HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New medicinal product
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TRANSPARENCY COMMITTEE OPINION SUMMARY

KYMRIAH (tisagenlecleucel), anti-CD19 CAR T

High clinical benefit in refractory B-cell acute lymphoblastic leukaemia, relapsed after transplantation, or after the second or later relapse in young adult patients up to the age of 25 years, and moderate clinical added value in the therapeutic strategy.

Main points

- KYMRIAH has been granted a marketing authorisation for the treatment of children and young adults up to the age of 25 years suffering from refractory B-cell ALL, relapsed after transplantation, or after the second or later relapse.
- CAR T cells are a gene therapy consisting of autologous T lymphocytes harvested by leukapheresis, then genetically modified *ex vivo* to express a chimeric receptor antigen targeting protein CD19 found on the B cell line. The re-injected anti-CD19 CAR T cells then multiply and activate *in vivo* after binding to target cells expressing CD19, thus inducing their apoptosis.
- High rates of complete remission have been achieved in two non-comparative studies (approximately 67% in the intention-to-treat population). During the last follow-up analysis, these remissions were maintained in approximately 40% of patients. KYMRIAH is associated with frequent adverse events whose severity can potentially require a stay in intensive care.
- Further data are awaited, considering the uncertainties concerning the efficacy, tolerance and complexity of the treatment process.
- The use of anti-CD19 CAR T is limited to a small number of specifically qualified centres.

Other indication*

KYMRIAH has also been granted a marketing authorisation for the third-line or later treatment of refractory or recurrent diffuse large B-cell lymphoma (DLBCL).

Therapeutic strategy

- As first-line treatment, the therapeutic strategy is based on induction polychemotherapy followed by consolidation chemotherapy, then by maintenance chemotherapy if complete remission is achieved. These treatments must be combined with a tyrosine kinase inhibitor (TKI) targeting the BCR-ABL fusion protein in Philadelphia chromosome positive ALL. The benefit of allogenic haematopoietic stem cell transplantation (HSCT) after first-line remission has not been clearly established in children and young adults, though it may be recommended in patients at high risk of relapse (cytogenetic characteristics of leukaemia, minimal residual disease status after achieving complete remission).
- The complete remission rate after first-line treatment is high (90 to 95%). The prognosis of first-line refractory patients is generally poor. Their treatment includes a second induction chemotherapy, followed by allogenic HSCT for eligible patients, after achieving complete remission.
- Between 15 and 20% of patients, who have achieved complete remission after first-line treatment, relapse. Relapse treatment has not been standardised in this population, but may include:

* This summary does not cover this indication.

- a new line of induction polychemotherapy, followed by allogenic HSCT consolidation if a second remission is achieved and if the patient is eligible,
- anti-BCR-ABL TKIs in patients with Philadelphia chromosome positive ALL,
- inotuzumab ozogamicin inadults , with CD22 positive B-ALL,
- blinatumomab for CD19 positive B-ALL
- palliative care.

- After first-line relapse, long-term remissions may be observed if a second remission is achieved (approximately 50% in the event of late relapse and 25% for relapse during treatment). In patients presenting with a second relapse or a refractory disease, recovery is exceptional (between 0 and 15%) and the median survival time is generally of less than 6 months (expert opinion). At this stage of the disease, there is no standardised treatment. Allogenic HSCT is recommended if not performed after the first relapse.

- **Role of the medicinal product in the therapeutic strategy**
- KYMRIAH is a first-line treatment in children and young adults up to the age of 25 years suffering from refractory B-cell ALL, in the event of relapse after transplantation or after the second relapse.
- Due to the lack of comparative data, the role of KYMRIAH compared to its therapeutic alternatives is not known. Considering the restrictions for inclusion in clinical trials, its efficacy and safety are not known in patients pre-treated with anti-CD19 (e.g.: blinatumomab), in patients with CD19 negative ALL and in patients younger than 3 years old at the time of inclusion or older than 21 years old at the time of diagnosis.
- Due to the necessary delays (from determination of patient eligibility for CAR T cell treatment, to leukapheresis, cell transport before and aftermanufacturing , creation of the genetically modified cells and lymphodepletingchemotherapy beforeinfusion) and to the significant short-term toxicity, the general condition and life expectancy of patients eligible for KYMRIAH must be compatible with these time frames.

Clinical data

- The assessment of KYMRIAH in this indication is based on two phase II non-comparative studies (ELIANA pivotal study and ENSIGN supportive study).
- Of the 97 patients included in the ELIANA study, 79 were treated with KYMRIAH. In the effectively treated population (ITTm), the overall remission rate at 3 months (primary endpoint corresponding to the sum of complete remissions with or without haematological recovery) was of 82.3% (65/79), of which 62% (49/79) complete remissions with haematological recovery. By conservative analysis of the included population (ITT), the overall response rate was of 67% (65/79), of which 50.5% (49/97) complete remissions with haematological recovery. After a median follow-up period of 9.07 months, 29 patients (44.6%) were still in remission, 19 (25.3%) had suffered a relapse and 17 were excluded from the analysis, in particular for having received another treatment (transplantation, other CAR T, antineoplastic drugs, etc.). The median overall survival and event free survival were not reached. The results of the ENSIGN study are comparable, though limited due to the small number of patients who could be assessed in this study (n=42 of the 73 patients included).
- KYMRIAH safety is underpinned by high risks of cytokine release syndrome, infection, severe neurotoxicity, tumor lysis syndrome, long-term B cell depletion (hypogammaglobulinaemia) and unresolved cytopenia at D28. Depending on the severity of these adverse events, admission in intensive care unit may be required.
- Many uncertainties remain concerning the persistence of efficacy and long-term safety, considering the lack of comparative studies and the lack of available perspective. Manufacturing timelines meant that a non-negligible proportion of patients could not be treated. The variability of these times could impact the efficacy of KYMRIAH under actual treatment conditions.

Special prescription requirements

- Medicinal product for hospital use only
- Prescription reserved for haematology specialists or physicians with expertise in blood disorders
- KYMRIAH must be administered in a qualified healthcare institution.

Benefit of the medicinal product

- The actual clinical benefit* of KYMRIAH is high.
- KYMRIAH provides a moderate improvement in actual clinical benefit (IACB III) in the management strategy for children and young adults suffering from refractory B-cell ALL, recurrent after transplantation, or after the second or later relapse.
- Approval for hospital treatment.

* The actual clinical benefit (ACB) of a medicinal product consists of its benefit particularly on the basis of its clinical performances and the severity of the disease treated. The HAS Transparency Committee assesses the ACB, which may be high, moderate, low, or insufficient for the medicinal product to be covered by public funding.

** The improvement in actual clinical benefit (IACB) consists of the clinical improvement offered by a medicinal product compared to existing treatments. The HAS Transparency Committee assesses the IACB rating from I, major, to IV, minor. An IACB rating of V (equivalent to "no IACB") denotes a "lack of clinical improvement"