Summary Report of Benefit-Risk Assessment

TEVIMBRA CONCENTRATE FOR SOLUTION FOR INFUSION 100MG/10ML

NEW DRUG APPLICATION

Active Ingredient(s)	Tislelizumab
Product Registrant	Beigene Singapore Pte. Ltd.
Product Registration Number	SIN17089P
Application Route	Abridged evaluation
Date of Approval	19 September 2024

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A INTRODUCTION

Tevimbra is indicated for the following:

Non-small cell lung cancer (NSCLC)

TEVIMBRA in combination with pemetrexed and platinum-containing chemotherapy is indicated for the first-line treatment of adult patients with non-squamous NSCLC whose tumours have PD-L1 expression on ≥50% of tumour cells with no EGFR or ALK positive mutations and who have:

- *locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or*
- *metastatic NSCLC.*

TEVIMBRA in combination with carboplatin and either paclitaxel or nab-paclitaxel is indicated for the first-line treatment of adult patients with squamous NSCLC who have:

- *locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or*
- *metastatic NSCLC.*

TEVIMBRA as monotherapy is indicated for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy.

Esophageal squamous cell carcinoma (ESCC)

TEVIMBRA as monotherapy is indicated for the treatment of patients with unresectable, recurrent, locally advanced, or metastatic esophageal squamous cell carcinoma (ESCC) after prior chemotherapy.

The active substance, tislelizumab, is a humanised immunoglobulin G4 (IgG4) variant monoclonal antibody that binds to the T-cell surface receptor programmed cell death protein 1 (PD-1). It competitively blocks the binding of both PD-L1 and PD-L2, inhibiting PD-1-mediated negative signalling and enhancing the functional activity in T cells.

Tevimbra is available as concentrate for solution for infusion containing 10 mg/mL of tislelizumab. Other ingredients in the vial are sodium citrate dihydrate, citric acid monohydrate, L-histidine hydrochloride monohydrate, L-histidine, trehalose dihydrate, polysorbate 20 and water for injections.

B ASSESSMENT OF PRODUCT QUALITY

Both the drug substance, tislelizumab, and the drug product, Tevimbra, are manufactured at Boehringer Ingelheim Biopharmaceuticals (China) Ltd, Shanghai, China. The manufacturer is compliant with Good Manufacturing Practice (GMP).

Drug substance:

Adequate controls have been presented for the reagents and cell bank. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. Proper process validation was conducted.

The characterisation of the drug substance and its impurities have been appropriately performed. Potential and actual impurities are adequately controlled in the specifications.

The drug substance specifications were established in accordance with ICH Q6B and the impurity limits have been considered appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2, with information on the reference standards used for identity, assay and impurities testing presented.

The packaging is 12L ethylene-vinyl acetate (EVA) bag. The stability data presented was adequate to support the storage of the drug substance at -70ºC with a shelf life of 24 months.

Drug product:

The manufacturing process involves pooling and homogenisation of the formulated drug substance, followed by prefiltration, sterile filtration and aseptic filling. This is considered a standard manufacturing process.

Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6B and impurity limits adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH Q2, with information on the reference standards used for identity, assay and impurities testing presented.

The container closure system is 20 mL glass vial with chlorobutyl rubber stoppers, with aluminium seals. The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at 2-8ºC. Tevimbra does not contain a preservative. Chemical and physical in-use stability has been demonstrated for 24 hours at 2-8ºC. The 24 hours include storage of the diluted solution under refrigeration (2-8ºC) for no more than 20 hours, time required for returning to room temperature (25ºC or below) and time to complete the infusion within 4 hours. The in-use period is supported with adequate in-use stability data.

C ASSESSMENT OF CLINICAL EFFICACY

ESCC

The clinical efficacy of tislelizumab for the treatment of unresectable, recurrent, locally advanced, or metastatic ESCC after prior chemotherapy was based primarily on one pivotal Phase 3, multicentre, randomised, open-label study (Study 302) that compared the efficacy and safety of tislelizumab versus investigator-chosen chemotherapy (ICC) in patients with unresectable recurrent locally advanced or metastatic ESCC who had progressed on or after first-line systemic platinum-based treatment. Patients were excluded if they had received prior anti-PD-1 inhibitor treatment or had received ≥2 prior lines of systemic treatments for advanced unresectable or metastatic ESCC.

Patients were randomised in a 1:1 ratio to receive either tislelizumab or the ICC treatment (choice of paclitaxel, docetaxel or irinotecan). Randomisation was stratified by region (Asia [excluding Japan] vs Japan vs US/EU), ECOG performance status (PS) (0 vs 1), and ICC option (paclitaxel vs docetaxel vs irinotecan). The choice of ICC treatment was determined by the investigator before randomisation.

Tislelizumab 200 mg was administered by intravenous (IV) infusion on Day 1 of each 21-day cycle (Q3W). The initial infusion of tislelizumab was administered over 60 minutes, and if well tolerated, subsequent infusions were administered over 30 minutes. Paclitaxel 135 to 175 mg/m^2 was administered by IV infusion Q3W starting on Day 1. Paclitaxel could also be given in doses of 80 to 100 mg/m^2 on a weekly schedule according to local and/or country-specific guidelines for standard of care. In Japan, paclitaxel was given at doses of 100 mg/m^2 on Days 1, 8, 15, 22, 29, and 36, followed by 1 week of rest. Docetaxel 75 mg/m^2 (or 70 mg/m^2 in Japan) was administered as an IV infusion Q3W starting on Day 1. Irinotecan 125 mg/m^2 was administered via IV infusion on Days 1 and 8, given Q3W. Study treatment continued until occurrence of disease progression, intolerable toxicity or other discontinuation criteria were met. The active comparators used in the study were standard of care treatment options at the time of the study and are currently recommended treatment options in clinical practice guidelines, hence are considered acceptable.

The primary efficacy endpoint was overall survival (OS) in the intent-to-treat (ITT) analysis set. The key secondary endpoint was OS in the PD-L1-positive analysis set, which included patients with PD-L1 expression status of visually-estimated Combined Positive Score (vCPS, now known as the Tumour Area Positivity [TAP] score) [PD-L1 score] ≥10% based on the Ventana PD-L1 (SP263) assay. Other secondary efficacy endpoints included objective response rate (ORR), duration of response (DOR) and progression-free survival (PFS), as assessed by the investigator per RECIST v1.1. Tumour imaging was performed at baseline, every 6 weeks for the first 6 months, and every 9 weeks thereafter.

The primary endpoint of OS was planned to be compared between the tislelizumab and ICC arms in the ITT analysis set by means of a stratified log-rank test, stratified by selected stratification factors of ECOG PS (0 vs 1) and ICC option (paclitaxel vs docetaxel vs irinotecan), using a significance level of one-sided 0.025. If the null hypothesis for OS in the ITT analysis set was rejected, the key secondary endpoint, OS in the PD-L1 positive analysis set, would be tested sequentially. The Type I error was strongly controlled at the one-sided level 0.025. Only OS in the ITT and in the PD-L1 positive analysis sets were planned with multiplicity control, all further analyses are descriptive. The statistical methods employed were appropriate for the endpoints studied.

A total of 512 patients were randomised and included in the ITT analysis set: 256 patients in the tislelizumab arm and 256 in the ICC arm. A total of 142 patients were included in the PD-L1 positive analysis set: 80 patients in the tislelizumab arm and 62 patients in the ICC arm. As of the data cut-off date (01 December 2020), the median study follow-up time was 8.49 months (range 0.2 to 31.7 months) for the tislelizumab arm and 5.80 months (range 0.0 to 30.8 months) for the ICC arm.

In the ITT analysis set, the median age was 62.0 years (range 35 to 86 years), with 37.9% of patients aged ≥65 years. The majority of patients were male (84.4%) and Asian (79.7%); 18.9% of patients were White. There were 24.6% of patients with ECOG PS 0 and 75.4% with ECOG PS 1; 27.7% of patients had PD-L1 score ≥10%, 43.4% had PD-L1 score <10%, and 28.9% had unknown baseline PD-L1 status. The majority of patients (95.1%) had metastatic disease at study entry. All patients (100.0%) had received at least one prior systemic anti-cancer

therapy, the majority of whom had received platinum-based systemic therapy (97.3%); 16.2% of patients had received prior neo-adjuvant/adjuvant treatment as first-line systemic therapy.

There were slight imbalances in baseline characteristics between treatment arms in terms of PD-L1 expression status. In the ITT analysis set, the proportion of patients with PD-L1 ≥10% was higher in the tislelizumab arm (31.3%) as compared to the ICC arm (24.2%), while PD-L1 expression was <10% in 39.1% of patients in the tislelizumab arm and 47.7% in the ICC arm. Sensitivity analyses conducted did not indicate any meaningful impact of the imbalance in PD-L1 expression status on the treatment outcome.

The primary efficacy endpoint was met, showing a statistically significant improvement in OS for the tislelizumab arm compared to the ICC arm. The median OS was 8.6 months (95% CI: 7.5, 10.4) in the tislelizumab arm vs 6.3 months (95% CI: 5.3, 7.0) in the ICC arm (stratified HR 0.70; 95% CI: 0.57, 0.85; one-sided p=0.0001). Consistent OS benefit was demonstrated across pre-specified sensitivity analyses and subgroup analyses conducted.

In contrast to the OS results, a PFS benefit was not demonstrated. The median PFS was 1.6 months (95% CI: 1.4, 2.7) in the tislelizumab arm vs 2.1 months (95% CI: 1.5, 2.7) in the ICC arm (stratified HR 0.83; 95% CI: 0.67, 1.01). The ORR (unconfirmed) was 20.3% (95% CI: 15.6, 25.8) in the tislelizumab arm and 9.8% (95% CI: 6.4, 14.1) in the ICC arm (difference 10.6%; 95% CI: 4.5, 16.7). A post-hoc analysis of ORR based on confirmed responses showed lower response rates compared to the unconfirmed analysis, although still numerically higher in the tislelizumab arm compared to the ICC arm (confirmed ORR 15.2% vs 6.6%; difference 8.6%; 95% CI: 3.3, 13.9). The median DOR (based on confirmed responses) was 10.3 months (95% CI: 6.5, 13.2) in the tislelizumab arm and 6.3 months (95% CI: 2.8, 8.5) in the ICC arm.

