2021 WHO Expert Committee on the Selection and Use of Essential Medicines

Application for the addition of Tislelizumab on the WHO Model List of Essential Medicines

Submitted by

BeiGene Co., Ltd.

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BeiGene

CONTENTS

General items

1. Summary statement of the proposal for inclusion, change or deletion

BeiGene (Beijing), Co., Ltd. (Hereinafter referred to as BeiGene) proposes the inclusion of Tislelizumab on the complementary list of the WHO Model List of Essential Medicines (EML) under the category of immunomodulators.

On April 9, 2020, Tislelizumab was approved by NMPA for its new indication for the treatment of patients with high PD-L1 expression with locally advanced or metastatic urothelial carcinoma (UC) who have failed platinum-containing chemotherapy (including neoadjuvant or adjuvant chemotherapy) that have progressed within 12 months.

Tislelizumab is the first PD-1(1) (Programmed Cell Death Protein 1) monoclonal antibody with Fc hinge modification in the Chinese market. This modification can protect T cells that can kill tumor cells and PD-1 monoclonal antibodies from the phagocytosis of macrophages (2, 3), thereby affecting the anti-tumor efficacy.

2. Relevant WHO technical department and focal point (if applicable)

N/A

3. Name of organization(s) consulted and/or supporting the application

N/A

4. International Nonproprietary Name and Anatomical Therapeutic Chemical code of the medicine

INN：Tislelizumab

ATC：N/A

5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate pediatric dose forms/strengths (if appropriate)

Tislelizumab is an intravenous infusion preparation, a single-dose vial contains 100 mg/10 Ml. It is clear to slightly opalescent and colorless to pale yellow liquid. The recommended dosage for locally

advanced or metastatic UC of Tislelizumab is 200 mg every 3 weeks, administered intravenously over 60 minutes until disease progression or unacceptable toxicity. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

The safety and effectiveness of Tislelizumab have not been established in pediatric patients less than 18 years old.

Currently, the application data of Tislelizumab in elderly patients aged over 65 years old is limited. It is recommended to use with caution under the guidance of physicians. If necessary, dose modification is not required.

At present, Tislelizumab has been approved for the treatment of patients with high PD-L1 expression with locally advanced or metastatic urothelial carcinoma(UC) who have failed platinum-containing chemotherapy (including neoadjuvant or adjuvant chemotherapy) that have progressed within 12 months on the Chinese market.

6. Whether listing is requested as an individual medicine or as representative of a pharmacological class

Individual medicine

Treatment details, public health relevance and evidence appraisal and synthesis

7. Treatment details (requirements for diagnosis, treatment and monitoring)

7.1 Disease diagnosis

7.1.2 Diagnostic criteria for UC

The diagnosis of UC is based on the patient's medical history, symptoms and signs, combined with laboratory tests, imaging tests, urine cytology, urine tumor markers, and cystoscopy. Cystoscopy is the most important examination. Pathological examination through biopsy under cystoscopy is the gold standard for the diagnosis of bladder cancer. Imaging examination of the upper urinary tract may reveal the presence of renal pelvis and/or ureteral tumors.(4)

7.2 Guidelines

Tislelizumab is recommended in the Guidelines of Chinese Society of Clinical Oncology (CSCO): urothelial cancer (2020 edition) for the treatment of patients with high PD-L1 expression with locally advanced or metastatic urothelial carcinoma (UC).(5)

Tislelizumab was also referred to be one of the immunotherapy and targeted therapy for the treatment of locally advanced or metastatic UC in the Chinese Guidelines for Diagnosis and Treatment of Urology and Andrology Diseases(2019).(6)

7.3 Usage and dosage

Tislelizumab is indicated for the treatment of patients with high PD-L1 expression with locally advanced or metastatic urothelial carcinoma (UC) who have failed platinum-containing chemotherapy (including neoadjuvant or adjuvant chemotherapy) that have progressed within 12 months.

Patients with high PD-L1 expression should be selected for the use of Tislelizumab in the treatment of locally advanced or metastatic UC. PD-L1 expression level is evaluated by a detection method approved by NMPA.

The expression of PD-L1 is measured by immunohistochemistry, and the high expression of PD-L1 is defined as:

- If the number of tumor infiltrating immune cells is greater than 1%, it is defined as 25% or more of

tumor cells or 25% or more of immune cells with PD-L1 expression;

• If the number of tumor infiltrating immune cells is less than or equal to 1%, it is defined as 25% or more of tumor cells or all immune cells (100%) have PD-L1 expression.

7.3.1 Recommended usage

Tislelizumab should be administered under the guidance of physicians experienced in tumor therapy. Tislelizumab is intended for intravenous infusion only. Administer the initial infusion over 60 minutes through an intravenous line with a sterile, non-pyrogenic, low-protein binding in-line filter (pore size of 0.2–0.22 micron). If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes.

