisagenlecleucel

KYMRIAH 1,2 x 10 exp6 and 6 x 10 exp8 cells,

dispersion for infusion

New indication

Adopted by the Transparency Committee on 7 December 2022

SUMMARY

The legally binding text is the original French opinion version

Key points

Approval of reimbursement for the treatment of adult patients presenting with follicular lymphoma after at least two lines of treatment:

- whose disease is refractory;
- or who relapse during or within 6 months following the end of their maintenance treatment;
- or who relapse after autologous haematopoietic stem cell transplantation.

Disapproval of reimbursement for other marketing authorisation contexts.

Therapeutic improvement?

No therapeutic improvement.

Role in therapeutic strategy?

The histological grading of follicular lymphoma is defined by WHO according to the centroblast count observed with a microscope. Grade 1-2 FL, and generally grade 3a, are indolent forms, whereas grade 3b FL cases are considered as aggressive forms of FL and treated as diffuse large B-cell lymphoma.[Erreur ! Signet non défini.]

The treatment initiation criteria are signs of clinical progression (inflammatory syndrome, LDH, beta 2 microglobulin or impact on general state of health assessed by the ECOG performance score) and the presence of a large or compressive tumour mass.

Currently, no treatments, including intensifications with stem cell transplantation, can be expected to achieve recovery.

As a **first-line treatment**, according to national**Erreur ! Signet non défini.** and international guidelines[Erreur ! Signet non défini.], the therapeutic options are based on immuno-chemotherapy, i.e. an association of rituximab + chemotherapy (such as R-CHOP, R-CVP or R-bendamustine mostly) followed by maintenance treatment based on rituximab.**Erreur ! Signet non défini.** In some cases, rituximab monotherapy treatment may be recommended (off-label). As an alternative to rituximab, obinutuzumab (GAZYVARO) may also be used in induction in association with chemotherapy (such as CHOP, CVP or bendamustine mostly), followed by maintenance treatment based on Obinutuzumab.**Erreur ! Signet non défini.**

In the event of failure to respond or progression, a **second-line** regimen is proposed. A further tumour sample biopsy optionally guided by PET-scan is recommended to rule out conversion to diffuse large B-cell lymphoma. The second-line treatment is dependent on the first-line treatment received, the type and duration of remission from the previous line and the spread of the disease. The treatments available **from the second line are**:

- a new immuno-chemotherapy regimen (R-CHOP, R-CVP, R-bendamustine, Obinutuzumab-bendamustine)**Erreur ! Signet non défini.** **Erreur ! Signet non défini.** **Erreur ! Signet non défini.**
- or radio-immunotherapy if permitted by the degree of medullary invasion,
- or autologous stem cell transplantation if permitted by age and particularly in the case of early relapse,
- or autologous stem cell transplantation which may also be proposed for some high-risk younger patients in the event of subsequent relapse or also for patients failing to respond to autologous transplantation,

For patients non-refractory to rituximab, in contexts where CHOP, bendamustine or CVP type chemotherapy is not feasible, lenalidomide (REVLIMID) may be used in association with rituximab.**Erreur ! Signet non défini.**

For **third and subsequent lines**, treatment with idelalisib (ZYDELIG) may be proposed (in the case of double-refractory disease).[Erreur ! Signet non défini.]

From the **fourth line**, the proprietary medicinal product YESCARTA (axicabtagene ciloleucel) which has been granted an early-access authorisation for this indication, may be proposed.[Erreur ! Signet non défini.]

Role of the medicinal product

KYMRIAH (tisagenlecleucel) is a third-line or subsequent treatment for relapsed follicular lymphoma (during or within 6 months following the end of their maintenance treatment, or relapsing

after autologous haematopoietic stem cell transplantation) or refractory follicular lymphoma after the second or subsequent line of systemic treatment.

Given the lack of methodologically robust comparative data, it is not possible to specify the role of KYMRIAH (tisagenlecleucel) in relation to the other therapeutic alternatives available.

Due to the time needed to make the product available (including the time to determine whether the patient is eligible for CAR-T cell treatment, leukapheresis, genetically-modified cell production, lymphodepleting chemotherapy until the patient is presented for reinjection) and the significant short-term toxicity, the general state of health and life expectancy of patients eligible for KYMRIAH (tisagenlecleucel) must be compatible with these time-frames.

The Committee also points out that:

- considering the high frequency of grade ≥ 3 adverse events (81.4% of patients of the ELARA pivotal study) and potential admissions to intensive care, and the constraints associated with the need for long hospital stays and the possible distance from the qualified centre, it is crucial that patients receive information on these constraints and the risks involved,
- KYMRIAH (tisagenlecleucel) must be administered in a healthcare organisation specifically qualified for the use of CAR-T cells,
- the summary of product characteristics (SPC) and the risk management plan (RMP) must be adhered to, and special monitoring during and after treatment is required.

