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	Other specified malignant neoplasms of bronchus or lung ICD11 code: 2C75.Y
Medicine type	Biological agent
List type	Complementary
Formulations	Parenteral > General injections > IV: 100 mg per 10 mL
EML status history	Application rejected in 2023 (TRS 1049)
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	Biological Cancer
Wikipedia	Tislelizumab
DrugBank	Tislelizumab

Expert Committee recommendation

The Committee acknowledged the global burden of lung cancer and noted that most patients are diagnosed with advanced disease with metastasis which results in poor 5-year survival rates. This is especially relevant to patients in low- and middle-income countries where diagnosis at advanced stages occurs frequently. The Expert Committee recognized that PD-1/PD-L1 immune checkpoint inhibitor therapy has become part of the standard treatment for patients with NSCLC wild-type or non-oncogene-addicted tumours because of improvements in clinical outcomes that meet the established thresholds for overall survival benefit for possible inclusion on the Model List. The Committee noted the evidence presented from randomized studies and additional single-arm trials comparing tislelizumab with chemotherapy for treatment of locally advanced and metastatic NSCLC which suggested promising clinical benefits. However, the Committee noted that survival data were still immature, with observation not yet reaching 2 years of follow-up, and therefore considered that the overall survival benefit associated with tislelizumab was uncertain. The Committee also noted that the trials did not include patients based on levels of PD-L1 tumour expression. The Committee considered that preselection of patients based on PD-L1 tumour expression, as seen in other studies on immune checkpoint inhibitors, might have enhanced the patient population that would benefit from tislelizumab. The Committee acknowledged that the reported price of tislelizumab in China (the only country where tislelizumab is current approved and available for this indication) was markedly lower than the price of other immune checkpoint inhibitors in this setting. The Expert Committee did not recommend the inclusion of tislelizumab on the WHO EML at this time because of uncertain survival benefit due to immature data.

Background

Tislelizumab has not previously been considered for inclusion on the Model List for NSCLC. In 2021, tislelizumab was considered for treatment of adults with relapsed or refractory Hodgkin lymphoma after at least one second-line chemotherapy. However, it was not recommended due to immature data and unknown cost–effectiveness (1). Currently, the Model List includes cytotoxic medicines (carboplatin, cisplatin, etoposide, gemcitabine, paclitaxel and vinorelbine) and targeted therapies (erlotinib, afatinib and gefitinib) for treatment of NSCLC. The PD-1 immune checkpoint inhibitor nivolumab (with a square box indicating pembrolizumab as a therapeutic alternative) was added to the EML in 2019 for first-line monotherapy in patients with unresectable and metastatic melanoma (2).

Public health relevance

Lung cancer is a leading cause of morbidity, disability and death worldwide (3). In 2020, 2.2 million patients received a diagnosis of lung cancer, corresponding to 11.4% of all cancers diagnosed; 1.8 million people died from this disease, constituting 18% of all cancer-related deaths. The economic impact of lung cancer is estimated to be about US$ 8 billion in productivity lost in developing countries (4). Moreover, in the absence of wide coverage of effective screening programmes globally, lung cancer diagnoses occur at locally advanced and metastatic stages in more than 60% of cases (5). People living in low- and middle-income countries are more likely to be diagnosed with late-stage disease due to poor access to care, lack of awareness, inadequate health care infrastructures and poor referrals to diagnosis and palliative care (6,7). Most patients diagnosed with lung cancer in an advanced or metastatic stage have a poor 5-year survival rate of 10% to 20% (3,6). The overall 5-year survival rate in the United States is 24% (8). In comparison, the 5-year survival rate in North Africa and the Middle East is only 8% (9). More than 80% of lung cancers are classified as NSCLC (10). Targeted therapies have redefined treatment for patients with genomic alterations in driver oncogenes (epidermal growth factor (EGFR) mutations, anaplastic lymphoma kinase rearrangements, ROS1 rearrangements, BRAF mutations, human epidermal growth factor receptor 2 mutations, or amplifications and neurotrophic tyrosine kinase 1-3 fusions) to guide the selection of treatments. However, the greatest proportion of NSCLC, both squamous and non-squamous histology type, do not carry specific pathogenetic genomic alterations that can be treated with targeted medicines, including EGFR, anaplastic lymphoma kinase or ROS1 (11). Historically, patients with non-oncogene-addicted NSCLC have experienced poor survival outcomes due to a lack of therapeutic options for advanced disease. For non-oncogene-addicted NSCLC, the treatments currently included in the EML are all chemotherapies, associated with a median overall survival of about 12 months.

