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

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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.

Tislelizumab was officially approved for marketing by the National Medical Products Administration (NMPA) of the People's Republic of China on December 26, 2019 which was indicated for the treatment of Relapsed or Refractory classical Hodgkin Lymphoma (R/R cHL) after at least one second-line chemotherapy.

Tislelizumab is the first PD-1 (1)(Programmed Cell Death Protein 1) monoclonal antibody with Fc hinge modification . 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 R/R cHL 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 Relapsed or Refractory classical Hodgkin Lymphoma (R/R cHL) after at least one second-line chemotherapy 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 of R/R cHL

According to the 2017 WHO classification, Hodgkin lymphoma is composed of two distinct disease entities: classical HL (cHL) and nodular lymphocyte predominant HL. Nodular sclerosis, mixed cellularity, lymphocyte depletion, and lymphocyte-rich HL are subgroups of cHL. The IHC markers that should be routinely tested for the diagnosis of HL include CD45 (LCA), CD20, CD15, CD30, PAX5, CD3, MUM1, Ki-67 and EBV-EBER. cHL often manifests as CD30 (+), CD15 (+) or (-), PAX5 weak (+), MUM1 (+), CD45 (-), CD20 (-) or weak (+), CD3 (-), BOB1 (-), OCT2 (-/+), EBV-EBER (+) in some cases. Corresponding markers need to be tested in the differential diagnosis to identify anaplastic large cell lymphoma (ALCL), diffuse large B cell lymphoma (DLBCL) and others(4).

### 7.2 Guidelines

Tislelizumab is recommended in the Chinese Society of Clinical Oncology (CSCO) Lymphoma Diagnosis and Treatment Guide (2020 edition) for the treatment of patients with R/R cHL due to comorbidities or failure of salvage chemotherapy who are not eligible for stem cell transplantation, and patients with R/R cHL who relapse after high-dose chemotherapy (HDCT) followed by an autologous stem cell transplantation (ASCT)(5).

### 7.3 Usage and dosage

Tislelizumab is indicated for the treatment of Relapsed or Refractory classical Hodgkin Lymphoma (R/R cHL) after at least one second-line chemotherapy.

#### 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 (9 mg/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 | Permanently discontinue |

| | | |
|---|---|---|
| | ULN.<br>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. | |
| 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<br>Grade 2 or 3 hyperthyroidism | Withhold dose until Grade 1 or resolved |
| | Grade 4 hypothyroidism<br>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<br>Grade 2 or 3 Pancreatitis<br>Grade 2 Myocarditis *<br>Grade 2 Encephalitis<br>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<br>Grade 3 or 4 Myocarditis<br>Grade 3 or 4 Encephalitis<br>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）<br>Grade 2 or 3 adverse reactions did not improve to Grade 0-1 after withhold dose 12 weeks（Endocrinopathies excluded）<br>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 population

**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

Hodgkin lymphoma (HL) belongs to malignant lymphoma (lymphoma) and is one of the common types of lymphoma. Among them, classic Hodgkin lymphoma (cHL) accounts for about 90%-95% of HL(4, 6).

In 2018, it is estimated that there will be 79,990 new HL patients worldwide, with an incidence rate of 1.0 per 100,000, a prevalence rate of 0.81 per 100,000, and a mortality rate of 0.34 per 100,000 (7). HL is a unique malignant disease of the lymphatic system, and its incidence varies significantly in different geographical locations. The incidence rates in the United States and Europe are as high as 2.8 per 100,000 and 2.49 per 100,000 respectively, while the incidence in China is only 0.35 per 100,000 (7-9).