Summary of efficacy results in Study 302 (ITT analysis set)

	Tislelizumab (N=256)	**ICC (N=256)**
OS		
OS events, n (%)	197 (77.0)	213 (83.2)
Median OS (months) (95% CI)	8.6 (7.5, 10.4)	6.3 (5.3, 7.0)
Stratified HR[a] (95% CI)	0.70 (0.57, 0.85)	
One-sided stratified log-rank p-value[b]	0.0001	
PFS		
PFS events, n (%)	223 (87.1)	180 (70.3)
Median PFS (months) (95% CI)	1.6 (1.4, 2.7)	2.1 (1.5, 2.7)
Stratified HR[a] (95% CI)	0.83 (0.67, 1.01)	
One-sided stratified log-rank p-value[c]	0.0292	
ORR (unconfirmed)[e]		
Best overall response, n (%) Complete response (CR) Partial response (PR) Stable disease (SD) Progressive disease (PD) Could not be determined	 5 (2.0) 47 (18.4) 68 (26.6) 116 (45.3) 20 (7.8)	 1 (0.4) 24 (9.4) 82 (32.0) 86 (33.6) 63 (24.6)
ORR, n (%) (95% CI)	20.3 (15.6, 25.8)	9.8 (6.4, 14.1)
Odds ratio (95% CI)	2.39 (1.42, 4.01)	
ORR difference (%) (95% CI)	10.6 (4.5, 16.7)	

CMH test p-value[d]	0.0008	
ORR (confirmed)[f]		
ORR, n (%) (95% CI)	15.2 (11.1, 20.2)	6.6 (3.9, 10.4)
Odds ratio (95% CI)	2.57 (1.40, 4.71)	
ORR difference (%) (95% CI)	8.6 (3.3, 13.9)	
CMH test p-value[d]	0.0017	
DOR (unconfirmed)[e]		
Median DOR (months) (95% CI)	7.1 (4.1, 11.3)	4.0 (2.1, 8.2)
DOR (confirmed)[f]		
Median DOR (months) (95% CI)	10.3 (6.5, 13.2)	6.3 (2.8, 8.5)

[a] Hazard ratio (tislelizumab vs ICC) was based on Cox regression model including treatment as covariate, and stratified by baseline ECOG status and ICC option.
[b] One-sided p-value was estimated from log-rank test stratified by ECOG status and ICC option.
[c] One-sided p-value was estimated from log-rank test stratified by ECOG status and ICC option, for descriptive purpose only.
[d] Cochran-Mantel-Haenszel (CMH) test is stratified by ECOG status and ICC option, p-value for descriptive purpose only.
[e] The pre-specified ORR and DOR analyses were based on unconfirmed responses, i.e., without repeat assessments to confirm the initial response determination.
[f] The confirmed ORR and DOR were conducted as post-hoc analyses, based on responses confirmed on repeat assessments at least 4 weeks after the initial response determination.

Pre-specified subgroup analyses by PD-L1 expression status showed a more pronounced effect of tislelizumab in patients with PD-L1 ≥10%, with a median OS of 10.0 months (95% CI: 8.5, 15.1) in the tislelizumab arm vs 5.1 months (95% CI: 3.8, 8.2) in the ICC arm (HR 0.49; 95% CI: 0.33, 0.74; one-sided p=0.0003). In the PD-L1 <10% subgroup, the median OS was 7.5 months (95% CI: 5.5, 8.9) in the tislelizumab arm and 5.8 months (95% CI: 4.8, 6.9) in the ICC arm (HR 0.83; 95% CI: 0.62, 1.12). Although the effect size was smaller and the 95% CI crossed 1 in the PD-L1 <10% subgroup, there was no evidence of a detrimental effect on survival in this subpopulation. Hence, the indication granted was for a broad population without restriction by PD-L1 expression status. The efficacy of tislelizumab in terms of OS, PFS and ORR by PD-L1 expression status is summarised in the table below.

Summary of efficacy results by PD-L1 status

	PD-L1 vCPS ≥10%		**PD-L1 vCPS <10%**		**Missing PD-L1 status**	
	Tislelizumab (N=80)	**ICC (N=62)**	**Tislelizumab (N=100)**	**ICC (N=122)**	**Tislelizumab (N=76)**	**ICC (N=72)**
OS						
Stratified HR (95% CI)	0.49 (0.33, 0.74)		0.83 (0.62, 1.12)		0.72 (0.49, 1.06)	
Median (95% CI) (months)	10.0 (8.5, 15.1)	5.1 (3.8, 8.2)	7.5 (5.5, 8.9)	5.8 (4.8, 6.9)	8.5 (6.2, 12.1)	7.0 (5.8, 8.6)
PFS						
Stratified HR (95% CI)	0.83 (0.54, 1.28)		0.95 (0.70, 1.29)		0.87 (0.58, 1.31)	
Median (95% CI) (months)	2.7 (1.5, 4.2)	2.3 (1.4, 3.0)	1.5 (1.4, 2.6)	1.7 (1.4, 2.7)	1.5 (1.4, 2.8)	2.1 (1.4, 2.8)
Unconfirmed ORR						
ORR, % (95% CI)	26.3 (17.0, 37.3)	11.3 (4.7, 21.9)	16.0 (9.4, 24.7)	9.0 (4.6, 15.6)	19.7 (11.5, 30.5)	9.7 (4.0, 19.0)
Difference (95% CI)	14.1 (1.7, 26.6)		5.7 (-3.2, 14.6)		10.8 (-0.5, 22.2)	
Confirmed ORR						
ORR, % (95% CI)	20.0 (11.9, 30.4)	8.1 (2.7, 17.8)	14.0 (7.9, 22.4)	6.6 (2.9, 12.5)	11.8 (5.6, 21.3)	5.6 (1.5, 13.6)

Difference (95% CI)	10.7 (-0.3, 21.8)	6.4 (-1.9, 14.7)	6.8 (-2.7, 16.3)

Overall, the efficacy of tislelizumab monotherapy in the treatment of unresectable, recurrent, locally advanced, or metastatic ESCC after prior systemic therapy had been demonstrated in the overall population based on statistically significant and clinically meaningful improvement in OS and supported by consistent benefits in terms of ORR and DOR, although PFS benefit was not shown.

NSCLC after prior chemotherapy

The requested indication for the use of tislelizumab monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy was based on one pivotal Phase 3 study (Study 303). This was a multicentre, randomised, open-label study of tislelizumab compared with docetaxel in patients with NSCLC of either squamous or non-squamous histology, who had progressed on a prior platinum-based regimen but no more than 2 prior lines of systemic chemotherapy for advanced or metastatic disease. The study excluded patients with known EGFR mutation or ALK rearrangement and patients who have received prior PD-(L)1 inhibitor or CTLA-4 inhibitor treatment.

Patients were randomised in a 2:1 ratio to receive either tislelizumab 200 mg Q3W or docetaxel 75 mg/m^2 Q3W. Randomisation was stratified by histology (squamous vs non-squamous), lines of therapy (second vs third), and PD-L1 expression (≥25% of tumour cells [TCs] vs <25% TCs). The proportion of PD-L1-negative patients (defined as <25% TCs) was capped at ≤60%. Treatment was continued until disease progression, intolerable toxicity, or withdrawal of consent. While immune checkpoint inhibitors have been approved and are available for the treatment of previously treated advanced NSCLC, docetaxel remains one of the recommended treatment options in clinical practice guidelines and is considered an acceptable active comparator in this setting.

The dual primary efficacy endpoints were OS in the ITT analysis set and OS in the PD-L1-positive analysis set (defined as ≥25% of TCs with PD-L1 membrane staining via the Ventana SP263 assay). The secondary endpoints included investigator-assessed PFS, ORR and DOR. Tumour assessments were performed every 9 weeks for the first 12 months and then every 12 weeks thereafter. The statistical methods employed were standard and acceptable for the endpoints studied. An interim analysis of OS was planned when approximately 426 deaths in the ITT analysis set was observed (i.e., approximately 76% of the target 560 OS events). Appropriate multiplicity adjustments were applied for the multiple endpoints evaluated and for the planned interim analysis.

A total of 805 patients were randomised to the study and included in the ITT analysis set: 535 patients in the tislelizumab group and 270 patients in the docetaxel group. A total of 343 patients were included in the PD-L1-positive analysis set: 227 patients in the tislelizumab group and 116 patients in the docetaxel group. At the final analysis (data cut-off date 15 July 2021), the median study follow-up time was 16.03 months (range 0.30 to 43.50 months) in the tislelizumab arm and 10.68 months (range 0.03 to 38.28 months) in the docetaxel arm.

The patient demographics and baseline characteristics were generally balanced between the two treatment groups. The majority of patients were male (77.3%) and Asian (79.9%), with a median age of 61.0 years (range 28 to 88 years). A total of 42.5% of patients had PD-L1-positive status (≥25% TCs), 57.0% had PD-L1-negative status (<25% TCs), 46.0% had squamous cell histology, 54.0% had non-squamous histology, 85.5% had metastatic disease,

14.5% had locally advanced disease, 84.7% of patients had received one prior therapy, and 15.3% had received two prior therapies. All patients (100%) had received prior treatment with platinum-based chemotherapy.

At the interim analysis (data cut-off date 10 August 2020), the study demonstrated statistically significant improvements in the primary endpoint of OS for tislelizumab over docetaxel, with a median OS of 17.2 months in the tislelizumab arm vs 11.9 months in the docetaxel arm (stratified HR 0.64; 95% CI: 0.53, 0.78; one-sided p<0.0001) in the ITT analysis set. The final analysis results (data cut-off date 15 July 2021) were consistent, with a median OS of 16.9 months vs 11.9 months (stratified HR 0.66; 95% CI: 0.56, 0.79; one-sided p<0.0001). The OS benefit was also demonstrated in the PD-L1-positive analysis set, with a median OS of 19.3 months (95% CI: 16.5, 22.6) in the tislelizumab arm and 11.5 months (95% CI: 8.2, 13.5) in the docetaxel arm (stratified HR 0.53; 95% CI: 0.41, 0.70; one-sided p<0.0001). Treatment benefit in terms of OS was consistently shown across pre-specified subgroups analysed, including in the Asian (HR 0.66) and White (HR 0.63) subgroups, and across PD-L1 expression subgroups (HRs ranging from 0.54 to 0.79), except for the "Other" race (HR 1.66) which had a very small sample size (n=25).

