HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
05 MAY 2021

The legally binding text is the original French opinion version

carfilzomib
KYPROLIS 10 mg powder for solution for infusion
KYPROLIS 30 mg powder for solution for infusion
KYPROLIS 60 mg powder for solution for infusion

New indication

Key points

Favourable opinion for reimbursement in combination with daratumumab and dexamethasone in the treatment of adult patients with multiple myeloma who have received at least one prior treatment.

What therapeutic improvement?

The design of the CANDOR study does not enable quantification of the contribution of KYPROLIS (carfilzomib) as triple therapy in so far as the product was present in both study groups.

This study only enables assessment of the addition of daratumumab in the triple therapy.

Role in the care pathway?

Over the last decade, numerous medicinal products have been added to the therapeutic arsenal for the second and later-line treatment of multiple myeloma, such as: daratumumab (DARZALEX), ixazomib (NINLARO), carfilzomib (KYPROLIS) or pomalidomide (IMNOVID), always in combination. The choice between these treatments should take into account whether or not the patient is refractory to lenalidomide and prior exposure to daratumumab as first-line therapy, as well as the level of evidence and the toxicity profile.

From the second relapse, in patients who have already been treated with VELCADE (bortezomib) and REVLIMID (lenalidomide), IMNOVID (pomalidomide) has an MA in combination with dexamethasone. However, given the evolution of the care pathway in multiple myeloma, with new medicinal products having been added to the therapeutic arsenal in earlier treatment lines, the role of IMNOVID (pomalidomide) in combination with dexamethasone has become more limited. In addition, earlier use of IMNOVID (pomalidomide) from the second line of treatment in combination with bortezomib and dexamethasone is likely to substantially reduce the benefit of pomalidomide-dexamethasone dual therapy in subsequent treatment lines. FARYDAK (panobinostat) combined with bortezomib and dexamethasone represents a last-resort treatment option for patients with relapsed and/or refractory myeloma having previously received two lines of treatment, including bortezomib and an immunomodulator. DARZALEX (daratumumab) is also an option in patients with relapsed and refractory multiple myeloma, whose prior therapies included a proteasome inhibitor and an immunomodulatory agent; however, its earlier use (currently possible from first-line therapy) in the context of combination with a proteasome inhibitor (PI) or an immunomodulator (IMiD), substantially reduces the benefit of this monotherapy in subsequent treatment lines. Recently, SARCLISA (isatuximab), a new anti-CD38 antibody has been added to the care pathway in combination with pomalidomide and dexamethasone in patients having received at least two prior treatments including lenalidomide and a PI.

Otherwise, in heavily pretreated patients in the very advanced stages of the disease, in particular those whose disease is refractory to at least one IP, one immunomodulatory agent, and an anti-CD38 monoclonal antibody such as daratumumab (DARZALEX), until recently there were no validated treatment options following the failure of an anti-CD38 antibody and patients were usually in a situation where all the treatment options had been exhausted. BLENREP (belantamab mafodotin) was recently added to the care pathway as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

Role of the medicinal product in the care pathway

The Committee highlights the fact that the CANDOR study included KYPROLIS (carfilzomib) in both treatment groups, meaning that the benefit of KYPROLIS (carfilzomib) cannot be defined in combination with the other two drugs. The study only enables assessment of the benefit of addition of DARZALEX (daratumumab) to carfilzomib and dexamethasone.

Although it is impossible to assess the efficacy and adverse effects of KYPROLIS (carfilzomib), in combination with the other two drugs in view of the CANDOR study design, the Committee considers that the KdD protocol is a treatment option in adult patients with multiple myeloma having received at least one prior treatment line, considering the following:

- demonstration of the superiority of the KdD protocol compared to the protocol combining KYPROLIS (carfilzomib) with dexamethasone (Kd protocol), a comparator considered to be clinically relevant on the date of implementation of the study, in terms of progression-free survival assessed blind by an independent review committee, in the open-label CANDOR study, with, however, a non-quantifiable absolute difference in the primary analysis after follow-up for approximately 17 months;
- the relevance of the results concerning achievement of negative (or no) minimal residual disease (MRD) in patients having had a complete response, with robust demonstration of superiority of the KdD protocol, although MRD is not currently a demonstrated substitution endpoint for overall survival.

And despite:

- The absence of a statistically significant difference in terms of overall survival in two interim analyses (hierarchical secondary endpoint) pending a third analysis and a final analysis scheduled in the protocol;
- The specific safety profile of the KdD protocol, marked, in particular, by thrombocytopenia, anaemia, diarrhoea, hypertension, upper respiratory tract infection, cardiac toxicity, infusion related reaction and peripheral neuropathy, with increased deaths related to an adverse event, particularly in patients over 65 years of age.

