HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New medicinal product
May 2018

TRANSPARENCY COMMITTEE OPINION SUMMARY

LARTRUVO (olaratumab), monoclonal antibody

Insufficient clinical benefit to justify its reimbursement in the treatment of adults with advanced soft tissue sarcoma, non-eligible for curative treatment by surgery or radiotherapy and not receiving doxorubicin pre-treatment

Main points

- LARTRUVO has MA in combination with doxorubicin, in the treatment of adults with advanced soft tissue sarcoma, non-eligible for curative treatment by surgery or radiotherapy and not having received doxorubicin pre-treatment.
- According to the data currently available from a single proof-of-concept study, and pending the results of an ongoing study, addition of LARTRUVO to doxorubicin up to 8 cycles, then continued in monotherapy, does not have a role in the treatment of soft tissue sarcoma, in adults ineligible for curative treatment by surgery or radiotherapy, and not having received doxorubicin pre-treatment.
- There are drug alternatives to this treatment line, in particular doxorubicin alone or in combination.

Therapeutic strategy

- In France, the diagnosis and treatment of a patient with soft tissue sarcoma is discussed at staff meetings in regional reference centres belonging to the sarcoma network, NETSARC.
- In patients with advanced soft tissue sarcoma, not eligible for curative treatment by surgery or radiotherapy, the treatment is based on systemic chemotherapy. Soft tissue sarcomas are tumours that are little chemo-sensitive, for which a small number of effective molecules are available. Despite the heterogeneity of pathogenesis, clinical outcome and sensitivity to systemic treatments, almost all soft-tissue sarcoma sub-types are treated with doxorubicin-based regimens in first-line.
- **Role of the medicinal product in the therapeutic strategy**
  Given the insufficient level of evidence from the phase 2 preliminary study, the role of LARTRUVO, in combination with doxorubicin up to 8 cycles, then continued in monotherapy, cannot be assessed. The results of this single proof-of-concept study are not likely to modify current therapeutic strategies.
  Addition of LARTRUVO to doxorubicin, then continued in monotherapy, does not have a role in the treatment of advanced soft tissue sarcoma in adults ineligible for curative treatment by surgery or radiotherapy and not pre-treated with doxorubicin.

Clinical data

- The efficacy and safety data for olaratumab are taken from a phase 2, open-label, randomised proof-of-concept study having compared olaratumab, in combination with doxorubicin, then continued in monotherapy, to doxorubicin alone.
  This study covered a small number (n=133) of patients with advanced soft tissue sarcoma, not eligible for radiotherapy or surgery. Among the numerous histological sub-types of soft tissue sarcoma, the most common were leiomyosarcoma (38.4%), undifferentiated pleomorphic sarcoma (18.1%) and liposarcoma (17.3%). Uneven distribution in histological sub-types at inclusion is noted in favour of the doxorubicin + olaratumab group, with a higher number of patients with generally more indolent sarcoma sub-types. Around half of patients (56%) had received previous adjuvant or metastatic chemotherapy.
  Median progression-free survival (primary endpoint) was 6.6 months in the doxorubicin + olaratumab followed by olaratumab monotherapy until progression group versus 4.1 months in the doxorubicin only group, HR=0.67 $CI_{95\%}$

[0.44; 1.02], p=0.06. The design of this study exhibits methodological limitations: risk of error of 20% (instead of the generally accepted 5%), primary endpoint evaluated by the investigators associated with the study being open-label. The level of demonstration is insufficient for confirming the therapeutic usefulness of adding this treatment to doxorubicin. The rationale of this proof-of-concept study was only to better prepare future phase 3 confirmatory studies, one of which is ongoing. In this context, the results on the secondary endpoints cannot be considered to be demonstrative.

The safety data cover a small number. Additional of olaratumab led to an increase in adverse events: more patients presented with a serious adverse event (42.2% versus 38.5%) or events ≥ grade 3 (79.7% versus 69.2%) than in the doxorubicin only group. Olaratumab-related adverse events ≥ grade 3 were reported in 45.3% of patients. The most frequently reported grade 3 and 4 adverse events included neutropenia (54.7% versus 33.9%), anaemia (12.5% versus 9.2%), febrile neutropenia (12.5% versus 13.8%) and thrombocytopenia (10.9% versus 7.7%). The most commonly observed adverse events included nausea, musculoskeletal pain, neutropenia and mucocitis. The percentage of patients having presented with an adverse event leading to treatment discontinuation was 12.5% in the doxorubicin + olaratumab group and 18.5% in the doxorubicin only group.

- Quality-of-life was not assessed.

Special prescription requirements

- Medicinal product for hospital use only
- Prescription by oncology and medical oncology specialists and departments
- Medicinal product requiring special monitoring during treatment

Benefit of the medicinal product

- The actual clinical benefit* of LARTRUVO is insufficient to justify public funding cover.
- Not approved for hospital treatment.

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This document was drafted on the basis of the Transparency Committee opinion dated 30 May 2018 (CT-16649) available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product consists of 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.