HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
9 MARCH 2022

The legally binding text is the original French opinion version

daratumumab
DARZALEX 20 mg/mL concentrate for solution for infusion

Re-evaluation

Key points

Favourable opinion for reimbursement in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

What therapeutic improvement?

Therapeutic improvement compared to the Rd protocol combining lenalidomide and dexamethasone.

◗ Role in the care pathway?

In symptomatic patients, first-line treatment is dependent on whether the subject is eligible or not for intensive chemotherapy combined with autologous haematopoietic stem cell transplantation.

When patients are not eligible for this procedure (in particular, due to their age, their comorbidities and/or their general condition), the therapeutic strategy is based on chemotherapy:

- either with lenalidomide (REVLIMID) combined with dexamethasone until disease progression, and the anti-CD38 monoclonal antibody daratumumab (DARZALEX) (DRd protocol),
- or with bortezomib (VELCADE), melphalan and daratumumab (D-VMP protocol) for a fixed treatment duration.

Role of the medicinal product in the care pathway

Given the superiority of the protocol combining DARZALEX (daratumumab) with lenalidomide and dexamethasone (D-Rd protocol) until disease progression demonstrated in comparison with the Rd protocol, now in terms of overall survival, the D-Rd protocol is the treatment option to be favoured over the Rd protocol for the treatment of patients with previously untreated multiple myeloma who are ineligible for autologous stem cell transplant.

In the absence of direct comparative data, the role of the D-Rd protocol compared to the D-VMP protocol (combining bortezomib, melphalan and prednisone with daratumumab) available in the same indication, is not known. The choice should therefore be made taking into account the patient and disease characteristics, the safety profile of the protocols and the preferences of patients.

The Committee wishes to draw the attention of prescribers to the need for specific vigilance with respect to the risk of immune deficiency induced by the long-term administration of DARZALEX (daratumumab). An excess of sometimes severe infectious episodes, particularly respiratory tract infection (including with opportunistic microorganisms), was observed in the study arm including DARZALEX (daratumumab), and is also reported in the literature. The benefit/risk ratio of the long-term continuation of DARZALEX (daratumumab) injections must therefore be reassessed regularly, before each administration, particularly in the event of an infectious episode.

Insofar as DARZALEX (daratumumab) has several marketing authorisations for the first and second-line treatment of myeloma, the Committee regrets that there are no ongoing studies capable of defining the optimal treatment sequence and encourages the implementation of a study of this type.

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.

◗ DARZALEX (daratumumab), in combination with lenalidomide and dexamethasone, is a specific curative treatment for multiple myeloma.

◗ The efficacy/adverse effects ratio of DARZALEX (daratumumab) in combination with lenalidomide and dexamethasone remains high.

◗ There are medicinal alternatives.

◗ This is a treatment option to be favoured in adult patients who are ineligible for autologous stem cell transplant in the context of its administration in combination with lenalidomide and dexamethasone until disease progression (see chapter 09 Role in the care pathway).

Public health impact

Considering:

- the seriousness of multiple myeloma,
- its incidence,
- the partially met medical need in the first-line treatment of patients ineligible for autologous stem cell transplant,
- the partial response to the identified medical need given:
    - the demonstrated impact of DARZALEX (daratumumab) on morbidity and mortality in the context of its administration in combination with the Rd protocol,
    - the absence of demonstration of the impact on quality of life, an exploratory endpoint in the study,
- but the dosage regimen for DARZALEX (daratumumab), in combination with lenalidomide and dexamethasone, requiring weekly IV infusion, every 2 weeks then every 4 weeks until progression, and the lack of evidence to support an improvement in the care pathway,

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

Given all these elements, the Committee deems that the clinical benefit of DARZALEX (daratumumab) remains substantial in the indication: "in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant".

The Committee issues a favourable opinion for maintenance of inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the indication: "in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant" and at the MA dosages.

Clinical Added Value

Considering:

- demonstration of the superiority of the addition of DARZALEX (daratumumab) in combination with lenalidomide and dexamethasone (D-Rd protocol) compared to the Rd protocol, administered until progression, in terms of overall survival (ranked secondary endpoint; HR = 0.68; $CI_{95\%}$ [0.53; 0.86], median increase not quantifiable to date) following a median follow-up of 56 months,
- data having demonstrated the superiority of this addition in terms of progression-free survival (primary endpoint; HR = 0.56; $CI_{95\%}$ [0.43; 0.73], median increase not quantifiable to date) following a median follow-up of 28 months,

and despite:

- the lack of demonstrated impact on quality of life in the absence of robust data for this endpoint,
- and the higher frequency of grade 3-4 adverse events with the D-Rd protocol compared to the Rd protocol (96% versus 88%), having mainly concerned severe neutropenia (54% versus 37%) and severe pneumonia (19% versus 11%),

the Committee considers that DARZALEX (daratumumab) in combination with lenalidomide and dexamethasone (Rd protocol), provides a moderate clinical added value (CAV III) compared to the Rd protocol in the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.