Nonetheless, the Committee highlights the uncertainties concerning the role of the KdD protocol compared to the protocols currently used, considering:

- The indirect comparison data, which do not enable any conclusions to be drawn with a high level of evidence with respect to the efficacy of the KdD protocol compared to the DVd and PomVd protocols, triple therapies that can be used as second and later-line therapy, including a PI and no lenalidomide.
- The absence of comparative data versus triple therapies including lenalidomide, such as the KRd (carfilzomib, lenalidomide and dexamethasone) or DRd (daratumumab, lenalidomide and dexamethasone) or IRd (ixazomib, lenalidomide and dexamethasone) protocols, despite the fact that 58% of the patients included in the study population had not received lenalidomide.
- The heterogeneity of the population included in the CANDOR study, particularly in terms of the number of prior treatment lines received by the patients.

In particular, the choice between these different treatment options should take into account whether or not the patient is refractory to lenalidomide and prior exposure to daratumumab as first-line therapy, as well as the level of evidence and the toxicity profile.

The Committee also highlights the fact that anti-CD38 antibodies, such as DARZALEX, now recommended from the first line of treatment, irrespective of the patient's status in terms of eligibility for autologous peripheral blood stem cell transplantation, have a decreasing role to play in situations of relapse following first-line treatment. However, there is still a proportion of patients not having received anti-CD38 antibodies and liable to do so in a subsequent treatment line.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Multiple myeloma is a serious blood disease that is life-threatening.

◗ KYPROLIS (carfilzomib) is a curative medicinal product.

◗ The efficacy/adverse effects ratio of KYPROLIS (carfilzomib) in the context of its combination with DARZALEX (daratumumab) and dexamethasone (KdD protocol) is not established in view of the design of the CANDOR study, which included KYPROLIS (carfilzomib) in both treatment groups (carfilzomib + daratumumab + dexamethasone group versus carfilzomib + dexamethasone group). The study only enables assessment of the benefit of addition of DARZALEX (daratumumab).

◗ There are alternatives in patients having received at least one prior treatment, in particular, as second-line therapy: daratumumab (DARZALEX), ixazomib (NINLARO) or pomalidomide (IMNOVID), in combination with bortezomib (VELCADE) or lenalidomide (REVLIMID) and dexamethasone, as well as the other protocols including KYPROLIS (carfilzomib) in combination with dexamethasone or lenalidomide and dexamethasone.

◗ Although it is impossible to establish the efficacy/adverse effects ratio of KYPROLIS (carfilzomib) within this triple combination, the KdD protocol is a treatment option for patients with multiple myeloma as second or later-line therapy. However, the Committee highlights the uncertainties with respect to the role of KdD compared to the other recommended protocols due to the absence of robust comparative data versus these protocols. In particular, the choice between these different treatment options should take into account whether or not the patient is refractory to lenalidomide and prior exposure to daratumumab as first-line therapy, as well as the level of evidence and the toxicity profile. The Committee also highlights the fact that anti-CD38 antibodies, such as DARZALEX (daratumumab), now recommended from the first line of treatment, irrespective of the patient's status in terms of eligibility for autologous peripheral blood stem cell transplantation, have a decreasing role to play in situations of relapse following first-line treatment. However, there is still a proportion of patients not having received anti-CD38 antibodies and liable to do so in a subsequent treatment line.

<u>Public health impact</u>

Considering:

- the seriousness of the disease and its incidence,
- the partially met medical need in patients who have already received at least one prior treatment,
- the lack of response to the identified need due to:
    - the absence of a demonstrated impact on morbidity and mortality and on quality of life,
    - the absence of data supporting an impact on the care and/or life pathway,

KYPROLIS (carfilzomib) in combination with DARZALEX (daratumumab) and dexamethasone is unlikely to have an additional impact on public health.

Considering all these elements, the Committee considers that the clinical benefit of KYPROLIS is substantial in the indication "in combination with daratumumab and dexamethasone in the treatment of adult patients with multiple myeloma who have received at least one prior treatment".

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the indication "in combination with daratumumab and dexamethasone in the treatment of adult patients with multiple myeloma who have received at least one prior treatment" and at the MA dosages.

Clinical Added Value

Considering:

- **demonstration of the superiority of the protocol combining KYPROLIS (carfilzomib) with DARZALEX (daratumumab) and dexamethasone (KdD protocol) compared to the protocol combining KYPROLIS (carfilzomib) with dexamethasone (Kd protocol), in terms of progression-free survival in the CANDOR study, with an improvement considered to be clinically relevant,**
- **but the impossibility of determining the therapeutic contribution of KYPROLIS (carfilzomib), in combination, in view of the design of the CANDOR study:**
    - **which included KYPROLIS (carfilzomib) in both treatment groups,**
    - **and hence enables assessment of the benefit of addition of daratumumab to carfilzomib plus dexamethasone,**

the Committee considers by default that KYPROLIS, in combination with DARZALEX and dexamethasone, provides no clinical added value (CAV V) in the care pathway.

In view of the design of the CANDOR study, the Committee would only be able to assess the contribution of DARZALEX (daratumumab), in combination with carfilzomib and dexamethasone, which is not the subject of the application.

<u>Estimation</u>
The incident target population of KYPROLIS (carfilzomib), in combination with DARZALEX (daratumumab) and dexamethasone, in the second and later-line treatment of multiple myeloma is a maximum of 3,240 patients per year.