



## **Tisagenlecleucel (Kymriah®) for the treatment of DLBCL**

Summary of recommendations by *Zorginstituut Nederland* (National Health Care Institute, the Netherlands) dated 7 March 2019

*Zorginstituut Nederland* carried out an assessment of the medicinal product tisagenlecleucel (Kymriah®), whereby the following conclusion was reached.

On 5 September 2018, the Minister of VWS asked the *Zorginstituut* to issue advice on the pharmaceutical product, tisagenlecleucel-T (Kymriah®), in connection with its being made subject to article 2.1 of the Health Insurance Regulation (also known as being placed in the 'waiting room' or 'sluice'), due to its expected high costs. Products can only be accepted into the insured package after the *Zorginstituut* has advised on their inclusion in the insured package, and, where applicable, subject to Ministry negotiations to arrive at a financial arrangement with the supplier.

The Minister placed tisagenlecleucel in the waiting room for two indications:

- 1 Paediatric and young adult patients up to the age of 25 years with B cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or later relapse (hereafter referred to as r/r B cell ALL) Adult patients with a relapsed or refractory diffuse large-cell B-cell lymphoma (r/r DLBCL) after two or more lines of systemic therapy.

*Zorginstituut Nederland* has in the meantime completed its assessment of tisagenlecleucel for the first indication mentioned, r/r B cell ALL, and informed the Minister about it in our letter dated 18 December 2018.

This letter describes the *Zorginstituut's* advice in relation to r/r DLBCL to inform the Minister about the outcomes of our assessment.

During this assessment, advice was requested from the *Zorginstituut's* Scientific Advisory Board (WAR). Interested parties were also consulted during the assessment procedure.

### ***Zorginstituut's* findings**

Tisagenlecleucel is an autologous immunocellular cancer therapy. In order to produce tisagenlecleucel, patients' own T-cells have to be obtained via leukapheresis. These cells are subsequently genetically modified, *ex vivo*, using a lentiviral vector that codes for an anti-CD19 chimeric antigen receptor (CAR). After the patient has been pretreated with lympho-depletion-chemotherapy, the patient's own (autologous) CAR-T-cells (tisagenlecleucel) are returned to the patient via a single intravenous infusion.

The *Zorginstituut* is of opinion that there is insufficient evidence of the intended effects of tisagenlecleucel, making it uncertain whether there is a clinically relevant difference in the overall survival compared to salvage chemotherapy (+ a stem cell transplantation). This means that tisagenlecleucel does not comply with established medical science and medical practice for the treatment of adult patients with a recurrent or refractory diffuse large-cell B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.



The effectiveness and safety of tisagenlecleucel was studied in a single arm study (C2201). A single infusion of tisagenlecleucel leads to an estimated median prolongation of survival of 2.1 months in comparison with salvage chemotherapy (+ stem cell transplantation). The quality of the evidence is very low, because this difference is based on an indirect comparison with the most suitable historic control group (SCHOLAR-1) whereby the patients' characteristics differed considerably.

When correcting for a number of differences between patient characteristics via an MAIC (*matching adjusted indirect comparison*) analysis, the survival advantage of tisagenlecleucel in comparison with the most suitable historic control remained unclear due to a broad confidence interval.

There is a possible trend towards a relatively higher plateau in the survival curve for the C2201 study in comparison with the SCHOLAR-1 study (in the individual studies, without a matched comparison). However, this remains uncertain due to the relatively small number of patients, lack of a matched survival curve and 1-year survival rates.

Furthermore, the effect of tisagenlecleucel cannot be separated from the bridging therapy, which was given to more than 90% of the patients.

This means that the quality of the evidence will remain very low even with a longer follow-up duration.

#### **Advice**

Tisagenlecleucel does not fulfil the statutory criterion, 'established medical science and medical practice', for the above-named indication. For this reason we advise the Minister not to include tisagenlecleucel in the insured package.

New published data, if the results point towards a clinically relevant benefit of effectiveness, can be a starting point for reviewing whether tisagenlecleucel does comply with established medical science and medical practice.

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*The original text of this excerpt from advice of Zorginstituut Nederland was in Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's advice.*

*Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.*