Tislelizumab

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

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

ATC codes: L01FF09

Indication	Malignant neoplasms of urinary tract ICD11 code: 2C9Z
Medicine type	Biological agent
List type	Complementary
Formulations	Parenteral > General injections > IV: 100 mg per 10 mL
EML status history	Application rejected in 2021 (TRS 1035)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Tags	Cancer
Wikipedia	Tislelizumab
DrugBank	Tislelizumab

Expert Committee recommendation

The Expert Committee noted that bladder cancer is a common malignancy worldwide and accounts for the vast majority of cases of urothelial carcinoma. The Committee noted that the EML currently includes the medicines in the cisplatin-based chemotherapy protocols that are considered the standard of care for first-line treatment of locally advanced and metastatic urothelial carcinoma. However, evidence for their use in the treatment of urothelial cancer has not been specifically reviewed. The Committee considered that the application for inclusion of tislelizumab on the EML for locally advanced or metastatic urothelial cancer was premature. The available data for the efficacy and safety of tislelizumab in patients with urothelial carcinoma were limited to one single-arm, non-randomized, open-label phase II study. Comparative evidence of efficacy and safety versus other treatments was also lacking. The available data were therefore considered insufficient to evaluate the benefits and harms of tislelizumab for listing as an essential medicine. The Committee also noted that tislelizumab is expensive, its cost–effectiveness is not known, and it has very limited global regulatory approval and availability. Therefore, the Committee did not recommend inclusion of tislelizumab on the EML as a second-line treatment for locally advanced or metastatic urothelial carcinoma. However, the Committee recognized the potentially important role of immune checkpoint inhibitors, as a therapeutic class, in the treatment of platinum-refractory urothelial cancer. The Committee advised that it would welcome an application, with more mature data, and including all immune checkpoint inhibitors used in the treatment of urothelial cancer, 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.

Background

Tislelizumab has not previously been considered for inclusion on the Model List. The Model List does not currently include medicines specifically for the treatment of urothelial carcinoma in any line of therapy.

Public health relevance

Urothelial carcinoma refers to tumours in the epithelial structure from the kidney's exit to the urethra. About 90–95% of urothelial carcinoma tumours originate from the bladder, with the remainder from the ureter, renal pelvis and proximal urethra (1). In 2020, bladder cancer ranked as the 11th most common tumour worldwide and 14th for mortality (2). According to GLOBOCAN, there were about 570 000 new cases of bladder cancer in 2020 and an estimated 212 000 deaths. The global age-standardized incidence and mortality rates were 5.6 and 1.9 per 100 000 persons, respectively (2). The survival rate of bladder cancer patients decreases with disease progression and relapse tends to occur early (3). Patients with distant metastases have a poor prognosis due to the inability to remove the tumour surgically and lack of effective treatments. In these patients the 5-year relative survival rate is about 5% (4). For the past 30 years, cisplatin-based combination chemotherapy has been the standard treatment for locally advanced/metastatic urothelial carcinoma. Classical therapies include: gemcitabine and cisplatin; methotrexate, vinblastine, doxorubicin and cisplatin; and dose-dense methotrexate, vinblastine, doxorubicin and cisplatin (5,6). The overall response rate to these treatments is about 40–50% and the median overall survival is about 14–15 months. However, about 40–50% of patients with metastatic urothelial carcinoma cannot tolerate cisplatin treatment due to their poor physical condition or impaired renal function. These patients can only use carboplatin-based treatment options, which have an overall response rate of about 30–40% with a median overall survival of 9–10 months (7,8). There is currently no standard second-line treatment for people with locally advanced/metastatic urothelial carcinoma and disease progression after first-line chemotherapy. Paclitaxel, pemetrexed, docetaxel, gemcitabine and doxorubicin are commonly used clinically, but their efficacy is limited with an overall response rate of about 12% and overall survival of 5–7 months (8,9).

