HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
NEW MEDICINAL PRODUCT
July 2015

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

ZYDELIG (idelalisib), kinase inhibitor

Moderate improvement, in combination with rituximab, in chronic lymphocytic leukaemia in second-line and subsequent therapy, and in the first line in case of deletion 17p or *TP53* mutation.
Minor improvement in follicular lymphoma refractory to two prior lines of treatment.

Main points

- ZYDELIG has Marketing Authorisation in two indications:
  - in combination with rituximab in the treatment of adults with chronic lymphocytic leukaemia (CLL) who have received at least one prior treatment or in the first line in case of deletion 17p or *TP53* mutation, in patients for whom immunochemotherapy is not appropriate.
  - in monotherapy in the treatment of adults with follicular lymphoma (FL) refractory to two prior lines of treatment.
- In treatment of CLL, in 2nd-line and subsequent therapy, ZYDELIG in combination with MABTHERA (rituximab) has shown an improvement in progression-free survival, in overall survival and in quality of life compared with rituximab alone.
- In 1st line treatment of patients with a deletion 17p (del17p) or *TP53* mutation, efficacy data are very limited.
- In refractory FL, therapeutic benefit was observed in a non-comparative study based on the overall response rate. ZYDELIG as monotherapy is an alternative treatment in patients with FL refractory to two prior lines of treatment.

Therapeutic use

In CLL

- The decision as to whether to treat a CLL patient depends on the patient's general condition (age and comorbidities) and on the stage of the disease and the presence or lack of factors pointing to a poor prognosis (time for doubling of peripheral lymphocytes less than 12 months, *TP53* mutation or del17p, etc.). Stages A (Binet) or 0, I and II (Rai), the most common, are asymptomatic and do not justify specific treatment. The existence of a del17p mutation gives poor sensitivity to chemotherapy, especially to purine analogues. The first-line treatment is therefore alemtuzumab (MABCAMPATH), available under a temporary authorisation for use.
- Standard treatments for CLL as second-line treatment are immunochemotherapies (bendamustine-rituximab, fludarabine-cyclophosphamide-rituximab) and ofatumumab (ARZERRA). Autologous stem cell transplantation is a therapeutic option, especially for young subjects. IMBRUVICA (ibrutinib) as monotherapy has an indication that coincides with that of ZYDELIG, in combination with rituximab.
- **Role of the medicinal product in the therapeutic strategy**
  ZYDELIG in combination with rituximab is a first-line treatment of CLL in case of deletion 17p or *TP53* mutation, as is ibrutinib as monotherapy.
  In other forms of CLL, ZYDELIG in combination with rituximab is a second-line and subsequent treatment, as is ibrutinib as monotherapy.

In FL

- Follicular lymphomas are often slow in progression and compatible with a normal life without treatment for several months or years. No treatment, including intensifications with an autologous transplant, allows a cure to be expected. The criteria leading to treatment are signs of clinical progression (inflammation syndrome or impact on general condition) and the existence of a significant tumour mass. When the disease progresses after a first-line treatment, various options are discussed (rituximab as monotherapy, immunochemotherapy or allogeneic

transplantation in young subjects with a proven poor prognosis (possibly followed by an autologous transplant)). In subsequent relapses, the following options may be proposed:

- radioimmunotherapy if the degree of bone marrow involvement allows it,
- use of alkylating agents as monotherapy or purine analogues (alone or in combination),
- radiotherapy, which may be capable of controlling tumour lesions.

Role of the medicinal product in the therapeutic strategy

ZYDELIG as monotherapy is an alternative treatment in patients with FL refractory to two prior lines of treatment.

Clinical data

In CLL

A randomised, double-blind study compared idelalisib + rituximab with placebo + rituximab in 220 patients with previously treated CLL. The median progression-free survival (primary efficacy endpoint) was 5.5 months in the group treated with placebo + rituximab and not reached in the group treated with idelalisib + rituximab after a median follow-up of 6.1 months in the idelalisib + rituximab arm and 4 months in the placebo + rituximab arm HR=0.18 ($_{95\%}$ CI [0.10; 0.32], p<0.001). In the subgroup of patients with del17p where the number was low (n=95), the median progression-free survival was 4 months in the placebo + rituximab group and was not reached in the idelalisib + rituximab group (HR=0.16 ($_{95\%}$ CI [0.07; 0.37]).

The median overall survival was not reached in either of the two groups due to the low number of events (26 deaths). The analysis of overall survival showed a 72% reduced risk of death for patients in the idelalisib + rituximab group compared with the placebo + rituximab (HR=0.28, ($_{95\%}$ CI [0.11; 0.69], p=0.003).

Treatment discontinuations due to the onset of an adverse event were uncommon (<10%). The most frequently reported events in all of the clinical studies were: neutropenia (25% to 27%), diarrhoea (19.1%, including some grade >3) and pneumonia. Rashes should also be noted (exfoliative dermatitis, rash, macular rash, maculopapular rash or pruritic rash).

The efficacy data of idelalisib + rituximab in 1st-line treatment of CLL with deletion 17p or *TP53* mutation were observed in a subgroup of 9 patients from a non-comparative phase II study. Of these 9 patients (14.1% of the total number), all obtained an overall response; 3 obtained a complete response and 6 a partial response. The median duration of response was not achieved.

In FL

A non-comparative study evaluated idelalisib as monotherapy in 125 patients with indolent non-Hodgkin lymphoma, including 72 with FL. The overall response rate (primary effficacy endpoint) was 56.8% [$_{95\%}$ CI [47.6; 65.6, p<0.001] after a medial follow-up of 9.7 months. Of the 72 patients with FL, 39 had an overall response, i.e. an overall response rate of 54.2% ($_{95\%}$ CI [42; 66]); it was overwhelmingly a partial response (33/39). The median progression-free survival was 11 months ($_{95\%}$ CI [8.2; 13.6]) for all patients and 8.5 months ($_{95\%}$ CI [5.7; 13.1]) in the subgroup of patients with FL.

Benefit of the medicinal product

- The actual benefit* of ZYDELIG is substantial.
- ZYDELIG in combination with rituximab, like IMBRUVICA as monotherapy, provides a moderate clinical added value** (CAV III) in the therapeutic strategy of adult patients with CLL who have received at least one prior treatment, or in the first line in patients with a deletion 17p or *TP53* mutation and for whom immunochemotherapy is not appropriate.
- ZYDELIG as monotherapy provides a minor clinical added value** (CAV IV) in patients with follicular lymphoma (FL) refractory to two prior lines of treatment.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 17 june 2015 (CT-13930) and is available at **www.has-sante.fr**

[i] * The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".