The prognosis of cHL is closely related to tissue type and clinical stage. The lymphocyte-dominated HL has the best prognosis, with a 5-year survival rate of 94.3%. Lymphocyte-depleted HL was the worst, with a 5-year survival rate of 27.4%. The 5-year survival rate of nodular sclerosis and mixed cell type are in between. From the clinical stage of HL, the 5-year survival rate is 92.5% for stage I, 86.3% for stage II, 69.5% for stage III, and 31.9% for stage IV. Patients with systemic symptoms have a worse prognosis than patients without systemic symptoms. Among people of different ages, the prognosis of children and the elderly is generally worse than that of the young and middle-aged; women are better than men after treatment (10).

HL patients have a high cure rate under traditional chemotherapy and radiotherapy. However, about 10%-30% of patients still experience relapse (relapse of disease after treatment) or refractory (treatment ineffective to disease) after first-line chemotherapy and eventually the disease developed into Relapsed or Refractory classical Hodgkin Lymphoma (R/R cHL)HL (11-14). After treatment of autologous stem-cell transplantation (ASCT), patients have a high risk of relapse, with a nearly 50% chance of relapse (15). The prognosis of R/R cHL patients who relapsed or progressed after ASCT treatment is very poor, with a median overall survival of 10.5 months to 27.6 months (16, 17).

### 8.2 Assessment of current use

According to the 2018 Chinese Lymphoma Diagnosis and Treatment Guideline published by National Health Commission (4)， the recommended treatment for R/R cHL is to perform high-dose chemotherapy combined with ASCT after second-line salvage chemotherapy. Salvage chemotherapy can choose DHAP (Dexamethasone, High-dose cytarabine, Cisplatin), ICE (Ifosfamide, Carboplatin, Etoposide), IGEV (Ifosfamide, Gemcitabine and Vinorelbine) etc. Patients with primary tumor resistance or who relapse within 12 months after first-line treatment or who have extranodal lesions at the time of relapse can be maintained with targeted drugs after ASCT.

Current treatment options for HL include traditional chemotherapy and radiotherapy, ASCT and targeted drug therapy. To a certain extent, these treatments have disadvantages such as high relapse rate, poor prognosis, and high price.

- With the application of modern chemotherapy and radiotherapy, 70%~90% of HL patients can be cured, but about 10%-30% of HL patients still have relapse or refractory (11-14).
- High-dose chemotherapy treatment will bring acute adverse reactions and long-term effects to patients, especially problems such as secondary tumors (11)，and it may also cause infertility and teratogenesis(6).
- After treatment of ASCT, patients have a nearly 50% chance of relapse (15)，and the prognosis of relapsed patients is very poor, the median overall survival time is only 1-3 years (18).

In general, an expanding list of novel drugs has exhibited promising single-agent activity and meets the high clinical needs in patients recurrent after ASCT or not eligible for ASCT.. The PD-1 monoclonal antibody (Tislelizumab) shows better and more safety clinical outcome on R/R cHL patients (ORR reaches 87.1%, CR reaches 62.9% (19).

## 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 summarized the results of a pivotal phase II trial (NCT03209973) that R/R cHL patients treated with tislelizumab was generally well tolerated and resulted in high overall response and CR rates. 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 (20).

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

The following studies describe the clinical development of Tislelizumab for R/R cHL:

- 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 cHL 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(21).
- BGB-A317-203 (NCT03209973) was an open label, single-arm, multi-center Phase 2 study aimed to evaluate the efficacy and safety of Tislelizumab in Chinese patients with R/R cHL. The primary endpoint was overall response rate (ORR) assessed by an independent review committee (IRC, per Lugano 2014 classification). The secondary endpoints include duration of response (DoR), time to response, progression free survival (PFS) and safety. As a result, treatment of patients with R/R cHL with Tislelizumab was generally well tolerated and resulted in high overall response and complete response (CR) rates, potentially translating into more durable responses for these patients.(19)

### 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) (22) , using the critical epitopes, Gln75, Thr76, Asp77 and Arg86 that are present on PD-1 (23). 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)(23).

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) (24, 25).

