HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

21 APRIL 2021

The legally binding text is the /original French opinion version

autologous anti-CD19-transduced CD3+ cells

TECARTUS 0.4 - 2 x 10^8 cells dispersion for infusion

First assessment

Key points

Favourable opinion for reimbursement in the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

What therapeutic improvement?

Therapeutic improvement compared to current treatment.

Role in the care pathway?

The therapeutic approach primarily depends on the stage of the disease, the tumour mass, the prognostic classification and the patient's age.

According to the treatment guidelines, first-line treatment in young patients (≤ 65 years) in good general condition is based on chemotherapy regimens including cytarabine, generally combined with rituximab, followed by autologous haematopoietic stem cell transplantation and maintenance therapy with rituximab. Elderly patients (> 65 years) or those not eligible for transplant, will receive immunochemotherapy (generally R-CHOP, R-BAC or R-Bendamustine, RiBVD, R-DHA, etc.) followed by maintenance therapy with rituximab. It should be noted that bortezomib (VELCADE) has an MA and is recommended in combination with rituximab, cyclophosphamide, doxorubicin and prednisone (VR-CAP) in previously untreated patients who are unsuitable for haematopoietic stem cell transplantation.

From the second line of treatment in relapsed and/or refractory patients, the guidelines mention the absence of any standard-of-care therapy in this disease. Treatment should be adapted on the basis of the characteristics of both the patient and the disease, as well as prior therapies and, in particular, the duration of remission. The authorised and recommended treatment options in patients with relapsed and/or refractory MCL are polychemotherapy regimens combined with rituximab (R-CHOP, R-DHAP, RiBVD R-Bendamustine, R-BAC etc.), followed by intensive chemotherapy with allogeneic haematopoietic stem cell transplantation in eligible patients, ibrutinib (IMBRUVICA), a Bruton's tyrosine kinase (BTK) inhibitor, lenalidomide (REVLIMID), an immunomodulatory agent, as well as temsirolimus (TORISEL), an m-TOR inhibitor, from the second relapse.

As regards ibrutinib (IMBRUVICA), at the time of its first assessment by the Committee in 2015, it was considered to be a salvage treatment for relapsed or refractory MCL based on non-comparative clinical data. When it was re-evaluated in 2017, based on a comparative study versus temsirolimus, the Transparency Committee considered that ibrutinib was a preferable option to temsirolimus on condition that the constraints related to its safety protocol, particularly for patients on antiplatelet or anticoagulant therapy, are complied with. The Committee also specified that the available data did not enable the success rate of potential allogeneic haematopoietic stem cell transplantation following IMBRUVICA (ibrutinib) therapy to be determined. Currently, ibrutinib is preferentially used from the first relapse, particularly in the event of early relapse, or in the event of refractory disease, considering recent grouped and long-term data reporting overall response rates of around 70%, including 27% complete responses, a median progression-free survival of 12.5 months and a superior overall survival in patients having received 1 prior treatment line. In these patients (use of ibrutinib from the first relapse), the median overall survival is estimated to be 24 months. Nonetheless, around two thirds of patients do not achieve a complete response with ibrutinib treatment and most patients will relapse within two years. The data available for post-ibrutinib relapse with an average of three prior lines of treatment report median overall survivals of 6 to 12 months. A recently published retrospective study reported an overall survival of 14 months (CI95% [8.1 – 19.8]) for the R-BAC combination for relapse following ibrutinib used as second-line therapy.

Lenalidomide (REVLIMID), possibly combined with rituximab, is considered to be a treatment option only in patients not eligible for transplantation and only in the absence of an available alternative treatment, and with close monitoring in the event of high tumour burden.

Although it is less used, temsirolimus (TORISEL) has an MA in refractory or relapsed patients and the Committee has positioned it in the care pathway as a third or later-line therapy.

It should be noted that bortezomib as monotherapy or in combination is regularly proposed off-label in clinical practice in the event of multiple relapses. Venetoclax (bcl-2 inhibitor) and obinutuzumab (anti-CD20) are sometimes used off-label. However, the available data is limited and their used in France is marginal in practice, and dependent of the centres.

Role of the medicinal product in the care pathway

TECARTUS (autologous anti-CD19-transduced CD3+ cells) is a third or later-line treatment for relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.