The results of the secondary endpoints were supportive of the treatment benefit favouring tislelizumab over docetaxel. The median PFS was 4.2 months in the tislelizumab arm compared to 2.6 months in the docetaxel arm (stratified HR 0.63; 95% CI: 0.53, 0.75; one-sided p<0.0001). The ORR (unconfirmed) was higher in the tislelizumab arm (22.6%; 95% CI: 19.1, 26.4) than the docetaxel arm (7.0%; 95% CI: 4.3, 10.8) (p<0.0001). A post-hoc analysis of ORR based on confirmed responses showed consistent results (confirmed ORR 20.9% in the tislelizumab arm vs 3.7% in the docetaxel arm). The median DOR based on confirmed responses was 14.7 months in the tislelizumab arm and 6.2 months in the docetaxel arm (HR 0.31; 95% CI: 0.16, 0.61; one-sided p=0.0002).

Overall, the efficacy of tislelizumab monotherapy in the treatment of locally advanced or metastatic NSCLC after prior chemotherapy had been adequately demonstrated in terms of statistically significant and clinically relevant improvements in OS, PFS, ORR and DOR.

Summary of efficacy results in Study 303 (ITT analysis set)

	Tislelizumab (N=535)	**Docetaxel (N=270)**
Interim analysis (data cut-off 10 Aug 2020)		
OS		
OS events, n (%)	275 (51.4)	166 (61.5)
Median OS (months) (95% CI)	17.2 (15.3, 20.0)	11.9 (10.2, 13.9)
Stratified HR[a] (95% CI)	0.64 (0.53, 0.78)	
One-sided stratified log-rank p-value[a,b]	<0.0001	
Final analysis (data cut-off 15 Jul 2021)		
OS		
OS events, n (%)	365 (68.2)	206 (76.3)
Median OS (months) (95% CI)	16.9 (15.2, 19.1)	11.9 (9.6, 13.5)
Stratified HR[a] (95% CI)	0.66 (0.56, 0.79)	
One-sided stratified log-rank p-value[a,c]	<0.0001	
PFS		
PFS events, n (%)	451 (84.3)	208 (77.0)
Median PFS (months) (95% CI)	4.2 (3.9, 5.5)	2.6 (2.2, 3.8)

Stratified HR[a] (95% CI)	0.63 (0.53, 0.75)	
One-sided stratified log-rank p-value[a]	<0.0001	
ORR (unconfirmed)[d]		
Best overall response, n (%) Complete response (CR) Partial response (PR) Stable disease (SD) Progressive disease (PD) Not evaluable	 9 (1.7) 112 (20.9) 157 (29.3) 198 (37.0) 39 (7.3)	 1 (0.4) 18 (6.7) 91 (33.7) 104 (38.5) 52 (19.3)
ORR, n (%) (95% CI)	121 (22.6) (19.1, 26.4)	19 (7.0) (4.3, 10.8)
Odds ratio (95% CI)	3.86 (2.34, 6.39)	
ORR difference (%) (95% CI)	15.6 (11.0, 20.3)	
ORR (confirmed)[e]		
ORR, n (%) (95% CI)	112 (20.9) (17.6, 24.6)	10 (3.7) (1.8, 6.7)
Odds ratio (95% CI)	6.89 (3.57, 13.29)	
ORR difference (%) (95% CI)	17.3 (13.2, 21.4)	
DOR (unconfirmed)[d]		
Median DOR (months) (95% CI)	13.5 (8.5, 19.6)	6.0 (2.1, 7.2)
HR (95% CI)	0.31 (0.18, 0.54)	
One-sided log-rank test p-value	<0.0001	
DOR (confirmed)[e]		
Median DOR (months) (95% CI)	14.7 (10.6, 21.8)	6.2 (4.1, 8.3)
HR (95% CI)	0.31 (0.16, 0.61)	
One-sided log-rank test p-value	0.0002	

[a] Stratified by stratification factors: histology (squamous vs non-squamous), lines of therapy (second vs third), and PD-L1 expression (≥25% TC vs <25% TC).
[b] The p-value met the pre-specified statistical boundary of 0.0120 for the interim analysis.
[c] The primary endpoint was met and statistical significance was achieved in the pre-specified interim analysis. Formally, there was no subsequent significance testing. The p-values in the final analysis are descriptive in nature.
[d] The pre-specified ORR and DOR analyses were based on unconfirmed responses, i.e., without repeat assessments to confirm the initial response determination.
[e] The confirmed ORR and DOR were conducted as post-hoc analyses, based on responses confirmed on repeat assessments at least 4 weeks after the initial response determination.

First-line treatment of non-squamous NSCLC

The use of tislelizumab in combination with pemetrexed and platinum-containing chemotherapy for the first-line treatment of non-squamous NSCLC was mainly supported by data from one pivotal Phase 3 study (Study 304). This was a multicentre, randomised, open-label study of tislelizumab combined with platinum (cisplatin or carboplatin) and pemetrexed compared with platinum (cisplatin or carboplatin) and pemetrexed alone as first-line treatment for patients with locally advanced (Stage IIIB) non-squamous NSCLC that was not amenable to curative surgery or radiotherapy, or metastatic (Stage IV) non-squamous NSCLC, who had no prior systemic chemotherapy. The study excluded patients with known EGFR mutation or ALK rearrangement.

Patients were randomised in a 2:1 ratio to one of the following treatment arms:

- Arm T+PP: tislelizumab + platinum + pemetrexed

- Arm PP: platinum + pemetrexed

Randomisation was stratified by disease stage (IIIB vs IV) and PD-L1 expression in tumour cells (<1% TC vs 1-49% TC vs ≥50% TC). The choice of platinum was determined by the investigator prior to randomisation. Tislelizumab 200 mg was administered by IV infusion Q3W. Cisplatin 75 mg/m^2 was administered as an IV infusion over 2 hours Q3W for 4 to 6 cycles. Carboplatin AUC5 was administered as an IV infusion over 15 minutes Q3W for 4 to 6 cycles. Pemetrexed 500 mg/m^2 was administered as an IV infusion over 10 minutes Q3W. After completion of the induction phase, patients entered the maintenance phase to continue treatment with tislelizumab + pemetrexed (Arm T+PP) or pemetrexed alone (Arm PP). Patients could continue tislelizumab until loss of clinical benefit as assessed by the investigator, withdrawal of consent, study completion, start of new anti-cancer therapy, or death, whichever occurred first. Patients in Arm PP who experienced disease progression were given the option to cross over to receive tislelizumab monotherapy.

Although immune checkpoint inhibitors in combination with chemotherapy are currently recommended as the preferred treatment regimen for the first-line treatment of non-squamous NSCLC in clinical practice guidelines, the platinum plus pemetrexed combination was a standard of care regimen in this setting at the time of the study initiation, hence was accepted as the comparator regimen in the study.

The primary efficacy endpoint was PFS assessed by the Independent Review Committee (IRC) per RECIST v1.1. The secondary endpoints included OS, PFS as assessed by the investigator, and ORR and DOR as assessed by the IRC and investigator. Tumour assessments were performed every 6 weeks for the first 6 months, every 9 weeks for the remaining 6 months of Year 1, and every 12 weeks thereafter. One interim analysis of PFS was planned when approximately 153 PFS events (i.e., approximately 71% of the target number of 215 PFS events) had been observed, and the interim boundary was appropriately adjusted based on Lan-DeMets O'Brien-Fleming approximation spending function.

A total of 334 patients were randomised to the study and included in the ITT analysis set: 223 in Arm T+PP and 111 in Arm PP. At the final analysis (data cut-off date 26 October 2020), the median study follow-up time was 16.11 months: 16.49 months (range 0.0 to 27.2) in Arm T+PP and 15.15 months (range 0.0 to 25.8) in Arm PP. There were 46 (36.0%) patients in Arm PP who crossed over to receive tislelizumab monotherapy upon IRC confirmed disease progression.

The majority of patients recruited in the study were male (74.0%) and all patients were Asian (100%). The median age was 61.0 years (range 25 to 75 years) and 29.0% of patients were aged ≥65 years. The majority of patients had Stage IV disease (81.7%), while 18.3% had Stage IIIB disease; 32.9% of patients had PD-L1 ≥50%, 24.0% had PD-L1 1-49% and 43.1% had PD-L1 <1%. The patient demographics and baseline characteristics were generally well balanced between the two treatment groups, except for patients aged ≥65 years (26.9% in the T+PP arm vs 33.3% in the PP arm), never smokers (34.1% vs 40.5%) and liver metastasis (9.0% vs 15.3%). Post-hoc sensitivity analysis conducted to adjust for these baseline characteristics showed consistent efficacy results, providing reassurance that these imbalances were unlikely to significantly impact the study results.

At the interim analysis (data cut-off date 23 January 2020), the study demonstrated statistically significant improvements in the primary endpoint of PFS per IRC for tislelizumab combination with chemotherapy (Arm T+PP) compared to chemotherapy alone (Arm PP) (median PFS 9.7

vs 7.6 months; stratified HR 0.651; 95% CI: 0.465, 0.912; one-sided p=0.0054). Consistent results were observed at the final analysis (data cut-off date 26 October 2020), with a median PFS of 9.8 months in Arm T+PP compared to 7.6 months in Arm PP (stratified HR 0.632; 95% CI: 0.467, 0.855; one-sided p=0.0013). Per investigator assessment, the median PFS was 9.7 months in the T+PP arm and 5.6 months in the PP arm (stratified HR 0.550; 95% CI: 0.415, 0.729). Consistent PFS benefit was shown with HRs <1 across all pre-specified subgroups analysed.