**9.2.3 Efficacy**

The results of BGB-A317-203 showed that all 70 patients were evaluable for efficacy. After median follow-up of 9.8 months (range,3.4–14.7), 61 (87.1%,95CI: 77.0, 93.9) patients achieved an objective response (OR), with 44 (62.9%) achieving a complete response (CR) and 17 (24.3%) achieved partial response (PR). Subgroup analysis revealed that responses to Tislelizumab were generally consistent

across all subgroups analyzed. Of the 13 patients who had previously undergone ASCT, 12 (92.3%) achieved an objective response with 9 patients (69.2%) achieving a CR, and of 4 patients having previously received brentuximab vedotin, all achieved a CR. Of the 25 patients with primary refractory disease, 20 (80%) achieved an objective response including 13 (52%) CRs. The median time to response was 12weeks (range, 8.9-42.1 weeks) (19).

After a median follow-up of 9.6 months (range, 2.6-13.1+ months), the median PFS has not been reached. At 9 months, the PFS rate was 74.5% (95CI: 70.5, 89.4). Likewise, after a median follow-up from first response of 6.7 months (range, 4.2-6.9 months), the median DoR has not been reached for the 61 patients who achieved a response. One patient died as of the data cutoff date due to disease progression, with a corresponding 9-month overall survival (OS) rate of 98.6% (19).The efficacy is detailed in Table 9-1.

**Table 9-1 Independent review committee-assessed efficacy outcomes(BGB-A317-203)**

| Efficacy variable | N=70 |
|---|---|
| Objective response, n (%) | |
| Complete response | 44 (62.9) |
| Partial response | 17 (24.3) |
| No response[a] | 9 (12.8) |
| ORR (%) | 87.1 (95CI: 77.0, 93.9) |
| 95% CI for overall response rate | (77.0, 93.9) |
| P-value[b] | <0.0001 |
| Time to response[c], weeks | |
| Median (range) | 12.0 (8.9 - 42.1) |
| DoR[c], months | |
| Median[d] (range) | NE (0.0+ to 10.3+) |
| Event-free rates[c] at 6 months (%) | 84.1 (95CI: 70.3, 91.8) |
| Progression free survival, months | |
| Median[d] (range) | NE (2.6 - 13.1+) |
| Event-free rates[c] at 9 months (%) | 74.5 (95CI: 70.5, 89.4) |

NE denotes not estimable. + denotes censored observations

[a] One patient who died from complications of progressive disease before any postbaseline tumor assessments is included in this category

[b] One-sided p-value was based on exact test comparison of Tislelizumab ORR versus reference rate (H0) of 0.35

[c] Event-free rates were estimated by Kaplan–Meier methodology with 95% confidence intervals estimated using Greenwood's formula

[d] Medians were estimated by Kaplan–Meier methodology with 95% confidence intervals estimated using the Brookmeyer and Crowley method

## 9.3 Summary of available estimates of comparative effectiveness

### 9.3.1 Comparison of Tislelizumab with other PD-1 monoclonal antibodies for R/R cHL

Direct comparative data are still lacking. Figure 9-1 summaries the comparison of efficacy for R/R cHL reported with Tislelizumab, Sintilimab, Camrelizumab, Pembrolizumab and Nivolumab. Table 9-

2 lists the data of efficacy for R/R cHL reported with Sintilimab, Camrelizumab, Pembrolizumab and Nivolumab. It can be seen that the ORR of Tislelizumab (87.1%) was better than that of Sintilimab (80.4%), Camrelizumab (76.0%), Pembrolizumab (71.9%) and Nivolumab (71.2%). Besides, the CR of Tislelizumab was 62.9%, while Sintilimab, Camrelizumab, Pembrolizumab and Nivolumab were 33.7%, 28.0%, 27.6% and 21.0%, respectively, which showed that Tislelizumab may had a good efficacy compared with other PD-1 monoclonal antibodies.