Benefits

The application presented evidence from six phase I–III clinical trials in which tislelizumab was used (12–17). All studies included patients with histologically confirmed, locally advanced (stage IIIB) or metastatic (stage IV) NSCLC. Patients were treated with tislelizumab 200 mg every 3 weeks. Only the three phase III trials are described below. First-line chemoimmunotherapy RATIONALE 304 was a randomized, open-label, multicentre phase III study evaluating tislelizumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone in 332 patients in China (13). The primary endpoint was progression-free survival. After 9.8 months of follow-up, progression-free survival was 9.7 months in the tislelizumab arm compared with 7.6 months in the chemotherapy arm (hazard ratio (HR) 0.65, 95% confidence interval (CI) 0.46 to 0.90). Objective response rates in the tislelizumab and chemotherapy arms were 57.4% (95% CI 50.6% to 64.0%) and 36.9% (95% CI 28.0% to 46.6%), respectively. Median overall survival was not reached in either treatment arm. The 6-month overall survival rate was higher in the tislelizumab arm (92.7%, 95% CI 88.3% to 95.5%) compared with the chemotherapy arm (84.6%, 95% CI 76.0% to 90.2%). RATIONALE 307 was a randomized, open-label, multicentre phase III study evaluating tislelizumab plus chemotherapy (carboplatin plus (nab)paclitaxel) versus chemotherapy alone in 360 patients in China (14). The primary endpoint was progression-free survival. After 8.6 months of follow-up, progression-free survival was 7.6 months in the tislelizumab arm compared with 5.5 months in the chemotherapy arm. Overall survival data were immature. The effect of tislelizumab on health-related quality of life was evaluated in patients enrolled in the RATIONALE 304 and RATIONALE 307 trials (18,19). Adding tislelizumab to platinum-based chemotherapy was associated with improvements in global health status/ quality-of-life scores, and reduced scores on symptom-specific subscales for coughing, chest pain, dyspnoea, haemoptysis and peripheral neuropathy. Second- and third-line monotherapy RATIONALE 303 was a randomized open-label, phase III study evaluating tislelizumab versus docetaxel in 805 patients with locally advanced or metastatic squamous or non-squamous NSCLC who had disease progression on a prior platinum-containing regimen (17). Coprimary endpoints were overall survival in the intention-to-treat population and the population of patients with PD-L1 tumour cell expression ≥ 25%. At the final analysis, in the intention-to-treat population, median overall survival was longer

with tislelizumab than docetaxel (16.9 months versus 11.9 months; HR 0.66, 95% CI 0.56 to 0.79). Median overall survival was also longer with tislelizumab than docetaxel in the population with PD-L1 ≥ 25% (19.3 months versus 11.5 months; HR 0.53, 95% CI 0.40 to 0.70). Median progression-free survival was also longer with tislelizumab compared with docetaxel (4.2 months versus 2.6 months; HR 0.63, 95% CI 0.53 to 0.75). Patients receiving tislelizumab also had a greater objective response rate (22.6% versus 7.0%) and a longer duration of response (13.5 months versus 6.0 months) compared with patients in the docetaxel group. The effect of tislelizumab on health-related quality of life was evaluated in patients enrolled in the RATIONALE 303 trial (20). The global health status/ quality-of-life score in the tislelizumab arm improved relative to baseline from cycles five through to 10 while it declined in cycles six through to 10 in the docetaxel arm. The tislelizumab arm showed a reduction from baseline at cycle 12 in the symptom scores of coughing, chest pain and dyspnoea while patients in the docetaxel arm experienced an increase in symptoms.