Tislelizumab should not be administered by intravenous injection or a single rapid intravenous injection. Tislelizumab is diluted with sodium chloride solution for injection (9mg / ml, 0.9%) to the concentration of 1-5mg / ml before intravenous infusion.

7.3.2 Recommended dosage

The recommended dosage of Tislelizumab is 200 mg every 3 weeks, administered intravenously over 60 minutes until disease progression or unacceptable toxicity.

7.3.3 Dose modification

It is possible to observe atypical response (e.g. temporary enlargement of the tumor or appearance of new lesions in the first few months, followed by tumor shrinkage or disappearance of new lesions). If the patient's clinical symptoms are stable or continue to alleviate, even if there is a preliminary manifestation of disease progression, based on the judgment of the overall clinical benefits, the drug can be considered to continue treatment until the disease progression is confirmed.

Depending on the safety and tolerability of the individual patient, suspension or permanent withdrawal may be required, and no dosage increases or reductions are recommended. Recommendations for dosage modifications are provided in Table 7-1(1).

Table 7-1 Recommended Dosage Modifications for Adverse Reactions

Immune-Mediated Adverse Reactions	**Severity**	**Dose Modification**
Pneumonitis	Grade 2	Withhold dose until Grade 1 or resolved
	Grade 3 or 4 or relapsed Grade 2	Permanently discontinue
Diarrhea and Colitis	Grade 2 or 3	Withhold dose until Grade 1 or resolved
	Grade 4	Permanently discontinue

Hepatitis	Grade 2, Aspartate aminotransferase/ alanine aminotransferase (AST/ALT) is within normal limits at baseline and increases to more than 3 and up to 5 times the upper limit of normal (ULN), and/or total bilirubin (TBiL) increases to more than 1.5 and up to 3 times the ULN.	Withhold dose until Grade 1 or resolved
	Grade 3, AST/ALT is more than 3 and up to 5 times ULN at baseline and increases to more than 5 and up to 20 times the ULN, or TBiL increases to more than 3 and up to 10 times the ULN. Grade 4, AST/ALT is more than 5 and up to 20 times ULN at baseline and increases to 20 times the ULN, or TBiL increases to 10 times the ULN.	Permanently discontinue
Nephritis	Grade 2 or 3 blood creatinine elevated	Withhold dose until Grade 1 or resolved
	Grade 4 blood creatinine increased	Permanently discontinue
Endocrinopathies		
Hypophysitis	Grade 2 or 3	Withhold dose until Grade 1 or resolved
	Grade 4	Permanently discontinue
Thyroid disease	Grade 2 or 3 hypothyroidism Grade 2 or 3 hyperthyroidism	Withhold dose until Grade 1 or resolved
	Grade 4 hypothyroidism Grade 4 hyperthyroidism	Permanently discontinue
Adrenal Insufficiency	Grade 2	Withhold dose until Grade 1 or resolved
	Grade 3 or 4	Permanently discontinue
Hyperglycemia OR Type 1 Diabetes Mellitus	Grade 3	Withhold dose until Grade 1 or resolved
	Grade 4	Permanently discontinue
Skin adverse reactions	Grade 3	Withhold dose until Grade 1 or resolved
	Grade 4 Stevens Johnson Syndrome（SJS）或 Toxic Epidermal Necrolysis（TEN）	Permanently discontinue
Thrombocytopenia	Grade 3	Withhold dose until Grade 1 or resolved

	Grade 4	Permanently discontinue
Other immune-mediated adverse reactions	Grade 3 or 4 blood Amylase or Lipase elevated Grade 2 or 3 Pancreatitis Grade 2 Myocarditis * Grade 2 Encephalitis Grade 2 or 3 other immune-mediated adverse reactions for the first time	Withhold dose until Grade 1 or resolved
	Grade 4 Pancreatitis or any grade of relapsed Pancreatitis Grade 3 or 4 Myocarditis Grade 3 or 4 Encephalitis Grade 4 other immune-mediated adverse reactions for the first time	Permanently discontinue
Relapsed or persistent adverse reactions	Grade 3 or 4 relapsed（Endocrinopathies excluded） Grade 2 or 3 adverse reactions did not improve to Grade 0-1 after withhold dose 12 weeks（Endocrinopathies excluded） Corticosteroid dose is not less than or equal to prednisone 10 mg per day (or equivalent) after withhold dose 12 weeks	Permanently discontinue
Infusion-Related Reactions	Grade 2	Interrupt or slow the rate of Infusion, When the symptoms are relieved, consider medication and observe closely
	Grade 3 or 4	Permanently discontinue

Note: The severity rating is determined according to the National Cancer Institute's Generic Term for Adverse Events Assessment Standard version 4.03 (NCI-CTCAEV4.03).

* The safety of retreatment with Tislelizumab after treatment of myocarditis until Grade 1 or resolved is not clear.