Due to the timeframes (from determination of patient eligibility for CAR-T cell treatment through to transportation to the patient for reinjection) and the significant short-term toxicity, the general condition and life expectancy of patients eligible for TECARTUS (autologous anti-CD19-transduced CD3+ cells) must be compatible with these timeframes. According to currently available data, the Committee considers that TECARTUS (autologous anti-CD19-transduced CD3+ cells) is the preferred treatment in these patients, subject to a production and transport time to qualified centres in France similar to that observed in the ZUMA-2 study.

Considering the high frequency of grade ≥ 3 adverse events (99% of patients), with, in particular, cytokine release syndromes and neurological adverse effects that can lead to admission to 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.

TECARTUS (autologous anti-CD19-transduced CD3+ cells) should be administered in a healthcare facility specifically qualified for its use. The summary of product characteristics (SPC) and the RMP must be complied with, and special monitoring during and after treatment is required.

Special recommendations

The use of TECARTUS (autologous anti-CD19-transduced CD3+ cells) is limited to a small number of centres specifically qualified in the use of medicinal products containing CAR T-cells given the complexity of the procedure. In this context, the Committee highlights the importance of overall care (in particular including travel and local accommodation near healthcare facilities, where required).

The Committee highlights the benefit to patients, and their carers if applicable, of having access to appropriate information on the complexity of the procedure for administering CAR-T cell-based medicinal products, the constraints related to prolonged hospitalisation and the risks to patients.

The summary of product characteristics (SPC) and the RMP must be complied with, and special monitoring during and after treatment is required.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Mantle cell lymphoma, characterised by rapid progression, resistance to treatments and repeated relapses, is the most aggressive form of indolent non-Hodgkin lymphoma. It is a serious disease that is rapidly life-threatening.

◗ The proprietary medicinal product TECARTUS (autologous anti-CD19-transduced CD3+ cells) is a specific curative treatment for mantle cell lymphoma.

◗ The efficacy/adverse effects ratio is high in the short term only. It remains to be determined in the longer term.

◗ There are therapeutic alternatives (see section 05 of this opinion).

◗ TECARTUS (autologous anti-CD19-transduced CD3+ cells) is a third or later-line treatment for relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor. (see section 08 of the present opinion)

Public health impact

Considering:

- the seriousness of the disease, particularly in relapsed patients or patients refractory to two or more lines of systemic therapy,
- its prevalence,
- the medical need considered to be partially met at this stage of the disease,
- the partial response to the identified need, due to:
    - an additional impact on morbidity and mortality in the short term, despite the absence of comparative data and uncertainties concerning the indirect comparisons performed,
    - the absence of a demonstrated impact on quality of life, due to the open-label and non-comparative nature of the study;
    - uncertainties concerning transposability given the highly selective population in the ZUMA-2 study,
    - and despite the absence of data relative to maintenance of efficacy in the medium and long term,
- the absence of an improvement in the care pathway of patients (as the dossier currently stands and given the short follow-up) 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),
    - hospitalisation of patients far from their homes,
    - the need to remain close to this hospital for monitoring for at least 4 weeks following infusion,
- and the impact on the organisation of care:
    - accreditation of hospitals based on precise criteria,
    - close coordination between the various departments of qualified centres to treat patients with CART cells (laboratories, internal pharmacy, clinical departments, etc.),

TECARTUS (autologous anti-CD19-transduced CD3+ cells) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of TECARTUS (autologous anti-CD19-transduced CD3+ cells) is substantial in the MA indication.

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the "treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor" and at the MA dosages.

Clinical Added Value

Considering:

- **relevant short-term efficacy data from a phase 2 non-comparative study (ZUMA-2), in terms of complete response (approximately 60% of the ITT population) and overall survival (69% of patients alive after a theoretical median follow-up of 16.8 months), in the life-threatening clinical situations observed for which the treatment options are limited and do not enable long-term remission to be envisaged, and despite the debatable clinical relevance of the primary endpoint (overall response rate) and the immaturity of the data,**
- **uncertainties with respect to the effect size in the absence of a direct comparison with the standard of care and the limitations of the indirect comparisons performed,**
- **uncertainties with respect to maintenance of the clinical efficacy in the longer term, particularly concerning achievement of cure in patients in lasting remission,**
- **significant short-term toxicity and the absence of long-term safety data,**

the Committee considers that, on the basis of currently available data, TECARTUS (autologous anti-CD19-transduced CD3+ cells) provides a moderate clinical added value (CAV III) in terms of efficacy compared to the current treatment of relapsed or refractory mantle cell lymphoma (MCL) after two or more lines of systemic therapy including a Bruton's tyrosine kinase (BTK) inhibitor.