Harms

In RATIONALE 304, 222/222 patients (100%) in the tislelizumab arm and 109/110 patients (99.1%) in the chemotherapy arm experienced at least one treatment-emergent adverse event. The most common treatment-emergent adverse events in both treatment arms were haematological (e.g. anaemia, leukopenia and thrombocytopenia), and most were grade 1 or 2 in severity. Serious treatment-emergent adverse events were reported in 97 patients (33.3% in the tislelizumab arm and 20.9% in the chemotherapy arm). Discontinuation of any treatment component because of treatment-emergent adverse events was reported in 25.7% and 9.1% of patients in the tislelizumab and chemotherapy arms, respectively. Treatment-emergent adverse events leading to permanent discontinuation of tislelizumab and dose modifications of tislelizumab occurred in 11.3% (25/222) of patients and 59.9% (133/222) of patients, respectively (13). In RATIONALE 307, 99.6% (237/238) of patients in the tislelizumab arm and 100.0% (117/117) of patients in the chemotherapy arm experienced at least one treatment-emergent adverse event. The most common treatment-emergent adverse event of grade 3 or higher was decreased neutrophil levels. Serious treatment-emergent adverse events were reported in 118 patients: 37.4% (89/238) of patients receiving tislelizumab and 24.8% (29/117) or patients receiving chemotherapy. Discontinuation of any treatment component because of treatment-emergent adverse events was reported in 21.0% (50/238) of patients receiving tislelizumab and in 15.4% (18/117) of patients receiving chemotherapy. Treatment-emergent adverse events leading to permanent discontinuation of tislelizumab occurred in 10.1% (24/238) of patients. Treatment-emergent adverse events leading to death were similar in treatment arms: 3.8% (9/238) for tislelizumab and 4.3% (5/117) for chemotherapy. Treatment-related adverse events occurred in 99.4% (353/355) of patients. The most common treatment-related adverse events were anaemia, alopecia and decreased neutrophil levels. Grade 3 or higher treatment-related adverse events occurred in 296 patients: 85.8% (202/238) of patients receiving tislelizumab and 80.3% (94/117) of patients receiving chemotherapy. Grade 3 or higher treatment-related adverse events were mostly haematological and consistent with known adverse events of chemotherapy. Six patients experienced treatment-related adverse events leading to death (three patients receiving tislelizumab and three patients receiving chemotherapy), none of which were solely attributed to tislelizumab. Hyperglycaemia, hypothyroidism and pneumonia were the most common immune-mediated adverse events in patients who received tislelizumab therapy. Most potential immune-mediated adverse events were grade 1 and 2 and did not lead to treatment discontinuation (14). In RATIONALE 303, 96.8% (517/534) of patients in the tislelizumab arm and 98.4% (254/258) of patients in the docetaxel arm experienced at least one treatment-emergent adverse event. There were fewer reported treatment-emergent adverse events of grade 3 or higher in the tislelizumab arm than in the docetaxel arm (42.1% versus 74.8%). The most common treatment-emergent adverse events of any grade in the tislelizumab arm were anaemia, cough and increases in liver enzymes. The incidence of immune-mediated treatment-emergent adverse events of all grades in the tislelizumab arm was 18.9%, with hypothyroidism (7.9%) and pneumonitis and immune-mediated lung disease (4.5%) being the most frequently occurring events. Treatment-related adverse events occurred in 74.9% (400/534) of patients in the tislelizumab arm and 93.8% (242/258) of patients in the docetaxel arm. The most common treatment-related adverse events of any grade in the tislelizumab arm were liver enzyme increases, anaemia and hypothyroidism. Grade 3 or higher treatment-related adverse events occurred in 15.7% (84/354) of patients in the tislelizumab arm and 66.3% (171/258) of patients in the docetaxel arm (17).

Cost / cost effectiveness

A study using data from the RATIONALE 304 trial assessed the cost–effectiveness of adding tislelizumab to first-line pemetrexed-platinum chemotherapy in locally advanced or metastatic non-squamous NSCLC without known sensitizing EGFR mutations or anaplastic lymphoma kinase rearrangements from the perspective of the Chinese health care system (21). For the entire patient population, first-line tislelizumab plus chemotherapy was associated with an incremental cost–effectiveness ratio of US$ 29 132

per quality-adjusted life year (QALY) gained compared with chemotherapy alone. In subgroup analyses based on factors including age, sex, performance status and PD-L1 tumour expression, the incremental cost–effectiveness ratios ranged from US$ 27 018 to US$ 33 074 per QALY gained. These values were below the willingness-to-pay threshold used in the analysis. Another study assessed the cost–effectiveness of tislelizumab versus docetaxel for patients who were previously treated for advanced NSCLC in China (22). Efficacy and safety data were based on the RATIONALE 303 trial. Costs were calculated from the perspective of Chinese health care system. Tislelizumab was associated with an incremental cost–effectiveness ratio of US$ 18 122 per QALY gained compared with docetaxel. This was lower than the cost-effective threshold of three times the gross domestic product per capita in China used in the analysis. Utility of progression-free survival, followed by the price of tislelizumab had the greatest impact on the incremental cost–effectiveness ratio. The application reported the current annual cost of tislelizumab as ¥49 300. In comparison, annual costs for pembrolizumab, nivolumab, atezolizumab and durvalumab were reported to range between ¥479 010 and ¥759 696.

WHO guidelines

WHO guidelines for treatment of NSCLC are not currently available.

Availability

Tislelizumab has regulatory approval from the National Medical Product Administration in China for nine indications, including those requested in the application. Applications for tislelizumab have been submitted to regulatory agencies in Australia, Europe, the Republic of Korea, New Zealand, Switzerland, United Kingdom and United States and are currently under review.

Other considerations

The technical team in cancer in the WHO Department of Noncommunicable Diseases did not provide comments on the application for tislelizumab.

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