7.3.4 USE IN SPECIFIC POPULATIONS

Hepatic insufficiency: there is no research data of Tislelizumab for patients with moderate or severe hepatic insufficiency, and it is not recommended for patients with moderate or severe liver insufficiency. Patients with mild hepatic insufficiency should use this product with caution under the guidance of physicians. If necessary, dose modification is not required (1).

Renal insufficiency: there is no research data of Tislelizumab for patients with severe renal insufficiency, and it is not recommended for patients with severe renal insufficiency. Patients with mild

or moderate renal insufficiency should use this product with caution under the guidance of physicians. If necessary, dose modification is not required (1).

Pediatric Use: the safety and effectiveness of Tislelizumab have not been established in pediatric patients less than 18 years old(1).

Geriatric Use: the application data of Tislelizumab in elderly patients aged over 65 years old is limited. It is recommended to use with caution under the guidance of physicians. If necessary, dose modification is not required. (1).

8. Information supporting the public health relevance

8.1 Epidemiology and disease burden

Urothelial carcinoma (UC) refers to the occurrence of tumors in the epithelial structure from the exit of the kidney to the urethra. About 90%-95% of tumors originates from the bladder, so it is also called urothelial bladder cancer (UBC). Cancers of the ureter, renal pelvis, and proximal urethra constitute approximately account for 5–10% of cases of urothelial carcinoma. UBC is the most common bladder cancer, accounting for more than 90% (7).

Bladder cancer is the 10th common tumor in the world. In 2018, there were 549,400 new patients worldwide, with an incidence rate of 7.2 per 100,000, of which males were 11.0 per 100,000, ranking sixth in the incidence of male malignant tumors; of which women were 3.3 per 100,000, ranking behind the 10th in the incidence of female malignant tumors(8). According to the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) database statistics, there are approximately 76,960 new cases of bladder cancer in the United States each year, of which 58,950 are men, ranking 4th in the incidence of common tumor in men(9). According to data from the International Agency for Research on Cancer (IARC), there were 82,270 new cases of bladder cancer in China in 2018, with an incidence rate of 5.8 per 100,000 (10).

According to IARC forecast data, in 2018, there were 431,919 bladder cancer patients worldwide, with a prevalence rate of 5.7 per 100,000, and the number of patients in 5 years was 1,648,482, with a prevalence rate of 21.6 per 100,000. In 2018, the number of bladder cancer patients in China was 58,715, with a prevalence rate of 4.1 per 100,000; the number of patients in 5 years was 222,962, with a prevalence rate of 15.7 per 100,000 (10). As the population ages, the prevalence of UC will increase further.

Globally, the mortality rate of bladder cancer ranks 13th among all tumors, and the mortality rate ranks

9th among male malignant tumors(4). In 2018, there were 199,000 deaths from bladder cancer worldwide, with a mortality rate of 2.6 per 100,000, of which 3.9 per 100,000 men and 0.9 per 100,000 women(10).

The survival rate of UBC patients decreases with disease progression, and they tend to relapse early. When UBC patients are first diagnosed, 75% are non-muscular invasive bladder cancer (NMIBC), and 25% are muscular invasive bladder cancer (MIBC), of which 10%-15% have metastasized, and about 7% are regional metastases , 5% belong to distant metastases(11). Patients with distant metastases have a poor prognosis due to the inability to surgically remove the tumor and lack of effective treatments. The 5-year relative survival rate is only 4.6%(12).

UBC has caused a heavy economic burden on patients, and it has also brought huge productivity losses to society. In China, the average cost of hospitalization for UBC patients is US$3,607 per case, and the average cost of outpatients is US$134 per case. The total cost of bladder cancer patients accounts for about 1.5% of the total cost of cancer.(13). An Italian study showed that in 2016, there were an estimated 330,000 UBC patients in Italy, with a total cost of approximately US$1.3 billion (14). In addition, the United States predicts that by 2020, the number of bladder cancer patients will reach 629,000, and the estimated expenditure will also increase to US$ 4.91 billion (15).

8.2 Assessment of current use

Surgical treatment of UC is developing rapidly, however, research on chemotherapy in the internal medicine system has been stagnant. In the past 30 years, cisplatin-based combination chemotherapy has been the standard treatment for locally advanced/metastatic UC. Classical therapies include GC (Gemcitabine, Cisplatin), MVAC (Methotrexate, Vinblastine, Adriamycin, Cisplatin) and DD-MVAC (dose-dense Methotrexate, Vinblastine, Adriamycin, Cisplatin) (4, 16), etc. The overall response rate (ORR) of the above therapies is about 40%~50%, and the median overall survival (OS) is about 14-15 months. However, about 40%~50% of patients with metastatic UC cannot tolerate cisplatin treatment due to poor physical condition or impaired renal function, and can only use carboplatin-based treatment options, with an ORR of about 30%~40% , and median OS is only 9-10 months (17, 18). The duration of response is short and almost everyone will progress. If the patient cannot tolerate cisplatin, OS will be shortened.

