HAUTE AUTORITÉ DE SANTÉ

**ONCOLOGY**
**New medicinal product**
**February 2018**

**TRANSPARENCY COMMITTEE OPINION SUMMARY**

# **DARZALEX** (daratumumab), monoclonal antibody

**High clinical benefit combined with lenalidomide/dexamethosone, or bortezomib/dexamethosone bitherapy, for multiple myeloma in patients having already received at least one previous treatment, and minor clinical added value compared to each of these bitherapies used alone**

## Main points

- DARZALEX has been granted marketing authorisation, in combination with lenalidomide and dexamethosone, or with bortezomib and dexamethosone, for the treatment of adults suffering from multiple myeloma and having received at least one prior treatment.
- The efficacy of these combinations is based primarily on progression-free survival results and response rates, though with no demonstrated gain in overall survival or quality of life.
- Pending overall survival data, DARZALEX, combined with a lenalidomide/dexamethosone or bortezomib/dexamethosone bitherapy, provides minor clinical added value compared to each of the bitherapies used alone in the treatment of multiple myeloma, after at least one prior treatment.

## 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**
  DARZALEX, combined with lenalidomide/dexamethosone or bortezomib/dexamethosone, is a second-line treatment in patients suffering from relapsed multiple myeloma.

## Clinical data

- Two open-label randomised studies evaluated the efficacy and safety of daratumumab in combination in the treatment of relapsed or refractory multiple myeloma after at least one prior treatment:
  - the CASTOR study evaluated, in patients not refractory to bortezomib, addition of daratumumab to the bortezomib/dexamethosone combination (DVd group), versus the same combination administered alone (Vd group)
  - the POLLUX study compared, in patients not refractory to lenalidomide, the addition of daratumumab to the lenalidomide/dexamethosone combination (DRd group), versus the same combination administered alone (Rd group)
- Main results of the CASTOR study, after median follow-up of 7.5 months:
  - median progression-free survival (primary endpoint) was 7.2 months in the Vd group and was not reached in the DVd group (HR = 0.39, $CI_{95\%}$: [0.28; 0.53], p<0.0001);
  - an improvement in time to progression in favour of daratumumab (HR = 0.30, $CI_{95\%}$: [0.21; 0.43], p<0.0001); median time to progression was not reached in the DVd group and was 7.3 months in the Vd group;
  - a higher response rate in the DVd group (83%) than in the Vd group (63%), p<0.0001;
  - median overall survival not reached in either of the two groups.
- Main results of the POLLUX study, after median follow-up of 13.5 months:
  - median progression-free survival (primary endpoint) was 18.4 months in the Rd group and was not reached in the DRd group (HR = 0.37, $CI_{95\%}$: [0.27; 0.52], p<0.0001);
  - an improvement in time to progression in favour of daratumumab (HR = 0.34, $CI_{95\%}$: [0.23; 0.48], p<0.0001); median time to progression was not reached in the DRd group and was 18.4 months in the Rd group;
  - a higher response rate in the DRd group (93%) than in the Rd group (76%), p<0.0001;
  - median overall survival not reached in either of the two groups.
- Daratumumab in combination (DVd or DRd) produced a slight increase in the toxicities usually observed for these treatments, mainly haematological (neutropenia and thrombocytopenia). Treatment discontinuations due to adverse events were similar for both groups (DRd: 7%, Rd: 8% and DVd: 7%, Vd 9%).

## 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 combination with lenalidomide/dexamethosone or bortezomib/dexamethosone bitherapy is high.
- DARZALEX, combined with lenalidomide/dexamethosone or bortezomib/dexamethosone provides clinical added value** (CAV IV, minor) compared to each of the bitherapies used alone in the treatment of multiple myeloma after at least one previous treatment.
- Approved for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 21 February 2018 (CT-16172) 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"