Benefits

The application presented the results of study BGB-A317-204, a single-arm, non-randomized, open-label, multicentre phase II trial conducted in China and South Korea that assessed the efficacy and safety of tislelizumab in 113 participants with locally advanced or metastatic urothelial carcinoma, who had disease progression with platinum-based chemotherapy and who had not received prior PD-(L)1 inhibitor treatment and who had ≥ 25% of tumour/immune cells expressing PD-L1 (10). The primary endpoint was the overall response rate assessed by an independent review committee. After median follow-up of 9.4 months, 20 (18%) participants continued to receive tislelizumab, while the remaining 93 (82%) discontinued treatment. Reasons for discontinuation were disease progression (53 participants), adverse events (19 participants), withdrawn consent (11 participants) and symptomatic deterioration (10 participants). Of 104 patients who could be evaluated, a confirmed objective response was observed in 25 (overall response rate (ORR) 24%, 95% confidence interval (CI) 16% to 33%), including 10 patients with complete response and 15 with partial response as assessed by the independent review committee. Median progression-free survival and overall survival were 2.1 months (95% CI 2.0 to 3.2 months) and 9.8 months (95% CI 7.5 to 12.5 months), respectively. Direct comparative data of tislelizumab with other PD-1 monoclonal antibodies for urothelial carcinoma are lacking. The application presented indirect comparisons of efficacy reported for tislelizumab (10), atezolizumab (11,12), durvalumab (13), avelumab (14), nivolumab (15) and pembrolizumab (16,17). Objective response rates (among PD-L1 positive patients, defined differently across the studies) were 24% for tislelizumab, 23–26% for atezolizumab, 28% for durvalumab, 24% for avelumab, 28% for nivolumab and 20–30% for pembrolizumab.

Harms

Safety results from study BGB-A317-204 were presented in the application (10). In this study, 106 (94%) participants experienced at least one adverse effect considered to be related to tislelizumab by the investigator. The most common treatment-related adverse events were anaemia (27%) and pyrexia (20%). Most treatment-related adverse events were grade 1–2 in severity. Anaemia (7%) and hyponatraemia (5%) were the only grade 3 or 4 events occurring in ≥ 5% of participants. Treatment-related adverse events led to treatment discontinuation in 14% of participants. Serious treatment-related adverse events occurred in 37% of participants, the most common being pyrexia (4%), and upper respiratory tract infection, urinary tract infection and drug

eruption (3% each). Among seven participants with a treatment-related adverse event leading to death, three were considered possibly related to the study treatment by the investigators (hepatic failure, two participants; respiratory arrest, one patient). In the study, 27% of participants experienced immune-related adverse events; events affecting ≥ 5% of participants included skin adverse reactions (12%), hypothyroidism (11%) and hyperthyroidism (6%). Eight (7%) participants had immune-related adverse events of grade ≥ 3; no fatal immune-related adverse events were reported. Overall, safety information of tislelizumab comes from two single-agent clinical studies of the use of tislelizumab in solid tumours (18,19) and a single-agent study of tislelizumab in Hodgkin lymphoma (20), involving a total of 821 participants. The tumour types of the participants included in these studies varied and included 39 participants with urothelial carcinoma. Participants received tislelizumab at a dose of either 200 mg or 5 mg/kg every 3 weeks. The median administration time of tislelizumab was 16 weeks (range 0.6–162 weeks). Tislelizumab treatment continued for at least 6 months in 35.7% of participants, while 20.0% of participants received tislelizumab treatment 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 ≥ 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 with other PD-1 monoclonal antibodies are available.

Cost / cost effectiveness

No cost–effectiveness analysis data for tislelizumab were presented in the application. Tislelizumab is priced at ¥ 10 688 per vial. The administered dose used in the phase II trial was 200 mg every 3 weeks. Vial prices for alternative anti-PD1 monoclonal antibodies presented in the application were US$ 6495 for nivolumab (240 mg/24 mL), US$ 3671 for durvalumab (500 mg/10 mL) and US$ 4800 for pembrolizumab (100 mg/4 mL). 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 of medical treatment. The minimum annual treatment cost is about ¥ 106 900.

WHO guidelines

WHO guidelines for the treatment of urothelial carcinoma are not available.

Availability

Tislelizumab received regulatory approval from the National Medical Products Administration of the People’s Republic of China in April 2020 for the treatment of patients with locally advanced or metastatic urothelial carcinoma with high PD-L1 expression, who have failed prior platinum-containing chemotherapy and whose disease has progressed within 12 months. Tislelizumab was not approved for marketing and use by other national regulatory agencies at the time of EML consideration.