For locally advanced/metastatic UC patients with disease progression after first-line chemotherapy, there is currently no standard second-line treatment. Paclitaxel, Pemetrexed, Docetaxel, Gemcitabine, Doxorubicin, etc. are commonly used clinically, but the efficacy is limited with an ORR of about 12% and OS is only 5-7 months (18, 19).

Before 2016, chemotherapy was the only option for systemic treatment of locally advanced/metastatic UC. Since 2016, the U.S. FDA has approved 5 PD-1/PD-L1 inhibitors for locally advanced/metastatic UC patients who are not suitable for cisplatin-based chemotherapy or platinum-based chemotherapy. The 5 PD-1/PD-L1 inhibitors are PD-1 (Nivolumab, Pembrolizumab) and PD-L1 (Atezolizumab, Durvalumab, and Avelumab). Patients are expected to benefit from PD-1/PD-L1 inhibitors in the long term. Tislelizumab is a new type of PD-1/PD-L1 inhibitor, and its good efficacy (objective response rate is 24%(95CI, 16-33), complete response rate is 10%)(20) brings benefits to patients with locally advanced and metastatic UC.

9. Review of benefits: summary of evidence of comparative effectiveness

9.1 Identification of clinical evidence (search strategy, systematic reviews identified, reasons for selection/exclusion of particular data)

Systematic reviews, technology assessment reports, and meta-analyses of controlled clinical trials involving Tislelizumab in at least one arm were searched on the database of Clinical Trials, PubMed, and Cochrane. However, no meta-analysis including Tislelizumab trials was reported.

Arnold Lee *et al*（2020）reviewed the history, mechanism of action, and clinical trials of Tislelizumab. It summarized all major clinical trials of Tislelizumab and explained the basic molecular mechanism of Tislelizumab. In addition, it also mentioned that Tislelizumab can significantly improve the prognosis of patients with R/R cHL who have experienced second-line chemotherapy. In December 2019, Tislelizumab was officially approved for marketing by NMPA in China for patients with R/R cHL after at least one second-line chemotherapy (21).

In April 2020, according to the latest news from NMPA of China, Tislelizumab was approved for its new indication for the treatment of patients with high PD-L1 expression with locally advanced or metastatic urothelial carcinoma(UC) who have failed platinum-containing chemotherapy (including neoadjuvant or adjuvant chemotherapy) that have progressed within 12 months (22).

9.2 Summary of available data (appraisal of quality, outcome measures, summary of results)

The following studies describe the clinical development of Tislelizumab for UC:：

- BGBA317-102 (NCT04068519) was a phase 1/2, open-label, non-comparative study which propose to examine the safety, tolerability, and antitumor activity of Tislelizumab in adult (at least

18 years old) Chinese patients with histologically or cytologically confirmed advanced solid tumors（including UC） with measurable disease. The phase 1 portion of the study consisted of a dose-verification study and a pharmacokinetic (PK) sub-study; phase 2 was an indication-expansion study including 11 solid tumor cohorts (23).

- BGB-A317-001 (NCT02407990) was a phase IA/IB, open label, multiple doses, dose escalation and expansion study to investigate the safety, pharmacokinetics and antitumor activities of the anti-PD-1 monoclonal antibody Tislelizumab in subjects with advanced tumors (including UC solid tumors). This study of Tislelizumab in patients with advanced tumors comprises 2 stages: Phase IA was mainly to count number of participants with adverse events to confirm the safety of Tislelizumab; Phase IB was to assess overall response among participants with select tumor types based on RECIST v 1.1(24).
- BGB-A317-204 (CTR20170071) was a single-arm, non-randomized, open label, multi-center Phase 2 study. The purpose of this study was to assessed the efficacy and safety of Tislelizumab in patients with locally advanced or metastatic urothelial carcinoma who have previously received PD-L1positive (PD-L1+) chemotherapy containing platinum. The primary efficacy endpoint was ORR (RECIST v1.1), assessed by IRC. Secondary efficacy endpoints included duration of response (DoR), progression free survival (PFS), and overall survival (OS); Adverse events (AEs) incidence and severity were secondary safety endpoints. The clinical outcomes showed that Tislelizumab was generally well tolerated and demonstrated clinical activity in patients with PD-L1+ UC. (20)

9.2.1 Pharmacokinetics

The pharmacokinetics of intravenous (IV) Tislelizumab 0.5, 2, 5 or 10 mg/kg once every 2 weeks, 2 or 5 mg/kg or 200 mg once every 3 weeks were investigated in a population pharmacokinetic analysis of 798 patients from three trials (NCT02407990, NCT04068519 and NCT03209973), and data from 112 patients in a non-compartmental pharmacokinetic model. After a single IV dose of Tislelizumab, exposure (C_{max} and AUC_{14d}) was linear over the dose range 0.5–10 mg/kg (1).