Special recommendations

The use of KYMRIAH (tisagenlecleucel) is limited to a restricted number of centres qualified for the use of CAR-T cells, given the complexity of the procedure, as set out in the order of 19 May 2021. In this context, the Committee points out the importance of comprehensive care (particularly including travel and accommodation close to qualified healthcare organisations, where necessary) as reported by patient and user associations.

The Committee points out the importance, for patients and their caregivers where applicable, of having information tailored to the complexity of the CAR-T procedure, the constraints associated with long hospital stays, and the risks involved for the patient.

The Committee calls for commitment from all stakeholders to ensure that the uncertainties in this dossier are addressed by the time of its reassessment. In this aim, the Committee calls for the participation of all qualified centres of the required category in order to obtain high-quality and exhaustive observational data.

Committee's conclusions

Clinical Benefit

- Follicular lymphomas are life-threatening slow-growing non-Hodgkin's lymphomas.
- The proprietary medicinal product KYMRIAH (tisagenlecleucel) is a curative medicinal product.
- The efficacy/adverse effect ratio is significant.
- Medicinal and non-medicinal (stem cell transplantation) alternatives are available.
- KYMRIAH (tisagenlecleucel) is a third-line or subsequent treatment for relapsed follicular lymphoma (during or within 6 months following the end of their maintenance treatment, or relapsing after autologous haematopoietic stem cell transplantation) or refractory follicular lymphoma after the second or subsequent line of systemic treatment.

  In other clinical contexts including follicular lymphoma patients who have relapsed after 6 months following the end of their maintenance treatment, KYMRIAH (tisagenlecleucel) has no role in the therapeutic strategy.

Public health benefit

Considering:

- the severity of the disease, which is life-threatening in the short term;
- its incidence,
- the medical need partially met by the alternatives available,
- the lack of response to the identified need (lack of evidence of additional impact on morbidity-mortality and/or on quality of life),
- the lack of elements supporting a lack of deterioration of the care and/or life pathway, particularly considering the systematic hospitalisation for the first 10 days following infusion and the need for patients to remain close to the qualified healthcare organisation for at least 4 weeks post-infusion,
- the impact on delivery of care, despite the logistic benefit provided by the option to freeze the apheresis of KYMRIAH (tisagenlecleucel) considering the need for
  - accreditation of organisations according to precise criteria,
  - coordination between the different departments of centres authorised to treat using CAR-T cells (laboratories, in-house pharmacy, clinical departments, etc.),

KYMRIAH (tisagenlecleucel) is not likely to have an additional impact on public health.

Considering all of these elements, the Committee deems that the actual clinical benefit of KYMRIAH (tisagenlecleucel) is:

- **significant for the treatment of adult patients presenting with follicular lymphoma after at least two lines of treatment whose disease is refractory, or who relapse during or within 6 months following the end of their maintenance treatment, or who relapse after autologous haematopoietic stem cell transplantation.**
- **insufficient to justify public funding in the other marketing authorisation contexts.**

The Committee approves inclusion in the list of proprietary medicinal products approved for community use for the treatment of adult patients presenting with follicular lymphoma after at least two lines of treatment whose disease is refractory, or who relapse during or within 6 months following the end of their maintenance treatment, or who relapse after autologous haematopoietic stem cell transplantation and at the marketing authorisation dosages.

The Committee disapproves inclusion in the list of proprietary medicinal products approved for community use for the other marketing authorisation contexts.

Clinical Added Value

Within the scope of reimbursement

Considering:

- the efficacy data from a non-comparative phase 2 study, with a complete response percentage of 68.1% [95%CI: [58,8; 78,3]) with a median survival of 28.9 months, in a life-threatening context,
- the uncertainty around the relative efficacy of this treatment considering the lack of direct comparison and the methodological weakness of the indirect comparison furnished, in a context where a direct comparison to an available therapeutic alternative with a robust methodology was possible,
- the safety profile marked by significant short- and medium-term toxicity,
- the uncertainties around clinical efficacy and safety in the longer term,

the Transparency Committee deems that, based on the current data, and particularly pending the findings of the randomised phase III study, KYMRIAH (tisagenlecleucel) provides no clinical added value (CAV V) for the treatment of adult patients presenting with follicular lymphoma after at least two lines of treatment whose disease is refractory, or who relapse during or within 6 months following the end of their maintenance treatment, or who relapse after autologous haematopoietic stem cell transplantation.