HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New medicinal product
November 2017

TRANSPARENCY COMMITTEE OPINION SUMMARY

DARZALEX (daratumumab), monoclonal antibody

High clinical benefit as monotherapy in relapsed and refractorymultiple myeloma, but no demonstrated clinical benefit in the therapeutic strategy.

Main points

- DARZALEX has been granted marketing authorisation for monotherapy treatment of adults suffering from relapsed and refractory multiple myeloma, for whom previous treatments included a proteasome inhibitor and an immunomodulator, and whose disease progressed during the last treatment.
- Considering the efficacy data derived from the subgroups of two phase II studies, along with the lack of comparative data, particularly versus third-line pomalidomide, DARZALEX monotherapy does not confer any clinical benefit in the therapeutic strategy.

Therapeutic strategy

- First-line treatment depends on whether the subject is eligible for intensive chemotherapy combined with autologous peripheral stem cell (PSC) transplantation. After autologous transplantation, the use of consolidation chemotherapy, followed by potential maintenance treatment, remains the subject of debate and is currently under investigation.
- There is no standard treatment for the first recurrence of multiple myeloma. The therapeutic decision is dependent on age, prior treatments, general health and comorbidities. Generally speaking, if the initial response duration is high, first-line treatment can be reused. For young patients, after remedial therapy, autologous, or allogeneic haematopoietic stem cell transplantation is proposed. In other cases, a number of combinations are used: VELCADE (off-label) in combinations, particularly with immunomodulators (lenalidomide or thalidomide) and with cyclophosphamide. Lenalidomide (REVLIMID) is used in combination with dexamethasone only. It is routine practice to administer an immunomodulator to a patient having received bortezomib as first-line treatment. Recently, other medicinal products were added to the therapeutic arsenal for second-line treatment such as ixazomib (NINLARO) or carfilzomib (KYPROLIS), both to be combined with lenalidomide and/or with dexamethasone. It should be noted that, in terms of efficacy, the bitherapy combining carfilzomib with dexamethosone is the only one to have demonstrated a gain in overall survival compared to the bortezomib/dexamethosone second-line combination.
- From the second relapse, the choice is governed by the same parameters, particularly the efficacy and safety of previous treatments. Combinations including immunomodulators, corticosteroids, anthracyclines or alkylating agents can still be used in patients having received 2 or 3 lines of treatment. Beyond this, for heavily pretreated and refractory patients at very advanced stages, therapeutic options are limited and the patients are most frequently at a therapeutic dead end. In this context, for patients previously treated with bortezomib and lenalidomide, pomalidomide combined with dexamethosone represents an alternative treatment. Panobinostat, combined with bortezomib and dexamethosone, represents a last resort treatment option for patients suffering from relapsed and/or refractory multiple myeloma, having previously received two lines of treatment, including bortezomib and an immunomodulator.
- **Role of the medicinal product in the therapeutic strategy**

  Failing any comparison to third-line pomalidomide, the role of DARZALEX in monotherapy remains to be defined. Moreover, the earlier, second-line use of daratumumab in combination with a proteasome inhibitor or immunomodulator plus dexamethosone, considerably reduces the benefit of this monotherapy in subsequent lines of treatment.

Clinical data

- Efficacy and safety data are derived from a subgroup of patients taken from two non-comparative phase II studies (MMY-2002 and GEN 501) evaluating daratumumab monotherapy in adults suffering from relapsed and refractory multiple myeloma, for whom previous treatments included a proteasome inhibitor and an immunomodulator and whose disease had progressed during the last treatment.
- In the subgroups treated at the MA dosage (16 mg/kg), 35.7% (15/42) of patients in the GEN-501 study and 63.2% (67/106) of patients in the MMY2002 study had received prior pomalidomide treatment.
- In the MMY2002 study, following median follow-up of 9.3 (0.5; 14.4) months, the overall response rate (primary endpoint) in the subgroup at MA dosage (16 mg/kg) was 29%, CI95% [20.8; 39.8].
- In terms of safety (primary endpoint of the GEN-501 study and secondary endpoint of the MMY2002 study), the most frequently reported adverse events during the two studies were: fatigue (40%), nausea (25%), anaemia (33%), neutropenia (23%), back pain (23%), cough (21%) and thrombocytopenia (26%).
- The proportion of patients who presented with a serious adverse event was 30% in both studies; the most frequent of these serious adverse events were pneumonia (6%), impairment of general condition (5%), fever or febrile episodes (5%) and hypercalcaemia (4%).
- DARZALEX monotherapy was not compared to the other therapies, thus preventing the assessment of its impact on overall survival or quality-of-life.

Special prescription requirements

- Medicinal product for hospital use only
- Prescription reserved for oncology or haematology specialists or physicians with expertise in oncology or blood disorders.

Benefit of the medicinal product

- The actual clinical benefit* of DARZALEX, in monotherapy, is high.
- DARZALEX does not provide any clinical added value** (CAV V) in the therapeutic strategy.
- Approval for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 22 November 2017 (CT-15400) available at **www.has-sante.fr**

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