An updated analysis of PFS was provided based on a data cut-off date of 15 July 2022, with an additional 21 months of follow-up from the final analysis cut-off date. The updated PFS analysis results showed minimal change compared to the final analysis. The median PFS was 9.8 months (95% CI: 8.9, 11.7) in the T+PP arm compared to 7.6 months (95% CI: 5.4, 8.0) in the PP arm (stratified HR 0.609; 95% CI: 0.455, 0.816).

The median OS was 21.4 months in Arm T+PP and 21.3 months in Arm PP (stratified HR 0.900; 95% CI: 0.631, 1.283). The OS results could have been confounded by post-progression crossover and much higher use of subsequent anti-cancer therapies in the control arm (68.5% in the PP arm vs 47.5% in the T+PP arm). There was also a higher proportion of patients in the PP arm who had received subsequent immune checkpoint inhibitors (50.5%) including 40 patients (36.0%) with in-study crossover, compared with the T+PP arm (7.2%). An updated OS analysis (data cut-off date 15 July 2022) showed similar results. With an additional 21 months of follow-up from the final analysis cut-off date, the updated median OS was 21.6 months in the T+PP arm vs 20.1 months in the PP arm (stratified HR 0.851; 95% CI: 0.634, 1.143).

The ORR (unconfirmed) as assessed by the IRC was 57.8% (95% CI: 51.1, 64.4) in the T+PP arm and 36.0% (95% CI: 27.1, 45.7) in the PP arm. The ORR (unconfirmed) as assessed by the investigator was 57.4% (95% CI: 50.6, 64.0) in the T+PP arm and 36.0% (95% CI: 27.1, 45.7) in the PP arm. Post-hoc analysis of ORR based on confirmed responses generally supported the unconfirmed ORR results (confirmed ORR per IRC: 50.7% vs 27.9%). The median DOR per IRC based on confirmed responses was 14.5 months (95% CI: 10.09, NE) in the T+PP arm and 8.4 months (95% CI: 5.95, 15.47) in the PP arm.

Summary of efficacy results in Study 304 (ITT analysis set)

	T+PP (N=223)	**PP (N=111)**
Interim analysis (data cut-off 23 Jan 2020)		
PFS per IRC		
PFS events, n (%)	104 (46.6)	54 (48.6)
Median PFS (months) (95% CI)	9.7 (7.7, 11.5)	7.6 (5.6, 8.0)
Stratified HR[a] (95% CI)	0.651 (0.465, 0.912)	
One-sided stratified log-rank p-value[a,b]	0.0054	
Final analysis (data cut-off 26 Oct 2020)		
PFS per IRC		
PFS events, n (%)	133 (59.6)	68 (61.3)
Median PFS (months) (95% CI)	9.8 (8.9, 11.7)	7.6 (5.6, 8.0)
Stratified HR[a] (95% CI)	0.632 (0.467, 0.855)	
One-sided stratified log-rank p-value[a,c]	0.0013	
PFS per investigator		
PFS events, n (%)	143 (64.1)	81 (73.0)
Median PFS (months)	9.7	5.6

(95% CI)	(7.7, 11.7)	(4.8, 7.9)
Stratified HR[a] (95% CI)	0.550 (0.415, 0.729)	
OS		
OS events, n (%)	96 (43.0)	46 (41.4)
Median OS (months) (95% CI)	21.4 (17.7, NE)	21.3 (15.6, NE)
Stratified HR[a] (95% CI)	0.900 (0.631, 1.283)	
Unconfirmed ORR per IRC[d]		
Best overall response, n (%) Complete response (CR) Partial response (PR) Stable disease (SD) Progressive disease (PD) Not evaluable	 11 (4.9) 118 (52.9) 67 (30.0) 15 (6.7) 9 (4.0)	 2 (1.8) 38 (34.2) 47 (42.3) 14 (12.6) 7 (6.3)
Unconfirmed ORR, n (%) (95% CI)	129 (57.8) (51.1, 64.4)	40 (36.0) (27.1, 45.7)
Odds ratio (95% CI)	2.65 (1.62, 4.32)	
ORR difference, n (%) (95% CI)	22.2 (11.6, 32.9)	
Confirmed ORR per IRC[e]		
Best overall response, n (%) Complete response (CR) Partial response (PR) Stable disease (SD) Progressive disease (PD) Not evaluable	 9 (4.0) 104 (46.6) 83 (37.2) 15 (6.7) 9 (4.0)	 2 (1.8) 29 (26.1) 56 (50.5) 14 (12.6) 7 (6.3)
Confirmed ORR, n (%) (95% CI)	113 (50.7) (43.9, 57.4)	31 (27.9) (19.8, 37.2)
Unconfirmed DOR per IRC[d]		
Median DOR (months) (95% CI)	10.6 (8.4, 15.8)	6.9 (5.0, 10.6)
Confirmed DOR per IRC[e]		
Median DOR (months) (95% CI)	14.5 (10.1, NE)	8.4 (6.0, 15.5)

NE = not estimable

[a] Stratified by stratification factors: disease stage (IIIB vs IV) and PD-L1 expression in tumour cell (≥50% TC vs 1-49% TC vs <1% TC).

[b] The p-value met the pre-specified statistical boundary of 0.0092 for the interim analysis.

[c] The primary endpoint was met and statistical significance was achieved in the pre-specified interim analysis. Formally, there was no subsequent significance testing. The p-values in the final analysis are descriptive in nature.

[e] The pre-specified ORR and DOR analyses were based on unconfirmed responses, i.e., without repeat assessments to confirm the initial response determination.

[e] The confirmed ORR and DOR were conducted as post-hoc analyses, based on responses confirmed on repeat assessments at least 4 weeks after the initial response determination.

Subgroup analyses by PD-L1 expression status showed a more pronounced treatment effect in patients with PD-L1 ≥50%. On the other hand, a potential detrimental effect in terms of OS in the PD-L1 <1% (HR 1.545) and 1-49% (HR 1.137) subgroups was observed. Although the subgroup analyses were limited by the smaller sample sizes and confounding due to crossover and higher rates of subsequent anti-cancer therapy use in the control arm, a potential detrimental effect of the treatment on survival could not be excluded.

In the PD-L1 ≥50% population, the median OS was not reached in the T+PP arm vs 13.1 months in the PP arm, with a stratified HR of 0.391 (95% CI: 0.215, 0.709). The median PFS per IRC was 14.6 months (95% CI: 11.5, NE) in the T+PP arm and 4.6 months (95% CI: 3.5, 9.7) in the PP arm (stratified HR 0.313; 95% CI: 0.179, 0.547). The confirmed ORR per IRC was 70.3% in the T+PP arm and 30.6% in the PP arm. Overall, based on clinically meaningful

improvements in terms of PFS, OS and ORR, the efficacy of tislelizumab in combination with pemetrexed and platinum chemotherapy in the first-line treatment of locally advanced or metastatic non-squamous NSCLC was demonstrated in the PD-L1 ≥50% population. Based on these results, the indication is restricted to patients whose tumours have PD-L1 expression on ≥50% of tumour cells.

Summary of efficacy results by PD-L1 subgroups

OS	**Median OS (95% CI)**		**Stratified HR (95% CI)[a]**
	T+PP	**PP**	
<1% TC (N=139)	16.8 (13.7, 18.7)	21.7 (14.9, NE)	1.545 (0.889, 2.686)
1-49% TC (N=80)	21.4 (16.9, NE)	NE (15.6, NE)	1.137 (0.520, 2.487)
≥50% TC (N=110)	NE (NE, NE)	13.1 (5.6, NE)	0.391 (0.215, 0.709)
PFS per IRC	**Median PFS (95% CI)**		**Stratified HR (95% CI)[a]**
	T+PP	**PP**	
<1% TC (N=139)	7.6 (5.0, 9.7)	7.6 (4.3, 7.9)	0.793 (0.508, 1.236)
1-49% TC (N=80)	9.7 (6.9, 11.7)	9.7 (5.6, 16.8)	0.893 (0.484, 1.650)
≥50% TC (N=110)	14.6 (11.5, NE)	4.6 (3.5, 9.7)	0.313 (0.179, 0.547)
Confirmed ORR per IRC	**ORR (95% CI)**		**ORR difference (95% CI)**
	T+PP	**PP**	
<1% TC (N=139)	35.2% (25.4, 45.9)	22.9% (12.0, 37.3)	13.3% (-1.6, 28.2)
1-49% TC (N=80)	49.1% (35.1, 63.2)	33.3% (16.5, 54.0)	15.6% (-6.2, 37.5)
≥50% TC (N=110)	70.3% (58.5, 80.3)	30.6% (16.3, 48.1)	39.5% (21.2, 57.9)

NE = not estimable

[a] Stratified by stratification factor: disease stage (IIIB versus IV).

First-line treatment of squamous NSCLC

The clinical efficacy of tislelizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel was supported by the pivotal Phase 3 study (Study 307). This was a multicentre, randomised, open-label study of tislelizumab combined with paclitaxel plus carboplatin or nab-paclitaxel plus carboplatin compared with paclitaxel plus carboplatin alone as first-line treatment for patients with locally advanced (Stage IIIB) squamous NSCLC that was not amenable to curative surgery or radiotherapy, or metastatic (Stage IV) squamous NSCLC, who had not received prior systemic chemotherapy. The study excluded patients with known EGFR mutation or ALK rearrangement.

Patients were randomised in a 1:1:1 ratio to receive one of the following treatment regimens:
Arm A (T+PC): tislelizumab + paclitaxel + carboplatin
Arm B (T+nPC): tislelizumab + nab-paclitaxel + carboplatin
Arm C (PC): paclitaxel + carboplatin

Randomisation was stratified by disease stage (IIIB vs IV) and PD-L1 expression in tumour cells (<1% TC vs 1-49% TC vs ≥50% TC). Tislelizumab 200 mg was administered by IV infusion Q3W. Paclitaxel 175 mg/m^2 was administered by IV infusion Q3W for 4 to 6 cycles. Nab-paclitaxel 100 mg/m^2 was administered by IV infusion on Days 1, 8 and 15 of each cycle for 4 to 6 cycles. Carboplatin AUC5 was administered as an IV infusion Q3W for 4 to 6 cycles, immediately after paclitaxel/nab-paclitaxel. Patients in the tislelizumab arms could continue tislelizumab until loss of clinical benefit as assessed by the investigator, withdrawal of consent, study termination by the sponsor, start of new anti-cancer therapy, or death, whichever occurred first. Patients in the control arm who developed disease progression were given the option to cross over to receive tislelizumab monotherapy.