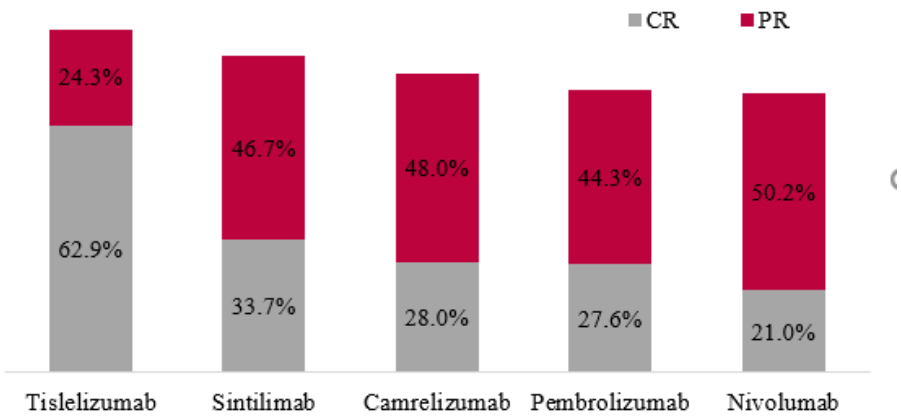


**Figure 9-1 Clinical outcomes of Phase II studies of PD-1 monoclonal antibody for R/R cHL***

*Not head to head comparative trial

**Table 9-2 Summary of clinical trials of PD-1 monoclonal antibody in the treatment of R/R cHL**

| Clinical trial | Phase | Intervention | N | median follow-up（months） | ORR | CR | PR | PFS | OS |
|---|---|---|---|---|---|---|---|---|---|
| Sintilimab ORIENT-1(26) | II | Intravenously 200mg q3w | 96 | 10.5 | IRRC-assessed：80.4%（95% CI, 70·9-88·0) | IRRC-assessed：33.7% | IRRC-assessed：46.7% | PFS rates at 6 months: 77.6% (95%CI, 66·6–85·4) | / |
| Camrelizumab SHR-1210(27) | II | Intravenously 200mg q2w | 75 | 12.9 | 76.0% (95% CI, 64.7-85.1) | 28.0% | 48.0% | PFS rates at 6 months: 81.1% | / |
| Pembrolizumab Two-year follow-up of KEYNOTE-087(28) | II | Intravenously 200mg q3w | 210 | 27.6 | 71.9% (95% CI, 65.3-77.9) | 27.6% | 44.3% | NR | / |
| Pembrolizumab KEYNOTE-087(29) | II | Intravenously 200mg q3w | 210 | 10.1 | 69% (95% CI, 62.3-75.2) | 22.4% (95% CI, 16.9- 28.6) | / | PFS rates at 6 months: 72.4%; PFS rates at 9 months: 97.5% | OS rates at 6 months: 99.5%; OS rates at 9 months: 63.4% |
| Pembrolizumab KEYNOTE-087 subgroup (30) | II | Intravenously 200mg q3w | 73 | 10.1 | 79.5% | 23.3% | / | PFS rates at 6 months: 79.6% | OS rates at 6 months: 100% |
| Nivolumab Extended CheckMate 205(31) | II | Intravenously 3mg/kg q2w | 80 | / | 71.2% (95% CI, 63-75) | 21.0% | / | Median PFS：15 | / |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | months (95% CI, 11.3-18.5) | |
| Nivolumab NCT02181738（CheckMate 205）(32) | II | Intravenously 3mg/kg q2w | 80 | 8.6 | IRRC-assessed：66.3% (95% CI 54·8-76·4) | IRRC-assessed：8.8% | / | PFS rates at 6 months: 76.9% (95% CI 64·9–85·3) | OS rates at 6 months: 98.7% (95% CI 91·0–99·8) |
| Nivolumab JapicCTI-142755(33) | II | Intravenously 3mg/kg q2w | 17 | 9.8 | 81.3% (95% CI 54.4-96.0) | 25% | / | PFS rates at 6 months: 60% (95% CI: 31.8-79.7%) | OS rates at 6 months: 100% |
| Nivolumab NCT02572167(34) | I/II | Brentuximab vedotin (1.8 mg/kg IV, 30-minute infusion) and Nivolumab (3.0 mg/kg IV, 60-minute infusion) in 3-week cycles for up to 12 weeks | 62 | / | 85% | 64% | / | / | / |
| Nivolumab NCT02572167(35) | I/II | Intravenously Nivolumab (3mg/kg), Brentuximab vedotin (1.8mg/kg) q3w | 62 | 7.8 | 82% (95% CI, 70-91) | 61% 61% (95% CI, 47-73) | / | PFS rates at 6 months: 89% (95% CI, 75-95) | / |

