Tislelizumab

REFUSÉE

Le Comité d'experts, après évaluation, refuse d'inscrire le médicament proposé dans la demande.
La Liste Modèle des Médicaments Essentiels fait état des raisons que les membres du Comité ont identifiées pour refuser l'inscription.

Section: 8. Immunomodulators and antineoplastics > 8.2. Antineoplastics and supportive medicines > 8.2.3. Immunomodulators

Codes ATC: L01FF09

Indication	Hodgkin lymphoma Code ICD11: 2C10.Z
Type de médicament	Biological agent
Type de liste	Liste complémentaire
Formulations	Parenteral > General injections > IV: 100 mg per 10 mL
Historique des statuts LME	Demande refusée en 2021 (TRS 1035)
Sexe	Tous
Âge	Adolescents et adultes
Équivalence thérapeutique	La recommandation concerne ce médicament spécifique
Renseignements sur le brevet	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Lire la suite sur les brevets.
Balises	Cancer
Wikipédia	Tislelizumab
DrugBank	Tislelizumab

Recommandation du comité d'experts

The Expert Committee acknowledged that Hodgkin lymphoma is a serious disease with a high incidence rate and costly treatment and follow-up. The Committee noted that the disease has a relatively high 5-year survival rate with conventional chemotherapy and radiotherapy. However, for patients with relapsed or refractory disease, the prognosis is poor and effective treatments are limited. The Committee considered that the application for inclusion of tislelizumab on the EML for Hodgkin lymphoma was premature. The available data for the efficacy and safety of tislelizumab in patients with Hodgkin lymphoma were limited to one phase II single-arm trial, with a small number of patients. Comparative evidence of efficacy and safety versus other treatments was also lacking. The available data were therefore considered insufficient to evaluate the clinical benefit and safety of tislelizumab as an essential medicine. The Committee also noted that tislelizumab is currently very expensive, has unknown cost–effectiveness and has very limited global regulatory approval and availability. Therefore, the Committee did not recommend inclusion of tislelizumab on the EML for the treatment of Hodgkin lymphoma. However, the Committee recognized the potentially important role of immune checkpoint inhibitors as a therapeutic class in the treatment of relapsed/refractory Hodgkin lymphoma. The Committee advised that it would welcome an application with more mature data and including all immune checkpoint inhibitors used in the treatment of Hodgkin lymphoma for consideration for EML listing in the future. The Committee also considered that immune checkpoint inhibitors could be flagged to the Medicines Patent Pool as candidates for consideration for negotiating public health-oriented licences, noting that negotiating such licences can take some time. The outcome of negotiations might provide important insight for future EML consideration on potential accessibility of this class of medicines in low- and middle-income countries.

Contexte

Tislelizumab has not previously been considered for inclusion on the Model List. Medicines for the treatment of Hodgkin lymphoma in both adults and children were comprehensively reviewed by the Expert Committee in 2015 (1). Medicines currently included on the Model Lists as part of treatment protocols for Hodgkin lymphoma are bleomycin, cyclophosphamide, dacarbazine, doxorubicin, etoposide, prednisolone, procarbazine, vinblastine and vincristine.

Pertinence pour la santé publique

Hodgkin lymphoma is a lymphoid malignancy of B-cell origin most often affecting young adults between the ages of 20 and 40 years. Classical Hodgkin lymphoma accounts for about 95% of all cases (2). According to GLOBOCAN, the number of new cases of Hodgkin lymphoma worldwide in 2020 was about 83 000, with an estimated 23 000 deaths. The estimated age-standardized incidence and mortality rates worldwide were 0.98 and 0.26 per 100 000 persons, respectively (3). The prognosis of classical Hodgkin lymphoma is strongly influenced by histological subtype and clinical stage. The lymphocyte-dominated form of the disease has the best prognosis, with a 5-year survival rate of 94%. The lymphocyte-depleted form, however, has a 5-year survival rate of only 27%. With regard to clinical stages, the 5-year survival rate is about 93% for stage I, 86% for stage II, 70% for stage III and 32% for stage IV. Patients with Hodgkin lymphoma have a high cure rate with traditional chemotherapy and radiotherapy. However, about 10–30% of patients have refractory disease following first-line chemotherapy or will experience relapse (4–7). Following autologous stem cell transplantation, patients have a risk of relapse of nearly 50% (8). The prognosis for patients who relapse or progress after autologous stem cell transplantation is extremely poor, with a reported median overall survival of 10.5–27.6 months (9,10). Treatment of relapsed/refractory Hodgkin lymphoma is complex and rapidly evolving. Hodgkin lymphoma cells (Reed–Sternberg cells) express high levels of PD-L1 and inhibition of PD-1 through immune checkpoint inhibitors is increasingly studied as treatment for Hodgkin lymphoma.