Tislelizumab is completely bioavailable following intravenous infusion. The volume of distribution is 4.41 L following a single infusion of Tislelizumab 200 mg, and 5.247 L at steady state. Following a single dose of Tislelizumab 200 mg, the clearance of Tislelizumab was 0.247 L/day and the half-life was 13.3 days, while after repeat administration in population pharmacokinetic analyses, the clearance was 0.171 L/day and the half-life was 26 days (1).

The effect of renal or hepatic impairment on Tislelizumab pharmacokinetics has not been directly

evaluated. Population pharmacokinetic analyses suggested that mild to moderate renal impairment and mild hepatic impairment had no effect on Tislelizumab pharmacokinetics. There are insufficient pharmacokinetic data in patients with severe renal impairment or moderate or severe hepatic impairment (1).

9.2.2 Pharmacodynamics

Tislelizumab binds to human PD-1 with high specificity and affinity (disassociation constant, KD 0.15 nmol/L) (25) , using the critical epitopes, Gln75, Thr76, Asp77 and Arg86 that are present on PD-1 (26). This is in contrast to Nivolumab and Pembrolizumab that do not require these epitopes for binding; Tislelizumab has a slower disassociation rate from PD-1 in comparison with Nivolumab (50-fold slower) and Pembrolizumab (100-fold slower)(26).

Immunodeficient mice who had been simultaneously injected with A431 cancer cells and peripheral blood monocytes showed significantly reduced tumor growth when Tislelizumab was administered, whereas those treated with the Tislelizumab S228P variant showed similar tumor progression to vehicle treated mice (3).

Tumor spheroids were treated with Tislelizumab, Nivolumab or Pembrolizumab, and incubated with tumor-infiltrating lymphocytes isolated from human colorectal cancers or colorectal liver metastases in an ex vivo study. All three PD-1 blocking antibodies demonstrated significant increases in IFN-γ production and proliferation of tumor-infiltrating lymphocytes. However, spheroids treated with Tislelizumab 0.1, 1 and 10 μg/mL yielded significantly higher quantities of IFN-γ compared with treatment with Nivolumab or Pembrolizumab. Incubation with Tislelizumab resulted in better activation of tumour-infiltrating lymphocytes isolated from colorectal liver metastases, which is hypothesized to be due to the higher frequency of macrophages in this tumor type (leading to FcγRI binding with Nivolumab or Pembrolizumab) (27, 28).

9.2.3 Efficacy

In BGB-A317-204 trial, the primary endpoint was overall response rate (ORR) as assessed by an independent review committee (IRC) based on RECIST v1.1. Between 04 Jul 2017 and 16 Sep 2019, 113 patients received Tislelizumab for a median of 15.3 weeks and were followed up for a median of 9.4 month, twenty (18%) patients remained on treatment and 93 (82%) discontinued tislelizumab. Reasons for discontinuation included disease progression (n = 53), AEs (n = 19), withdrawal of consent (n = 11), and symptomatic deterioration (n = 10).(20)

Of 104 evaluable patients, a confirmed objective response was observed in 25 patients (ORR=24%, 95% CI:16, 33), including 10 complete response (CR) and 15 partial response (PR) per IRC assessment. Median DoR per IRC was not reached at the time of protocol-defined analysis; 17(68%) responders

had ongoing responses at data cutoff. Median PFS and OS were 2.1(95%CI,2.0-3.2) and 9.8 (95%CI, 7.5-12.5) months, respectively. (20)

9.3 Summary of available estimates of comparative effectiveness

9.3.2 Comparison of Tislelizumab with other PD-1/PD-L1 monoclonal antibodies for UC

Direct comparative data are still lacking. Table 9-1 lists the data of efficacy for UC reported with Tislelizumab and other PD-1/PD-L1 monoclonal antibodies. The data shows that the ORR of Tislelizumab (24%) is higher than that of most monoclonal antibodies, and the CR (10%) is the highest, showing that Tislelizumab has a better efficacy than other monoclonal antibodies.

Table 9-1 Data of efficacy for locally advanced/metastatic UC reported with different PD-1/PD-L1 monoclonal antibodies