Other considerations

Tislelizumab has not yet been scored on the European Society for Medical Oncology’s magnitude of clinical benefit scale for this indication (21). The application was reviewed by the EML Cancer Medicines Working Group. The Working Group advised that it did not support the inclusion of tislelizumab on the EML for treatment of urothelial carcinoma 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), the cost of tislelizumab is high and its cost–effectiveness is not known for this indication. 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. The technical department suggested that tislelizumab for this indication could be reconsidered in the future based on additional evidence and increased understanding of the feasibility of its appropriate use in low-resource settings.

1. Warren M, Kolinsky M, Canil CM, Czaykowski P, Sridhar SS, Black PC, et al. Canadian Urological Association/Genitourinary Medic al Oncologists of Canada consensus statement: Management of unresectable locally advanced and metastatic urothelial carcinoma. Can Urol Assoc J. 2019;13(10):318–27.
2. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global cancer observatory: cancer today. Lyon: International Agenc y for Research on Cancer; 2021 (https://gco.iarc.fr/today, accessed 16 April 2021).
3. Cancer stat fact sheets: bladder cancer [internet] Bethesda, MD: National Cancer Institute; 2020 (https://seer.cancer.gov/statfa

cts/html/urinb.html, accessed).
4. SEER cancer statistics review, 1975–2016 [internet]. Bethesda, MD: National Cancer Institute; 2019 (https://seer.cancer.gov/csr/1975_2016/, accessed).
5. Chinese guidelines for diagnosis and treatment of urothelial carcinoma of bladder 2018 (English version). Chin J Cancer Res. 2019;31(1):49–66.
6. NCCN guidelines. Bladder cancer (version 2.2020) [internet]. Plymouth Meeting, PA: National Comprehensive Cancer Network; 2020 (https://www.nccn.org, accessed 16 April 2021).
7. De Santis M, Bellmunt J, Mead G, Kerst JM, Leahy M, Maroto P, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol. 2012;30(2):191–9.
8. Kim HS, Seo HK. Immune checkpoint inhibitors for urothelial carcinoma. Investig Clin Urol. 2018;59(5):285–96.
9. Galsky MD, Pal SK, Lin SW, Ogale S, Zivkovic M, Simpson J, et al. Real-world effectiveness of chemotherapy in elderly patients with metastatic bladder cancer in the United States. Bladder Cancer. 2018;4(2):227–38.
10. Ye D, Liu J, Zhou A, Zou Q, Li H, Fu C, et al. Tislelizumab in Asian patients with previously treated locally advanced or metastatic urothelial carcinoma. Cancer Sci. 2021;112(1):305–13.
11. Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet. 2016;387(10031):1909–20.
12. Powles T, Durán I, van der Heijden MS, Loriot Y, Vogelzang NJ, De Giorgi U, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2018;391(10122):748–57.
13. Powles T, O'Donnell PH, Massard C, Arkenau HT, Friedlander TW, Hoimes CJ, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. JAMA Oncol. 2017;3(9):e172411.
14. Patel MR, Ellerton J, Infante JR, Agrawal M, Gordon M, Aljumaily R, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. Lancet Oncol. 2018;19(1):51–64.
15. Sharma P, Retz M, Siefker-Radtke A, Baron A, Necchi A, Bedke J, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2017;18(3):312–22.
16. Balar AV, Castellano D, O'Donnell PH, Grivas P, Vuky J, Powles T, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2017;18(11):1483–92.
17. Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med. 2017;376(11):1015–26.
18. Desai J, Deva S, Lee JS, Lin CC, Yen CJ, Chao Y, et al. Phase IA/IB study of single-agent tislelizumab, an investigational anti-PD-1 antibody, in solid tumors. J Immunother Cancer. 2020;8(1).
19. Shen L, Guo J, Zhang Q, Pan H, Yuan Y, Bai Y, et al. Tislelizumab in Chinese patients with advanced solid tumors: an open-label, non-comparative, phase 1/2 study. J Immunother Cancer. 2020;8(1).
20. Song Y, Gao Q, Zhang H, Fan L, Zhou J, Zou D, et al. Treatment of relapsed or refractory classical Hodgkin lymphoma with the anti-PD-1, tislelizumab: results of a phase 2, single-arm, multicenter study. Leukemia. 2020;34(2):533–42.
21. ESMO-Magnitude of Clinical Benefit Scale. The ESMO-MCBS Score Card [internet]. Lugano: European Society for Medical Oncology; 2015 (https://www.esmo.org/score/cards, accessed 16 April 2021).