Bénéfices

The application presented the results of study BGB-A317-203, an open-label, single-arm, multicentre phase II trial in China that evaluated the efficacy and safety of tislelizumab in 70 participants with relapsed/refractory classical Hodgkin lymphoma (11). After median follow-up of 9.8 months, 61 (87.1%) participants achieved an objective response, with 44 (62.9%) participants achieving a complete response and 17 (24.3%) participants achieving a partial response. Of the 13 participants who had previously undergone autologous stem cell transplantation, 12 (92.3%) achieved an objective response, with nine (69.2%) achieving a complete response. All four participants who had previously received the antibody-drug conjugate brentuximab vedotin achieved a complete response. Of the 25 participants with primary refractory disease, 20 (80%) achieved an objective response, including 13 (52%) who achieved a complete response. The median time to response was 12 weeks (range 8.9 to 42.1 weeks). After a median follow-up of 9.6 months, the median progression-free survival had not been reached. At 9 months, the progression-free survival rate was 74.5% (95% confidence interval (CI) 70.5% to 89.4%). After a median follow-up from the first response of 6.7 months, the median duration of response had not been reached for the 61 participants who achieved a response. One patient had died by the data cut-off date due to disease progression. The 9-month overall survival rate was 98.6%. Direct comparative data of tislelizumab with otherPD-1 monoclonal antibodies or other treatments such as brentuximab vedotin for relapsed/refractory classical Hodgkin lymphoma are lacking. The application presented indirect comparisons of efficacy reported for tislelizumab (11), sintilimab (12), camrelizumab (13), pembrolizumab (14,15) and nivolumab (16–20). Objective response rates were 87.1% for tislelizumab, 80.4% for sintilimab, 76.0% for camrelizumab, 71.9% for pembrolizumab and 71.2% for nivolumab. The complete response rate for tislelizumab was 62.9%, while for sintilimab, camrelizumab, pembrolizumab and nivolumab they were 33.7%, 28.0%, 27.6% and 21.0%, respectively.

Torts

The safety results of trial BGB-A317-203 were presented in the application (11). In this study, 65/70 (92.9%) of participants experienced adverse events, most of which were grade 1 or 2. Grade 3 or above adverse events occurred in 15/70 (21.4%) of participants including two participants with grade 4 events (increased serum creatinine phosphokinase and thrombocytopenia). No grade 5 adverse events were reported. The most common adverse events were fever (54.3%), hypothyroidism (32.9%), weight gain (30.0%), upper respiratory infection (30.0%), leukopenia (18.6%), cough (17.1%) and pruritus (17.1%). The most common adverse

events of grade 3 and above were upper respiratory tract infection and pneumonia. Overall, safety information of tislelizumab comes from BGB-A317-203, and two additional single-agent clinical studies of tislelizumab in solid tumours – BGB-A317-001 (21) and BGBA317-102 (22) involving 821 participants in total. Across the three trials, the median administration time of tislelizumab was 16 weeks (range 0.6 to 162 weeks). Up to 35.7% of participants received tislelizumab treatment for at least 6 months and 20.0% received tislelizumab treatment for at least 12 months. The incidence of adverse events of all grades was 71.0% among the 821 participants treated with tislelizumab. Adverse events with an incidence greater than or equal to 10% included fatigue, rash, hypothyroidism, increased alanine aminotransferase and increased aspartate aminotransferase. Since tislelizumab has only completed a single-arm phase II clinical trial and the phase III clinical trial comparing tislelizumab with other products is still in progress, no comparative safety data for tislelizumab versus other PD-1 monoclonal antibodies are available.

Rapport coût/efficacité

No cost–effectiveness analysis data were presented in the application. Tislelizumab is priced at ¥ 10 688 per 100 mg vial. The administered dose used in the phase II trial was 200 mg every 3 weeks. The China Primary Health Care Foundation, in conjunction with BeiGene, initiated the Patient assistance programme “Wei Ni, Qian Fang Bai Ji”. This programme reduces the cost of first-time medication and the cost for patients who need long-term medication. Patients only need to pay for five cycles of treatment and get 1-year medical treatment. The annual treatment cost for patients for tislelizumab under the patient assistance programme is about ¥ 106 900. The annual treatment cost for other PD-1 antibodies for classical Hodgkin lymphoma in China under the patient assistance programme are reported as ¥ 99 000 for sintilimab and ¥ 119 000 for camrelizumab.

Directives de l'OMS

WHO guidelines for the treatment of Hodgkin lymphoma are not available.

Disponibilité

Tislelizumab received regulatory approval from the National Medical Products Administration of the People’s Republic of China in December 2019 for the treatment of relapsed/refractory classical Hodgkin lymphoma after at least one second-line chemotherapy. Tislelizumab had not been approved for marketing and use by other national regulatory agencies at the time of consideration by the Expert Committee.

Autres considérations

The EML Cancer Medicines Working Group advised that it did not support the inclusion of tislelizumab on the EML for treatment of relapsed/refractory Hodgkin lymphoma at this time, noting that the available data for efficacy and safety are very limited (early phase trials, with small patient numbers and with short follow-up), its high price and unknown cost–effectiveness. Comments were received from the WHO Department of Noncommunicable Diseases which advised that, in line with the findings from the EML Cancer Medicines Working Group, there were insufficient mature data on the efficacy and safety of tislelizumab for it to be included in the EML at this time.

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