Drug (Clinical trial)	Phase	Type of patients	Definition of PD-L1 positive rate	N	ORR	CR	PR	mPFS	mOS
Tislelizumab (NCT04004221)(20)	II	PD-L1+ patients	≥25%	104	24% (95%CI,16,33)	10%	14%	2.1 (95%CI,2.0-3.2)	9.8 (95%CI, 7.5-12.5)
Atezolizumab (IMvigor210)(29)	II	All patients	/	310	15% (95%CI, 11-19)	5%	10%	2.1 (95%CI,2.1-2.1)	7.9 (95%CI, 6.6 -9.3)
		PD-L1+ patients	≥5%	100	26% (95% CI,16-36)	11%	15%	2.1	11.4 (95%CI, 9.0-NE)
Atezolizumab (IMvigor211)(30)	III	All patients	/	467	13.4% (95%CI,10.5-16.9)	3%	10%	2.1 (95%CI, 2.1-2.2)	11.3 (95% CI, 8.7-13.2)
		PD-L1+ patients	≥5%	116	23.0% (95%CI, 15.6-31.9)	7%	16%	2.4 (95%CI, 2.1-4.2)	17.8 (95%CI, 9.7-NE)
Durvalumab (study1108)(31)	I/II	All patients	/	191	17.8% (95%CI, 12.7-24.0)	3.7%	14.1%	1.5 (95% CI, 1.4-1.9)	18.2 (95% CI, 8.1- NE)
		PD-L1+ patients	≥25%	98	27.6% (95%CI, 19.0-37.5)	4.1%	2.5%	2.1 (95% CI, 1.4-2.8)	20.0 (95% CI, 11.6-NE)
Avelumab (JVAELIN)(32)	I	All patients	/	161	17% (95% CI, 11-24)	6%	11%	1.5 (95% CI, 1.4-2.4)	6.5 (95% CI, 5.8-9.5)

Nivolumab (Checkmate-275)(33)	II	PD-L1+ patients	≥5%	63	24% (95% CI, 14-36)	10%	14%	2.8 (95% CI, 1.4-3.9)	8.2 (95% CI, 5.7-13.7)
		All patients	/	265	19.6% (95% CI, 15.0-24.9)	2%	17%	2.0 (95% CI, 1.87–2.63	8.74 (95% CI, 6.05-NR)
		PD-L1+ patients	≥5%	81	28.4% (95% CI, 18.9-39.5)	/	/	/	/
Pembrolizumab (keynote-052)(34)	II	All patients	/	370	24% (95% CI, 20-29)	5%	19%	2 (95% CI 2–3)	6
		PD-L1+ patients	1%-10%	139	20% (95% CI, 14–28)	/	/	/	/
		PD-L1+ patients	≥10%	80	39% (95% CI, 28–50)	/	/	/	/
Pembrolizumab (keynote-045)(35)	III	All patients	/	270	21.1% (95% CI, 16.4-26.5)	NA	NA	2.1 (95% CI, 2.0 to 2.2)	10.3 (95% CI, 8.0- 11.8)

10.Review of harms and toxicity: summary of evidence of safety

10.1 Estimate of total patient exposure to date

The estimated cumulative clinical trial exposure to Tislelizumab from May 2015 to now is 5800 patients(20, 23, 24, 36).

10.2 Description of the adverse effects/reactions and estimates of their frequency

The following section details the undesirable effects of Tislelizumab.

Safety results of BGB-A317-204 (20)showed that a total of 106 (94%) patients experienced at least 1 AE considered to be related to Tislelizumab by the investigator (AEs definitely related, probably related, possibly related, or possibly unrelated to Tislelizumab, as well as those missing causal relationships, were defined as related AEs). Anemia (n = 31; 27%) and pyrexia (n = 22； 20%) were the most common treatment-related AEs (TRAEs). Most reported TRAEs were grade 1-2 in severity; anemia (n = 8; 7%) and hyponatremia (n = 6; 5%) were the only grade 3-4 TRAEs occurring in ≥5% patients . TRAEs led to treatment discontinuation of 16 (14%) patients; drug eruption (n = 3; 3%) and renal failure (n = 2; 2%) were the only TRAEs occurring in at least 1 patient.

Immune-related AEs (irAEs) occurred in 31 (27%) patients; irAEs occurred in ≥5% of patients included skin adverse reactions (n = 13; 12%), hypothyroidism (n = 12; 11%), and hyperthyroidism (n = 7; 6%). Eight (7%) patients had irAEs of grade ≥ 3; no fatal irAEs were reported. Serious TRAEs occurred in 42 (37%) patients, the most common being pyrexia (n = 4; 4%) and upper respiratory tract infection, urinary tract infection, and drug eruption (n = 3; 3% each). Among the 7 patients with a TRAE leading to death, 3 were considered possibly related to study treatment by the investigators (hepatic failure, n = 2; respiratory arrest, n = 1); 3 were considered possibly unrelated to study treatment by the investigators (renal failure, n = 1; renal impairment, n = 1; general physical health deterioration, n = 1); and 1 patient did not have causality of death assigned by the investigator (unexplained death, n = 1).