# 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 (19, 21, 36, 37).

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

The following section details the undesirable effects of Tislelizumab.

### 10.2.1 Safety results of BGB-A317-203 (19)

92.9% (n=65) of patients had adverse events (AEs), most of which were grade 1 or grade 2 AEs. 21.4% (n=15) of patients reported grade 3 and above AEs, 2 patients had grade 4 AEs (increased serum creatine phosphokinase and thrombocytopenia), and no grade 5 AEs. The most common AEs were fever(54.3%), hypothyroidism(32.9%), weight gain(30%), upper respiratory infection(30%), leukopenia (18.6%), cough (17.1%), and pruritus(17.1%). The most common AEs of grade 3 and above are upper respiratory tract infection and pneumonia. 11 patients had at least one dose interruption or delay (dose reduction is not allowed) to deal with AEs.

## 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 (NCT04068519)[n=300], BGB-A317-203[n=70]）(19, 21, 37) 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.(38)

### 11.2 Economic evaluation for R/R cHL treatment

The monoclonal antibodies currently on the market in China include Tislelizumab, Sintilimab and Camrelizumab, which are used for the treatment of patients with R/R cHL after at least one second-line chemotherapy. The unit price of Sintilimab after entering the medical insurance is ¥2,843 (100mg/ vials). The monthly treatment cost is ¥8,123, and the annual treatment cost is about ¥99,000. Besides, the price of Camrelizumab is ¥19,800 (200mg/ vials), and the annual medication cost is ¥515,000. After the patient assistance program, the annual medication cost is ¥119,000. The price of Tislelizumab is ¥10,688 (100mg/ vials). After the patient assistance program, for patients who need long-term medication, the minimum annual treatment cost is about ¥106,900. Based on the results above, the price of Tislelizumab is similar to that of Sintilimab, and it has a price advantage compared to Camrelizumab. What's more, patients using Tislelizumab are more likely to reduce the cost of subsequent treatment, because Tislelizumab has a good efficacy, and it is more likely to make the patient reach CR and withdrawal.

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

Tislelizumab was officially approved for marketing by NMPA of the People's Republic of China on December 26, 2019, which is indicated for the treatment of Relapsed or Refractory classical Hodgkin Lymphoma (R/R cHL) after at least one second-line chemotherapy. Tislelizumab is priced at ¥10,688 (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 pharmacopoeial 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.

# ***References***

## 14.Comprehensive reference list and in-text citations

1. BeiGene. Tislelizumab; China prescribing information [Chinese].2019. Available from: http://drugs.medlive.cn/drugref/html/21697.shtml.

2. Arlauckas SP, Garris CS, Kohler RH, Kitaoka M, Cuccarese MF, Yang KS, et al. In vivo imaging reveals a tumor-associated macrophage-mediated resistance pathway in anti-PD-1 therapy. Science translational medicine. 2017;9(389).

3. Zhang T, Song X, Xu L, Ma J, Zhang Y, Gong W, et al. The binding of an anti-PD-1 antibody to FcγRI has a profound impact on its biological functions. Cancer immunology, immunotherapy : CII. 2018;67(7):1079-90.