Although immune checkpoint inhibitors in combination with chemotherapy are currently recommended as the preferred treatment regimen for the first-line treatment of squamous

NSCLC in clinical practice guidelines, the carboplatin + paclitaxel/nab-paclitaxel combination was a standard of care regimen for first-line squamous NSCLC at the time of the study initiation, hence is considered acceptable as the comparator regimen in the study.

The primary efficacy endpoint was PFS as assessed by the IRC per RECIST v1.1. The secondary endpoints included OS, PFS as assessed by the investigator, and ORR and DOR as assessed by the IRC and investigator. Tumour assessments were performed every 6 weeks for the first 6 months, every 9 weeks for the remainder of the first year, and every 12 weeks thereafter. Hypothesis testing for the primary endpoint of PFS (Arm T+PC vs Arm PC followed by Arm T+nPC vs Arm PC) was carried out sequentially to control the Type I error at the one-sided alpha of 0.025. One interim analysis of PFS was planned when approximately 130 PFS events (i.e., approximately 75% of the target number of 173 PFS events) was observed in each primary comparison. The interim boundary for PFS was based on Lan-DeMets O'Brien-Fleming approximation spending function.

A total of 360 patients were randomised to the study and included in the ITT analysis set: 120 patients in Arm T+PC, 119 patients in Arm T+nPC and 121 patients in Arm PC. At the final analysis (data cut-off date 30 September 2020), the median study follow-up time was 16.66 months: 16.97 months (range 1.0 to 26.1) in Arm T+PC, 17.15 months (range 0.1 to 24.2) in Arm T+nPC and 16.13 months (range 0.1 to 23.5) in Arm PC. There were 68 (56.2%) patients in Arm PC who crossed over to receive tislelizumab monotherapy upon IRC-confirmed disease progression.

The majority of patients were male (91.7%) and all patients were Asian (100%). The median age was 62 years (range 34 to 74 years), with 35.3% of patients aged ≥65 years. The majority of patients had Stage IV disease (66.1%) and 33.9% had Stage IIIB disease; 34.7% had PD-L1 ≥50%, 25.3% had PD-L1 1-49%, and 40.0% had PD-L1 <1%. The patient demographics and baseline characteristics were generally well balanced between the treatment groups, except for patients aged ≥65 years (32.5% in T+PC arm, 43.7% in T+nPC arm vs 29.8% in PC arm), ECOG PS of 1 (74.2% in T+PC arm, 81.5% in T+nPC arm vs 73.6% in PC arm), and former or current smokers (80.0% in T+PC arm, 89.9% in T+nPc arm vs 81.0% in PC arm). Post-hoc sensitivity analysis conducted to adjust for these baseline characteristics showed consistent efficacy results, providing reassurance that these imbalances were unlikely to significantly impact the study results.

The study demonstrated statistically significant improvements in the primary endpoint of PFS per IRC for both the tislelizumab combination with chemotherapy arms (Arms T+PC and T+nPC) compared to the chemotherapy alone arm (Arm PC) at the interim analysis (data cut-off date 06 December 2019), and consistent results were demonstrated at the final analysis (data cut-off date 30 September 2020). The median PFS per IRC at the final analysis was 7.7 months in Arm T+PC vs 5.5 months in Arm PC (stratified HR 0.450; 95% CI: 0.326, 0.619; one-sided $p<0.0001$) and 9.6 months in Arm T+nPC vs 5.5 months in Arm PC (stratified HR 0.428; 95% CI: 0.308, 0.595; one-sided $p<0.0001$). Consistent results were observed based on PFS assessed by the investigator. Pre-specified subgroup analyses also showed consistent PFS benefit across all subgroups analysed.

An updated analysis of PFS was provided based on a data cut-off date of 15 July 2022. With an additional 21 months follow-up from the final analysis, the PFS results remained consistent. The updated PFS HRs were 0.452 (95% CI: 0.329, 0.620) for Arm T+PC vs Arm PC and 0.450 (95% CI: 0.327, 0.620) for Arm T+nPC vs Arm PC.

The median OS was 22.8 months in the T+PC arm vs 20.2 months in the PC arm (stratified HR 0.678; 95% CI: 0.455, 1.010) and not reached in the T+nPC arm vs 20.2 months in the PC arm (stratified HR 0.752; 95% CI: 0.504, 1.120). It should be noted that there was a higher proportion of patients in the PC arm (66.1%) who had received subsequent systemic anti-cancer therapies compared to the T+PC arm (35.8%) and the T+nPC arm (35.3%). In Arm PC, a high proportion of patients (61.2%) received subsequent immunotherapy, including 56.2% of patients who crossed over to tislelizumab following disease progression. These imbalances in use of subsequent anti-cancer therapies could have confounded the OS results.

An updated OS analysis based on a data cut-off date of 15 July 2022 showed similar OS results: median OS was 26.1 months for Arm T+PC and 23.3 months for Arm T+nPC vs 19.4 months for Arm PC. The updated OS HRs were 0.690 (95% CI: 0.503, 0.946) for Arm T+PC vs Arm PC and 0.837 (95% CI: 0.614, 1.141) for Arm T+nPC vs Arm PC.

The other secondary endpoints provided additional evidence supporting the efficacy. The ORR (unconfirmed) as assessed by the IRC was 74.2% (95% CI: 65.4, 81.7) in Arm T+PC, 73.9% (95% CI: 65.1, 81.6) in Arm T+nPC and 47.9% (95% CI: 38.8, 57.2) in Arm PC. The ORRs assessed by the investigator were generally consistent with those of the IRC. A post-hoc analysis of ORR based on confirmed responses showed generally consistent results (confirmed ORR 61.7% in Arm T+PC and 62.2% in Arm T+nPC vs 37.2% in Arm PC). The median DOR based on confirmed responses was 13.2 months in Arm T+PC and 10.4 months in Arm T+nPC compared to 4.8 months in Arm PC.

Summary of efficacy results in Study 307 (ITT analysis set)

	T+PC (N=120)	**T+nPC (N=119)**	**PC (N=121)**
Interim analysis (data cut-off 06 Dec 2019)			
PFS per IRC			
PFS events, n (%)	60 (50.0)	56 (47.1)	75 (62.0)
Median PFS (months) (95% CI)	7.6 (6.0, 9.8)	7.6 (5.8, 11.0)	5.4 (4.2, 5.6)
Stratified HR[a] (95% CI)	0.483 (0.340, 0.686)	0.450 (0.316, 0.642)	
One-sided stratified log-rank p-value[a,b]	<0.0001	<0.0001	
Final analysis (data cut-off 30 Sep 2020)			
PFS per IRC			
PFS events, n (%)	80 (66.7)	79 (66.4)	86 (71.1)
Median PFS (months) (95% CI)	7.7 (6.7, 10.4)	9.6 (7.4, 10.8)	5.5 (4.2, 5.6)
Stratified HR[a] (95% CI)	0.450 (0.326, 0.619)	0.428 (0.308, 0.595)	
One-sided stratified log-rank p-value[a,c]	<0.0001	<0.0001	
OS			
OS events, n (%)	48 (40.0)	47 (39.5)	52 (43.0)
Median OS (months) (95% CI)	22.8 (19.1, 26.1)	NE (18. 6, NE)	20.2 (16.0, NE)
Stratified HR[a] (95% CI)	0.678 (0.455, 1.010)	0.752 (0.504, 1.120)	
Unconfirmed ORR per IRC[d]			
Best overall response, n (%)			
Complete response (CR)	7 (5.8)	8 (6.7)	1 (0.8)
Partial response (PR)	82 (68.3)	80 (67.2)	57 (47.1)
Stable disease (SD)	16 (13.3)	20 (16.8)	39 (32.2)
Progressive disease (PD)	12 (10.0)	5 (4.2)	11 (9.1)
Missing	3 (2.5)	6 (5.0)	12 (9.9)

Unconfirmed ORR, n (%) (95% CI)	89 (74.2) (65.4, 81.7)	88 (73.9) (65.1, 81.6)	58 (47.9) (38.8, 57.2)
Odds ratio (95% CI)	3.36 (1.92, 5.88)	3.16 (1.82, 5.49)	
ORR difference (95% CI)	27.0 (15.4, 38.7)	26.1 (14.3, 37.9)	
Confirmed ORR per IRC[e]			
Best overall response, n (%) Complete response (CR) Partial response (PR) Stable disease (SD) Progressive disease (PD) Not evaluable	 7 (5.8) 67 (55.8) 31 (25.8) 12 (10.0) 3 (2.5)	 6 (5.0) 68 (57.1) 34 (28.6) 5 (4.2) 6 (5.0)	 1 (0.8) 44 (36.4) 52 (43.0) 11 (9.1) 12 (9.9)
Confirmed ORR, n (%) (95% CI)	74 (61.7) (52.4, 70.4)	74 (62.2) (52.8, 70.9)	45 (37.2) (28.6, 46.4)
DOR (unconfirmed) per IRC[d]			
Median DOR (months) (95% CI)	8.4 (5.0, 15.8)	8.6 (7.1, 12.5)	4.3 (2.9, 5.4)
DOR (confirmed) per IRC[e]			
Median DOR (months) (95% CI)	13.2 (7.9, 18.8)	10.4 (8.3, 17.2)	4.8 (4.0, 5.7)

NE = not estimable

[a] Stratified by stratification factors: disease stage (IIIB vs IV) and PD-L1 expression in tumour cell (≥50% TC vs 1-49% TC vs <1% TC).

[b] The p-value met the pre-specified statistical boundary of 0.0115 for the comparison of Arm T+PC vs Arm PC and 0.0103 for the comparison of Arm T+nPC vs Arm PC interim analysis.

[c] The primary endpoint was met and statistical significance was achieved in the pre-specified interim analysis. Formally, there was no subsequent significance testing. The p-values in the final analysis are descriptive in nature.