10.3 Summary of available data (appraisal of quality, summary of results)

The safety information of Tislelizumab comes from three single-agent clinical studies（BGB-A317-

001[n=451], BGBA317-102[n=300], BGB-A317-203 (NCT03209973) [n=70]）(23, 24, 36) involving 821 patients. Tumor types include non-small cell lung cancer (n=105), esophageal cancer (n=81), gastric cancer (n=78), classic Hodgkin's lymphoma (n=70), hepatocellular carcinoma (n=69), Colorectal cancer (n=54), ovarian cancer (n=51), urothelial carcinoma (n=39), renal cell carcinoma (n=37), melanoma (n=36), breast cancer (n=32), head and neck squamous cell carcinoma (n=29), nasopharyngeal carcinoma (n=27), cholangiocarcinoma (n=18), pancreatic cancer (n=10), small cell neuroendocrine carcinoma (n=10) , Sarcoma (n=10), mesothelioma (n=9), cervical cancer (n=7), other types of tumors (n=49). In the above studies, 383 patients received 200 mg Tislelizumab every 3 weeks, and 355 patients received 5 mg/kg Tislelizumab every 3 weeks. Each of 26 patients received 2 mg/kg or 5 mg/kg Tislelizumab every 2 weeks, and 21 patients received 2 mg/kg Tislelizumab every 3 weeks. 7 patients received 10 mg/kg Tislelizumab every 2 weeks, and 3 patients received 0.5 mg/kg Tislelizumab every 2 weeks. The median administration time of Tislelizumab was 16 weeks (range: 0.6~162 weeks). 35.7% of patients received Tislelizumab treatment at least 6 months, and 20.0% received Tislelizumab treatment at least 12 months.

The incidence of AEs of all grades was 71.0% among the 821 patients treated with Tislelizumab, with an incidence of greater than or equal to 10% including fatigue, rash, hypothyroidism, increased alanine aminotransferase, and increased aspartate aminotransferase.

The incidence of grade 3 and above adverse reactions was 18.4%, and the incidence of more than 1% included: increased glutamyl transferase, pulmonary inflammation, increased aspartate aminotransferase, increased alanine aminotransferase, severe skin reaction, anemia.

10.4 Summary of comparative safety

Since Tislelizumab has only completed a single-arm Phase II clinical trial, and the Phase III clinical trial compared with other products is still in progress, so there is still a lack of safety data for this part.

10.5 Identification of variation in safety that may relate to health systems and patient factors

10.5.1 Pregnancy & Lactation & Reproductive Potential

Pregnancy: there are no available data on the use of Tislelizumab in pregnant women. Human IgG4 is known to cross the placental barrier and Tislelizumab is an immunoglobulin G4 (IgG4), therefore, Tislelizumab has the potential to be transmitted from the mother to the developing fetus. Unless the

clinical benefit outweighs the potential risk, Tislelizumab is not recommended for treatment during pregnancy(1).

Lactation: there is no information regarding the presence of Tislelizumab in human milk, the effects on the breastfed infant, or the effects on milk production. As human IgG is excreted in human milk, the potential for absorption and harm to the infant is unknown. Because of the potential for serious adverse reactions in breastfed infants from Tislelizumab, advise women not to breastfeed during treatment and for at least 5 months after the last dose(1).

Contraception: advise females of reproductive potential to use effective contraception during treatment with Tislelizumab and for at least 5 months following the last dose(1).

Reproductive: Tislelizumab has limited application information in females and males of reproductive potential, therefore, the effect of Tislelizumab on male and female fertility is unknown(1).

10.5.2 Pediatric

The safety and effectiveness of Tislelizumab have not been established in pediatric patients less than 18 years old(1).

10.5.3 Geriatric

In current clinical trials of Tislelizumab, 30.1% patients were 65 years old or older. In older patients and younger patients:

- The incidence of AEs of all grades under 65 years old are 69.2% and 67.8%, respectively;
- The incidence of AEs of grade 3 and above were 18.2% and 18.5%, respectively;
- The incidence of AEs leading to suspension of dosing was 5.3% and 2.3%, respectively;
- The incidence of AEs leading to permanent discontinuation were 5.9% and 6.1%, respectively.

No dose modification were made to elderly patients in clinical studies. Tislelizumab has limited application information in geriatric patients at least 65 years old. It is recommended to use it with caution under the guidance of a doctor. If necessary, dose modification is not required(1).

11.Summary of available data on comparative cost and cost-effectiveness of the medicine

11.1 Price

Tislelizumab is priced at ¥10,688 (100mg/ vials).

The China Primary Health Care Foundation, in conjunction with BeiGene, initiated the Patient Assistance Program "Wei Ni, Qian Fang Bai Ji". Eligible patients will be assisted by the patient

assistance project for 2 cycles of medication after using 2 cycles of Tislelizumab injection at their own expense for the first time. In subsequent applications, eligible patients can choose 3 cycles of treatment at their own expense according to the disease status, and then obtain Tislelizumab (up to a maximum 11 cycles) needed within one year until the disease progression or the project is terminated; In addition, patients can also purchase 2 cycles again, and after approval by the foundation, they will be assisted for 2 cycles of medication and this plan will cycle within one year until the disease progresses or the project is terminated. This program not only reduces the cost of first-time medication; but also the cost for patients who need long-term medication. Patients only need to pay for 5 cycles of treatment and get 1-year medical treatment. The minimum annual treatment cost is about ¥106,900.(37)

11.2 Economic evaluation for UC treatment

11.2.1 Cost comparative advantage

At present, except for Tislelizumab, no other monoclonal antibodies have been approved for locally advanced or metastatic UC in China. Comparing the international prices of Tislelizumab with similar drugs marketed abroad, the results are shown in Table 11-1. Table 11-2 shows the price comparison of Tislelizumab and other monoclonal antibodies (not approved for this indication in China) for locally advanced or metastatic UC in China. Whether it is international or domestic, it can be seen that Tislelizumab has a price advantage in the treatment of locally advanced or metastatic UC.