4. National Health Commission of the People 's Republic of China. Chinese Lymphoma Diagnosis and Treatment Guideline(Version 2018). Journal of Multidisciplinary Cancer Management (Electronic Version). 2019;5(4):50-71.

5. CSCO. Guidelines of Chinese Society of Clinical Oncology(CSCO):Lymphoid Malignancies. People's Medical Publishing House. 2020.

6. Shi Y, Sun Y, Liu T. Chinese Lymphoma Diagnosis and Treatment Guideline(Version 2015). Chinese Journal of Oncology. 2015(2):148-58.

7. International agency for research on cancer. China Source:Globocan 2018. Available from: https://gco.iarc.fr/today/data/factsheets/populations/160-china-fact-sheets.pdf.

8. Sant M, Allemani C, Tereanu C, De Angelis R, Capocaccia R, Visser O, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010;116(19):3724-34.

9. Li X, Li G, Gao.Zifen, Zhou.Xiaoge, Zhu.Xiongzheng. Distribution pattern of lymphoma subtypes in China: A nationwide multicenter study of 10002 cases. Journal of Diagnostics Concepts & Practice. 2012;11(02):111-5.

10. Wu M. Review of Lymph Node Enlargement and Lymphoma. [media release] 3 Feb 2015. Available from: https://www.jst-hosp.com.cn/Html/News/Articles/3196.html.

11. Wan W, Tian L, Ke.Xiaoyan. Research progress of Hodgkin lymphoma. Journal of Leukemia & Lymphoma.

2014;23(05):308-11.

12. Chen R, Palmer JM, Martin P, Tsai N, Kim Y, Chen BT, et al. Results of a Multicenter Phase II Trial of Brentuximab Vedotin as Second-Line Therapy before Autologous Transplantation in Relapsed/Refractory Hodgkin Lymphoma. Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation. 2015;21(12):2136-40.

13. Connors JM, Jurczak W, Straus DJ, Ansell SM, Kim WS, Gallamini A, et al. Brentuximab Vedotin with Chemotherapy for Stage III or IV Hodgkin's Lymphoma. The New England journal of medicine. 2018;378(4):331-44.

14. Moskowitz AJ, Hamlin PA, Jr., Perales MA, Gerecitano J, Horwitz SM, Matasar MJ, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(4):456-60.

15. Gopal AK, Chen R, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. Blood. 2015;125(8):1236-43.

16. Arai S, Fanale M, DeVos S, Engert A, Illidge T, Borchmann P, et al. Defining a Hodgkin lymphoma population for novel therapeutics after relapse from autologous hematopoietic cell transplant. Leukemia & lymphoma. 2013;54(11):2531-3.

17. Crump M. Management of Hodgkin lymphoma in relapse after autologous stem cell transplant. Hematology American Society of Hematology Education Program. 2008:326-33.

18. Li M, Xu C. Research progress of treatment in Hodgkin lymphoma. Journal of Leukemia & Lymphoma. 2016;39(04):355-9.

19. 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.

20. Lee A, Keam SJ. Tislelizumab: First Approval. Drugs. 2020;80(6):617-24.

21. 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. Journal for immunotherapy of cancer. 2020;8(1).

22. Zhang T, Song J, Li Y, Ma J, Shi Y, Wu X, et al. Abstract 2226: Anti-human PD-1 antibody BGB-A317 exhibits potent immune cell activation. Cancer Research. 2016;76:2226-.

23. Feng Y, Hong Y, Hanzi S, Zhang B, Wu H, Li K, et al. Abstract 2383: The molecular binding mechanism of tislelizumab, an investigational anti-PD-1 antibody, is differentiated from pembrolizumab and nivolumab2019. 2383.

24. Wu X, Zhang T, Fu C, Zhang Y, Guo A, Zhang l, et al. Activation of tumor infiltrating lymphocytes from colorectal cancer and colorectal liver metastasis patients by anti-human PD-1 Antibody BGB-A317 in a 3D spheroid system. Journal of Clinical Oncology. 2016;34:e14560-e.