[d] The pre-specified ORR and DOR analyses were based on unconfirmed responses, i.e., without repeat assessments to confirm the initial response determination.

[e] The confirmed ORR and DOR were conducted as post-hoc analyses, based on responses confirmed on repeat assessments at least 4 weeks after the initial response determination.

Results across all PD-L1 subgroups showed consistent efficacy of tislelizumab in combination with chemotherapy in the first-line treatment of squamous NSCLC, as summarised in the table below.

Summary of efficacy results by PD-L1 subgroups

PFS	**Median PFS (95% CI)**			**Stratified HR (95% CI)[a]**	
	T+PC	**T+nPC**	**PC**	**T+PC vs PC**	**T+nPC vs PC**
<1% TC (N=138)	7.6 (5.5, 14.5)	7.6 (5.4, 9.9)	5.5 (4.2, 7.0)	0.539 (0.322, 0.901)	0.603 (0.366, 0.993)
1-49% TC (N=91)	10.4 (5.5, 20.0)	10.1 (7.4, 12.0)	5.0 (2.8, 6.5)	0.369 (0.191, 0.712)	0.303 (0.152, 0.604)
≥50% TC (N=125)	7.7 (6.0, 9.8)	9.7 (5.6, NE)	5.5 (4.1, 7.0)	0.443 (0.260, 0.755)	0.324 (0.178, 0.587)
OS	**Median OS (95% CI)**			**Stratified HR (95% CI)[a]**	
	T+PC	**T+nPC**	**PC**	**T+PC vs PC**	**T+nPC vs PC**
<1% TC (N=138)	22.8 (11.6, NE)	20.5 (14.2, NE)	17.4 (11.5, NE)	0.726 (0.402, 1.309)	0.682 (0.366, 1.272)
1-49% TC (N=91)	26.1 (15.2, 26.1)	NE (14.1, NE)	NE (11.4, NE)	0.604 (0.269, 1.359)	0.710 (0.314, 1.605)
≥50% TC (N=125)	NE (18.1, NE)	NE (16.9, NE)	20.5 (14.4, NE)	0.721 (0.346, 1.499)	0.862 (0.430, 1.726)
Confirmed ORR	**ORR (95% CI)**			**ORR difference (95% CI)**	
	T+PC	**T+nPC**	**PC**	**T+PC vs PC**	**T+nPC vs PC**
<1% TC (N=138)	59.6% (44.3, 73.6)	52.2% (36.9, 67.1)	40.0% (25.7, 55.7)	19.8 (-0.1, 39.6)	12.4 (-7.8, 32.7)
1-49% TC (N=91)	60.0% (40.6, 77.3)	63.3% (43.9, 80.1)	25.8% (11.9, 44.6)	36.5 (14.2, 58.8)	37.7 (14.5, 60.9)
≥50% TC (N=125)	64.3% (48.0, 78.4)	71.4% (55.4, 84.3)	43.9% (28.5, 60.3)	20.6 (-1.1, 42.3)	27.4 (6.7, 48.1)

NE = not estimable
[a] Stratified by stratification factor: disease stage (IIIB versus IV).

Overall, the treatment benefits demonstrated in terms of PFS and supported by OS, ORR and DOR are considered adequate to support the efficacy of tislelizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel for the first-line treatment of patients with locally advanced or metastatic squamous NSCLC.

D ASSESSMENT OF CLINICAL SAFETY

ESCC

The safety of tislelizumab monotherapy for the treatment of unresectable, recurrent, locally advanced or metastatic ESCC after prior chemotherapy was supported primarily by safety data from the pivotal Phase 3 study (Study 302; N=495), involving 255 patients treated with tislelizumab 200 mg Q3W and 240 patients treated with investigator-chosen chemotherapy (ICC) comprising paclitaxel, docetaxel or irinotecan. Safety data were also pooled from ESCC patients treated with tislelizumab 200 mg Q3W from Study 302 and two early phase studies 102 and 001 (ESCC Population; N=307), as well as from patients with different tumour types treated with any dose of tislelizumab monotherapy across 7 clinical studies (All Doses All Indications Population; N=1972).

In the pivotal study (Study 302), the median duration of treatment exposure was 2.8 months in the tislelizumab arm and 1.5 months in the ICC arm. The median duration of exposure to tislelizumab was 2.8 months in the ESCC Population and 4.1 months in the All Doses All Indications Population. The total safety database was considered adequate to assess the safety profile of tislelizumab monotherapy for the intended ESCC population.

Summary of treatment-emergent adverse events (AEs)

	Study 302		ESCC Population (N=307)	All Doses All Indications Population (N=1972)
	Tislelizumab (N=255)	ICC (N=240)		
At least one AE	244 (95.7%)	236 (98.3%)	294 (95.8%)	1891 (95.9%)
Treatment-related AE	187 (73.3%)	225 (93.8%)	217 (70.7%)	1374 (69.7%)
Grade ≥3 AE	118 (46.3%)	163 (67.9%)	142 (46.3%)	868 (44.0%)
Treatment-related Grade ≥3 AE	48 (18.8%)	134 (55.8%)	52 (16.9%)	289 (14.7%)
Serious AE (SAE)	105 (41.2%)	105 (43.8%)	126 (41.0%)	680 (34.5%)
Treatment-related SAE	36 (14.1%)	47 (19.6%)	38 (12.4%)	207 (10.5%)
AE leading to death	35 (13.7%)	28 (11.7%)	40 (13.0%)	136 (6.9%)
Treatment-related AE leading to death	7 (2.7%)	8 (3.3%)	7 (2.3%)	21 (1.1%)
AE leading to treatment discontinuation	49 (19.2%)	64 (26.7%)	57 (18.6%)	225 (11.4%)
Treatment-related AE leading to treatment discontinuation	17 (6.7%)	33 (13.8%)	17 (5.5%)	108 (5.5%)
AE leading to dose modification	58 (22.7%)	115 (47.9%)	71 (23.1%)	522 (26.5%)
Treatment-related AE leading to dose modification	34 (13.3%)	106 (44.2%)	41 (13.4%)	285 (14.5%)

In Study 302, the majority of patients in both treatment arms experienced AEs (95.7% in the tislelizumab arm vs 98.3% in the ICC arm). The most commonly reported AEs in the tislelizumab arm and their incidences (tislelizumab vs ICC) were anaemia (30.6% vs 44.6%),

weight decreased (23.1% vs 18.8%), cough (16.9% vs 11.7%), pyrexia (16.1% vs 14.2%), decreased appetite (15.7% vs 35.0%), and constipation (15.3% vs 18.8%). The common AEs with a higher incidence in the tislelizumab arm compared to the ICC arm included cough (16.9% vs 11.7%), AST increased (14.5% vs 4.6%), ALT increased (12.9% vs 7.5%), and hypothyroidism (11.4% vs 0.4%).

The most frequently reported AEs in the ICC arm were predominantly related to haematologic, general disorders and administration site conditions, which were consistent with the safety profile of paclitaxel, docetaxel and irinotecan. The common AEs with a higher incidence in the ICC arm were anaemia (30.6% in the tislelizumab arm vs 44.6% in the ICC arm), decreased appetite (15.7% vs 35.0%), nausea (14.1% vs 30.0%), diarrhoea (12.5% vs 32.1%), vomiting (10.6% vs 20.0%), malaise (6.3% vs 15.0%), white blood cell (WBC) count decreased (3.5% vs 40.8%), leukopenia (3.1% vs 12.5%), neutrophil count decreased (2.4% vs 39.2%), neutropenia (0.8% vs 12.9%), peripheral sensory neuropathy (0.8% vs 9.6%), alopecia (0.0% vs 17.5%), and febrile neutropenia (0.0% vs 5.0%).

The incidence of treatment-related AEs was lower in the tislelizumab arm compared to the ICC arm (73.3% vs 93.8%). The treatment-related AEs reported with a higher incidence in the tislelizumab arm compared to the ICC arm were AST increased (11.4% vs 3.8%) and hypothyroidism (10.2% vs 0%).

Grade ≥3 AEs were reported at a lower incidence in the tislelizumab arm (46.3%) compared to the ICC arm (67.9%). The most frequently reported Grade ≥3 AEs in the tislelizumab arm were dysphagia (6.3% vs 2.9%), anaemia (5.9% vs 10.8%), hyponatraemia (5.5% vs 4.2%) and pneumonia (4.7% vs 7.1%), with dysphagia being the only Grade ≥3 AE reported with a higher incidence in the tislelizumab arm. The Grade ≥3 AEs reported with higher incidence in the ICC arm included neutrophil count decreased (0.0% in the tislelizumab arm vs 26.3% in the ICC arm), WBC count decreased (0.4% vs 20.0%), anaemia (5.9% vs 10.8%), lymphocyte count decreased (2.4% vs 7.5%), leukopenia (0.0% vs 7.1%), neutropenia (0.4% vs 6.7%), and diarrhoea (1.2% vs 6.3%).

SAEs were reported at similar incidences between the tislelizumab arm (41.2%) and the ICC arm (43.8%). The most frequently reported SAEs in the tislelizumab arm were pneumonia (7.1% vs 7.1%), dysphagia (4.7% vs 1.7%), pneumonitis (2.0% vs 0.8%), and esophageal obstruction (2.0% vs 0.4%). In the ICC arm, higher incidences compared to the tislelizumab arm were mainly reported for serious haematological events.

The incidence of AEs leading to treatment discontinuation was lower in the tislelizumab arm (19.2%) compared to the ICC arm (26.7%). The most frequently reported AEs leading to treatment discontinuation for tislelizumab were pneumonia (2.0% vs 1.7%), pneumonitis (1.2% vs 0.8%), immune-mediated pneumonitis (1.2% vs 0.0%), and upper gastrointestinal haemorrhage (1.2% vs 1.3%). The most frequently reported AEs leading to treatment discontinuation in the ICC arm were diarrhoea (0.4% in the tislelizumab arm vs 2.1% in the ICC arm), asthenia (0.4% vs 1.7%), febrile neutropenia (0.0% vs 1.7%), and pneumonia (2.0% vs 1.7%).