Table 11-1 International price comparison of monoclonal antibody for the treatment of advanced UC

Drug	Cost（$）	Composition	Cost ($) /unit(mg)	Usage and dosage	Median PFS（months）	Cost of a course ($)
Tislelizumab	1,579	100mg:10mL	15.79	200mg every 3 weeks	2.2	10,069
Nivolumab	6,495	240mg:24mL	27.06	3mg/kg every 2 weeks	2	23,141
Durvalumab	3,671	500mg:10mL	7.34	10mg/kg every 2 weeks	2.1	21,976
Pembrolizumab	4,800	100mg:4mL	48.00	2mg/kg every 3 weeks	2.1	19,154

Table 11-2 Price comparison of monoclonal antibodies for advanced UC in China

Drug	Cost（¥）	Composition	Cost (¥) /unit(mg)	Usage and dosage	Median PFS（months）	Cost of a course (¥)
Tislelizumab	10,668	100mg:10mL	106.68	200mg every 3 weeks	2.2	68,034
Atezolizumab	32,800	1200mg:20mL	27.33	1200mg every 3 weeks	2.4	114,097
Nivolumab	9,250	100mg:10mL	92.50	3mg/kg every 2 weeks	2	79,095
Durvalumab	18,088	500mg:10mL	36.18	10mg/kg every 2 weeks	2.1	108,266
Pembrolizumab	17,918	100mg:4mL	179.18	2mg/kg every 3 weeks	2.1	71,499

11.2.2 Cost-effectiveness analysis

At present, there are no cost-effectiveness analysis of Tislelizumab. However, there are studies that access the cost-effectiveness of PD-1 monoclonal antibody and chemotherapy in the treatment of advanced UC (Table 11-3). The results show that PD-1 monoclonal antibody is likely to be cost-effective compared with chemotherapy. As a PD-1 monoclonal antibody, Tislelizumab has a better clinical outcome (ORR and CR) than other PD-1 monoclonal antibodies in the treatment of PD-L1 positive locally advanced or metastatic UC. Therefore, patients reach CR faster and reduce the subsequent treatment cost.

Furthermore, the China Primary Health Care Foundation, in conjunction with BeiGene, initiated the Patient Assistance Program "Wei Ni, Qian Fang Bai Ji".(37) Through the patient assistance program, the annual cost of Tislelizumab for patients is lower, and the lowest annual treatment cost is about ¥106,900, which is in the lower price range among all PD-1/L1 monoclonal antibodies.

Table 11-3 Economic evaluation of PD-1 monoclonal antibodies in the treatment of locally advanced/metastatic UC

Research	Region	Clinical trials	Disease	Intervention	ICER （$/QALY)	Threshold	Conclusions
Michal Sarfaty-2018(38)	US, UK, Canada, Australia	Keynote 045	Second-line advanced bladder cancer	Pembrolizumab versus chemotherapy	US: $122,557 UK: $91,995 Canada: $90,099 Australia: $99,966	US: $100,000–150,000 UK: $25,000–65,000 Canada: $16,000–80,000 Australia: $32,000–60,000	Pembrolizumab may be considered cost-effective in the US but not in the other countries examined.
Karl Patterson-2019(39)	Sweden	KEYNOTE-052	Advanced, Unresectable, or Metastatic UC Ineligible for Cisplatin-based Therapy	Pembrolizumab versus ① carboplatin plus gemcitabine ② gemcitabine	① €53,055.42 ($59,209.85) ② €54,414.78 ($60726.89)	€100,000 （$111,600）	Pembrolizumab is a cost-effective treatment versus carboplatin plus gemcitabine and versus gemcitabine.

12.Summary of regulatory status and market availability of the medicine

On April 9, 2020, Tislelizumab was approved by NMPA for its new indication for the treatment of patients with high PD-L1 expression with locally advanced or metastatic urothelial carcinoma(UC) who have failed platinum-containing chemotherapy (including neoadjuvant or adjuvant chemotherapy) that have progressed within 12 months, which is priced at ¥10688 (100mg/ vials). Tislelizumab does not have marketing approval in other jurisdictions, but will be planned to submit drug marketing application to other countries.

13.Availability of pharmacopeial standards (British Pharmacopoeia, International Pharmacopoeia, United States Pharmacopoeia, European Pharmacopeia)

Currently, Tislelizumab has not been included in the British Pharmacopoeia, the International Pharmacopoeia, the United States Pharmacopoeia or the European Pharmacopoeia.

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