25. Luo L, Wu X, Zhang T, Fu C, Zhang Y, Guo A, et al. Abstract 5626: Investigation of T cell activation by anti-human PD-1 antibodies Nivolumab, Pembrolizumab and BGB-A317 using tumor-infiltrating lymphocytes (TILs) from colorectal cancer and colorectal liver metastasis patients. Cancer Research. 2017;77(13 Supplement):5626.

26. Shi Y, Su H, Song Y, Jiang W, Sun X, Qian W, et al. Safety and activity of sintilimab in patients with relapsed or refractory classical Hodgkin lymphoma (ORIENT-1): a multicentre, single-arm, phase 2 trial. The Lancet Haematology. 2019;6(1):e12-e9.

27. Song Y, Wu J, Chen X, Lin T-Y, cao j, Liu Y-Y, et al. A Single-Arm, Multicenter, Phase II Study of Camrelizumab in Relapsed or Refractory Classical Hodgkin Lymphoma. Clinical Cancer Research. 2019;25:clincanres.1680.2019.

28. Chen R, Zinzani PL, Lee HJ, Armand P, Johnson NA, Brice P, et al. Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087. Blood. 2019;134(14):1144-53.

29. Chen R, Zinzani PL, Fanale MA, Armand P, Johnson NA, Brice P, et al. Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2017;35(19):2125-32.

30. Zinzani PL, Fanale MA, Chen R, Armand P, Johnson N, Brice P, et al. PEMBROLIZUMAB MONOTHERAPY IN PATIENTS WITH PRIMARY REFRACTORY CLASSICAL HODGKIN LYMPHOMA: SUBGROUP ANALYSIS OF THE PHASE 2 KEYNOTE-087 STUDY. Hematological Oncology. 2017;35:136-7.

31. Armand P, Engert A, Younes A, Fanale M, Santoro A, Zinzani PL, et al. Nivolumab for Relapsed/Refractory Classic Hodgkin Lymphoma After Failure of Autologous Hematopoietic Cell Transplantation: Extended Follow-Up of the Multicohort Single-Arm Phase II CheckMate 205 Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(14):1428-39.

32. Younes A, Santoro A, Shipp M, Zinzani PL, Timmerman JM, Ansell S, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. The Lancet Oncology. 2016;17(9):1283-94.

33. Maruyama D, Hatake K, Kinoshita T, Fukuhara N, Choi I, Taniwaki M, et al. Multicenter phase II study of nivolumab in Japanese patients with relapsed or refractory classical Hodgkin lymphoma. Cancer science. 2017;108(5):1007-12.

34. Herrera AF, Moskowitz AJ, Bartlett NL, Vose JM, Ramchandren R, Feldman TA, et al. INTERIM RESULTS FROM a PHASE 1/2 STUDY OF BRENTUXIMAB VEDOTIN IN COMBINATION WITH NIVOLUMAB IN PATIENTS WITH RELAPSED OR REFRACTORY HODGKIN LYMPHOMA. Hematological Oncology. 2017;35:85-6.

35. Herrera AF, Moskowitz AJ, Bartlett NL, Vose JM, Ramchandren R, Feldman TA, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2018;131(11):1183-94.

36. Ye D, Liu J, Zhou A, Zou Q, Li H, Fu C, et al. 920P - First report of efficacy and safety from a phase II trial of tislelizumab, an anti-PD-1 antibody, for the treatment of PD-L1+ locally advanced or metastatic urothelial carcinoma (UC) in Asian patients. Annals of Oncology. 2019;30:v367.

37. 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. Journal for immunotherapy of cancer. 2020;8(1).

38. The China Primary Health Care Foundation. The Patient Assistance Program "Wei Ni, Qian Fang Bai Ji". [media release] 6 Mar 2020. Available from: http://www.cphcf.org.cn/zgcb/contents/656/26564.html.