The majority of deaths in both treatment arms were due to the disease under study (59.6% in the tislelizumab arm vs 67.9% in the ICC arm). AEs leading to death were similar in incidence between the tislelizumab arm and the ICC arm (13.7% vs 11.7%). Treatment-related AEs leading to death were reported in 2.7% of patients in the tislelizumab arm and 3.3% in the ICC arm. Treatment-related events in the tislelizumab arm were esophageal obstruction, upper gastrointestinal haemorrhage, haemoptysis, pulmonary arterial hypertension, multiple organ

dysfunction syndrome, pneumonia, and platelet count decreased, all reported in 1 patient each. Treatment-related events in the ICC arm included septic shock (3 patients) and multiple organ dysfunction syndrome, death with no cause given, general physical health deterioration, pneumonia, and febrile neutropenia, reported in 1 patient each.

Immune-mediated AEs were reported in 21.2% of patients in the tislelizumab arm of Study 302; 3.5% experienced Grade ≥3 immune-mediated AEs and 5.9% experienced serious events. The most common immune-mediated AEs were hypothyroidism (9.0%), pneumonitis (7.1%), and skin adverse reactions (2.0%). All patients with immune-mediated hypothyroidism were treated with hormone therapy, while all other patients with immune-mediated AEs were treated with systemic corticosteroids.

Immune-mediated AEs by category

	Study 302 Tislelizumab (N=255)	**ESCC Population (N=307)**	**All Doses All Indications Population (N=1972)**
Any immune-mediated AE	54 (21.2%)	58 (18.9%)	305 (15.5%)
Hypothyroidism	23 (9.0%)	24 (7.8%)	132 (6.7%)
Pneumonitis	18 (7.1%)	19 (6.2%)	75 (3.8%)
Skin adverse reaction	5 (2.0%)	5 (1.6%)	24 (1.2%)
Colitis	3 (1.2%)	4 (1.3%)	17 (0.9%)
Hepatitis	3 (1.2%)	4 (1.3%)	34 (1.7%)
Myositis/rhabdomyolysis	3 (1.2%)	3 (1.0%)	14 (0.7%)
Adrenal insufficiency	2 (0.8%)	2 (0.7%)	6 (0.3%)
Myocarditis	2 (0.8%)	2 (0.7%)	6 (0.3%)
Pituitary dysfunction	1 (0.4%)	1 (0.3%)	1 (0.1%)
Hyperthyroidism	0 (0.0%)	0 (0.0%)	12 (0.6%)
Nephritis and renal dysfunction	0 (0.0%)	0 (0.0%)	7 (0.4%)
Thyroiditis	0 (0.0%)	0 (0.0%)	7 (0.4%)
Other immune-mediated reactions	0 (0.0%)	0 (0.0%)	6 (0.3%)
Arthritis	0 (0.0%)	0 (0.0%)	3 (0.2%)
Immune-mediated arthritis	0 (0.0%)	0 (0.0%)	1 (0.1%)
Pericarditis	0 (0.0%)	0 (0.0%)	1 (0.1%)
Polymyalgia rheumatica	0 (0.0%)	0 (0.0%)	1 (0.1%)

Infusion-related reactions were infrequent and reported at a similar incidence in both treatment arms (3.1% vs 4.6%). The most frequently reported events in the tislelizumab arm were pyrexia (1.6% vs 0.4%) and rash (1.2% vs 0.4%). Infusion-related reactions were either Grade 1 or 2 in severity.

Overall, the safety data for tislelizumab monotherapy in the treatment of patients with ESCC generally reflected the known toxicity profile of immune checkpoint inhibitors as monotherapy. No new safety issues have been identified. The safety profile of tislelizumab is tolerable and manageable in the target patient population.

NSCLC after prior chemotherapy

The safety profile of tislelizumab monotherapy in the treatment of patients with previously treated locally advanced or metastatic NSCLC was primarily supported by safety data from the pivotal Phase 3 study (Study 303; N=792), in which 534 patients were treated with tislelizumab 200 mg Q3W and 258 patients with docetaxel. Safety data were also pooled from previously treated NSCLC patients who received tislelizumab monotherapy from Study 303 and two early phase studies 001 and 102 (2L+ NSCLC Population; N=636), as well as from patients with

different tumour types treated with any dose of tislelizumab monotherapy from 7 clinical studies (All Doses All Indications Population; N=1972).

In the pivotal study (Study 303), the median duration of treatment exposure was 5.4 months for tislelizumab and 2.1 months for docetaxel. The median duration of exposure to tislelizumab was 4.8 months in the 2L+ NSCLC Population and 4.1 months in the All Doses All Indications Population. The size of the safety population and duration of exposure were considered adequate to describe the safety profile of tislelizumab monotherapy in the target population of previously treated NSCLC patients.

Summary of treatment-emergent AEs

	Study 303		2L+ NSCLC (N=636)	All Doses All Indications (N=1972)
	Tislelizumab (N=534)	Docetaxel (N=258)		
At least one AE	509 (95.3%)	254 (98.4%)	610 (95.9%)	1891 (95.9%)
Treatment-related AE	390 (73.0%)	242 (93.8%)	457 (71.9%)	1374 (69.7%)
Grade ≥3 AE	206 (38.6%)	193 (74.8%)	256 (40.3%)	869 (44.1%)
Treatment-related Grade ≥3 AE	77 (14.4%)	171 (66.3%)	93 (14.6%)	289 (14.7%)
Serious AE (SAE)	174 (32.6%)	83 (32.2%)	213 (33.5%)	680 (34.5%)
Treatment-related SAE	67 (12.5%)	59 (22.9%)	78 (12.3%)	207 (10.5%)
AE leading to death	32 (6.0%)	11 (4.3%)	37 (5.8%)	136 (6.9%)
Treatment-related AE leading to death	8 (1.5%)	4 (1.6%)	9 (1.4%)	21 (1.1%)
AE leading to treatment discontinuation	56 (10.5%)	32 (12.4%)	69 (10.8%)	225 (11.4%)
Treatment-related AE leading to treatment discontinuation	32 (6.0%)	25 (9.7%)	40 (6.3%)	108 (5.5%)
AE leading to dose modification	119 (22.3%)	89 (34.5%)	152 (23.9%)	522 (26.5%)
Treatment-related AE leading to dose modification	68 (12.7%)	77 (29.8%)	83 (13.1%)	285 (14.5%)

AEs were reported in 95.3% of patients in the tislelizumab arm and 98.4% in the docetaxel arm in Study 303. The most commonly reported AEs in the tislelizumab arm and their incidences (tislelizumab vs docetaxel) were anaemia (28.5% vs 43.4%), ALT increased (19.9% vs 14.7%), cough (19.5% vs 15.5%), AST increased (18.9% vs 12.0%), decreased appetite (15.4% vs 22.9%), and weight decreased (15.2% vs 10.1%). The common AEs reported with a higher incidence in the tislelizumab arm compared to the docetaxel arm were ALT increased (19.9% vs 14.7%), AST increased (18.9% vs 12.0%), weight decreased (15.2% vs 10.1%), hypothyroidism (10.7% vs 0.8%), and pruritus (6.9% vs 1.9%). Similar to that observed in the ESCC studies, the common AEs reported with higher incidence in the tislelizumab arm reflect events consistent with the known safety profile of PD-1/PD-L1 inhibitors.

The common AEs with a higher incidence in the docetaxel arm were alopecia (0.9% in the tislelizumab arm vs 47.3% docetaxel arm), neutrophil count decreased (2.8% vs 36.8%), neutropenia (1.7% vs 31.4%), WBC count decreased (3.7% vs 28.7%), leukopenia (2.8% vs 26.7%), decreased appetite (15.4% vs 22.9%), asthenia (12.5% vs 21.7%), diarrhoea (6.6% vs 13.6%), and febrile neutropenia (0.0% vs 12.8%). These are expected AEs and represent the known safety profile of docetaxel.

Treatment-related AEs were reported at a lower incidence in the tislelizumab arm compared to the docetaxel arm (73.0% vs 93.8%). The most common treatment-related AE reported at a higher incidence in the tislelizumab arm was hypothyroidism (10.7% vs 0.0%).

The incidence of Grade ≥3 AEs was lower in the tislelizumab arm compared to the docetaxel arm (38.6% vs 74.8%). The most frequently reported Grade ≥3 AEs in the tislelizumab arm were pneumonia (7.1% vs 9.3%), anaemia (3.4% vs 6.2%), and hypertension (2.4% vs 0.4%).

The incidence of SAEs was comparable between the tislelizumab and docetaxel arms (32.6% vs 32.2%). A higher incidence of serious respiratory, thoracic and mediastinal disorders was reported in the tislelizumab group vs the docetaxel group (13.3% vs 6.6%), with differences observed for pneumonitis (2.8% vs 0.0%), immune-mediated pneumonitis (1.3% vs 0.0%) and interstitial lung disease (1.3% vs 0.0%). SAEs reported with higher incidence in the docetaxel arm were mainly blood and lymphatic system disorders (14.0% vs 0.9%) and investigations (4.3% vs 0.9%).

The incidence of AEs leading to treatment discontinuation were similar between the tislelizumab and docetaxel groups (10.5% vs 12.4%). The most common AEs leading to treatment discontinuation were pneumonitis (1.7% vs 0.0%), interstitial lung disease (1.1% vs 0.0%), pneumonia (1.3% vs 1.6%), and neutrophil count decreased (0.0% vs 1.2%). All cases of pneumonitis, interstitial lung disease and neutrophil count decreased were considered treatment-related, while treatment-related pneumonia was reported at an incidence of 0.2% in the tislelizumab arm vs 1.6% in the docetaxel arm.

AEs leading to death were reported in 6.0% of patients in the tislelizumab arm and 4.3% in the docetaxel arm. The incidence of treatment-related AEs leading to death were 1.5% in the tislelizumab arm and 1.6% in the docetaxel arm. Treatment-related AEs leading to death reported in more than 1 patient in the tislelizumab group were respiratory failure (2 patients), pneumonia (2 patients), and death with no cause given (2 patients). The remaining events were reported in 1 patient each: pneumonitis, multiple organ dysfunction syndrome, and hepatic function abnormal. Treatment-related AEs leading to death reported in the docetaxel arm (all reported in 1 patient each) were pneumonia, septic shock, and cardiogenic shock. There was one death with no cause given.

A total of 17.6% of patients in the tislelizumab arm in Study 303 reported immune-mediated AEs, with similar percentages in the 2L+ NSCLC Population (18.2%) and the All Doses All Indications Population (15.5%). The most common immune-mediated AEs in Study 303 were hypothyroidism (7.9%) and pneumonitis (5.8%). The types and incidences of immune-mediated AEs with tislelizumab monotherapy in the second/third-line NSCLC population were comparable to that observed in the ESCC study (Study 302), and fall within the expected profile for the class of PD-1/PD-L1 inhibitors.

Summary of immune-mediated AEs

	Study 303 Tislelizumab (N=534)	**2L+ NSCLC (N=636)**	**All Doses All Indications (N=1972)**
Any immune-mediated AE	94 (17.6%)	116 (18.2%)	305 (15.5%)
Grade ≥3 immune-mediated AE	30 (5.6%)	38 (6.0%)	88 (4.5%)
Serious immune-mediated AE	37 (6.9%)	41 (6.4%)	98 (5.0%)
Immune-mediated AE leading to treatment modification	24 (4.5%)	30 (4.7%)	92 (4.7%)
Immune-mediated AE leading to treatment discontinuation	21 (3.9%)	26 (4.1%)	60 (3.0%)
Immune-mediated AE leading to death	2 (0.4%)	3 (0.5%)	4 (0.2%)
Immune-mediated AE treated with systemic steroids	54 (10.1%)	69 (10.8%)	180 (9.1%)
Immune-mediated AE treated with immunosuppressants	4 (0.7%)	4 (0.6%)	9 (0.5%)

Immune-mediated AE treated with hormone therapy	47 (8.8%)	55 (8.6%)	143 (7.3%)

Immune-mediated AEs by category

	Study 303 Tislelizumab (N=534)	2L+ NSCLC (N=636)	All Doses All Indications (N=1972)
Any immune-mediated AE	94 (17.6%)	116 (18.2%)	305 (15.5%)
Hypothyroidism	42 (7.9%)	49 (7.7%)	132 (6.7%)
Pneumonitis	31 (5.8%)	36 (5.7%)	75 (3.8%)
Hepatitis	7 (1.3%)	11 (1.7%)	34 (1.7%)
Myositis/rhabdomyolysis	7 (1.3%)	7 (1.1%)	14 (0.7%)
Thyroiditis	6 (1.1%)	6 (0.9%)	7 (0.4%)
Nephritis and renal dysfunction	4 (0.7%)	4 (0.6%)	7 (0.4%)
Skin adverse reaction	3 (0.6%)	7 (1.1%)	24 (1.2%)
Adrenal insufficiency	2 (0.4%)	2 (0.3%)	6 (0.3%)
Colitis	2 (0.4%)	3 (0.5%)	17 (0.9%)
Myocarditis	2 (0.4%)	3 (0.5%)	6 (0.3%)
Hyperthyroidism	1 (0.2%)	4 (0.6%)	12 (0.6%)
Pituitary dysfunction	0 (0.0%)	0 (0.0%)	1 (0.1%)
Other reactions	3 (0.6%)	4 (0.6%)	6 (0.3%)
Arthritis	1 (0.2%)	1 (0.2%)	3 (0.2%)
Immune-mediated arthritis	1 (0.2%)	1 (0.2%)	1 (0.1%)
Pericarditis	1 (0.2%)	1 (0.2%)	1 (0.1%)
Polymyalgia rheumatica	0 (0.0%)	1 (0.2%)	1 (0.1%)

Infusion-related reactions were reported in 0.9% of patients in the tislelizumab arm vs 3.5% in the docetaxel arm. The most commonly reported were infusion-related reaction (0.0% vs 1.2%), drug hypersensitivity (0.0% vs 1.2%), and infusion-site extravasation (0.0% vs 0.8%), all reported in the docetaxel arm only. The remaining AEs were reported in 1 patient each.

The overall safety profile of tislelizumab monotherapy in previously treated patients with locally advanced or metastatic NSCLC was comparable with that documented in the ESCC indication and also consistent with the known safety profile of PD-1/PD-L1 inhibitors. No new safety issues were identified in the previously treated NSCLC monotherapy studies.

First-line treatment of NSCLC

The safety of tislelizumab in combination with chemotherapy for the first-line treatment of patients with locally advanced or metastatic NSCLC was supported by data from the following patient populations:

- Pivotal Phase 3 study (Study 304; N=332) in patients with advanced or metastatic non-squamous NSCLC, comprising 222 patients treated with tislelizumab in combination with pemetrexed and platinum (cisplatin or carboplatin) (T+PP arm) and 110 patients treated with pemetrexed plus platinum (cisplatin or carboplatin) (PP arm);
- Pivotal Phase 3 study (Study 307; N=355) in patients with advanced or metastatic squamous NSCLC, comprising 120 patients treated with tislelizumab in combination with paclitaxel and carboplatin (T+PC arm), 118 patients treated with tislelizumab in combination with nab-paclitaxel and carboplatin (T+nPC arm) and 117 patients treated with paclitaxel and carboplatin (PC arm);
- NSCLC Combination Pool including all patients from Studies 304 and 307 and the Phase 2 study 206 who received tislelizumab in combination with chemotherapy (N=497) or chemotherapy alone (N=227).

In Study 304, the median duration of exposure to tislelizumab in the T+PP arm was 7.85 months, and was 2.92 months to cisplatin/carboplatin in the T+PP arm, 2.79 months to cisplatin/carboplatin in the PP arm, 7.49 months to pemetrexed in the T+PP arm, and 4.91 months to pemetrexed in the PP arm. In Study 307, the median duration of exposure to tislelizumab was 9.25 months in the T+PC arm and 10.17 months in the T+nPC arm. The median duration of exposure to paclitaxel/nab-paclitaxel was 3.47 months in the T+PC arm, 3.22 months in the T+nPC arm and 3.09 months in the PC arm, and that for carboplatin was 3.47 months in the T+PC arm, 3.22 months T+nPC arm and 3.09 months in the PC arm. The safety population and exposure were considered adequate to characterise the safety profile of tislelizumab in combination with chemotherapy for the indicated first-line NSCLC populations.

Summary of treatment-emergent AEs

	Study 304 (Non-squamous)		Study 307 (Squamous)			NSCLC Pool	
	T+PP (N=222)	PP (N=110)	T+PC (N=120)	T+nPC (N=118)	PC (N=117)	T+Chemo (N=497)	Chemo (N=227)
At least one AE	222 (100.0%)	109 (99.1%)	120 (100.0%)	117 (99.2%)	117 (100.0%)	496 (99.8%)	226 (99.6%)
Treatment-related AE	222 (100.0%)	107 (97.3%)	119 (99.2%)	117 (99.2%)	117 (100.0%)	495 (99.6%)	224 (98.7%)
Tislelizumab-related	190 (85.6%)	NA	105 (87.5%)	105 (89.0%)	NA	431 (86.7%)	NA
Chemotherapy-related	221 (99.5%)	107 (97.3%)	119 (99.2%)	117 (99.2%)	117 (100.0%)	492 (99.0%)	224 (98.7%)
Grade ≥3 AE	154 (69.4%)	62 (56.4%)	107 (89.2%)	103 (87.3%)	99 (84.6%)	394 (79.3%)	161 (70.9%)
Treatment-related Grade ≥3 AE	143 (64.4%)	51 (46.4%)	104 (86.7%)	99 (83.9%)	94 (80.3%)	372 (74.8%)	145 (63.9%)
Tislelizumab-related	74 (33.3%)	NA	46 (38.3%)	51 (43.2%)	NA	177 (35.6%)	NA
Chemotherapy-related	137 (61.7%)	51 (46.4%)	102 (85.0%)	97 (82.2%)	94 (80.3%)	359 (72.2%)	145 (63.9%)
Serious AE (SAE)	87 (39.2%)	25 (22.7%)	52 (43.3%)	50 (42.4%)	29 (24.8%)	199 (40.0%)	54 (23.8%)
Treatment-related SAE	52 (23.4%)	15 (13.6%)	31 (25.8%)	31 (26.3%)	17 (14.5%)	123 (24.7%)	32 (14.1%)
Tislelizumab-related	41 (18.5%)	NA	25 (20.8%)	22 (18.6%)	NA	95 (19.1%)	NA
Chemotherapy-related	36 (16.2%)	15 (13.6%)	18 (15.0%)	25 (21.2%)	17 (14.5%)	82 (16.5%)	32 (14.1%)
AE leading to death	9 (4.1%)	2 (1.8%)	4 (3.3%)	7 (5.9%)	5 (4.3%)	21 (4.2%)	7 (3.1%)
Treatment-related AE leading to death	4 (1.8%)	1 (0.9%)	1 (0.8%)	2 (1.7%)	3 (2.6%)	8 (1.6%)	4 (1.8%)
Tislelizumab-related	4 (1.8%)	NA	1 (0.8%)	2 (1.7%)	NA	8 (1.6%)	NA
Chemotherapy-related	1 (0.5%)	1 (0.9%)	1 (0.8%)	2 (1.7%)	3 (2.6%)	4 (0.8%)	4 (1.8%)
AE leading to treatment discontinuation	68 (30.6%)	11 (10.0%)	21 (17.5%)	38 (32.2%)	18 (15.4%)	141 (28.4%)	29 (12.8%)
Tislelizumab discontinuation	32 (14.4%)	NA	17 (14.2%)	15 (12.7%)	NA	71 (14.3%)	NA
Chemotherapy discontinuation	58 (26.1%)	11 (10.0%)	11 (9.2%)	31 (26.3%)	18 (15.4%)	111 (22.3%)	29 (12.8%)
AE leading to treatment modification[a]	158 (71.2%)	57 (51.8%)	77 (64.2%)	109 (92.4%)	51 (43.6%)	366 (73.6%)	108 (47.6%)
Tislelizumab modification	142 (64.0%)	NA	57 (47.5%)	94 (79.7%)	NA	312 (62.8%)	NA
Chemotherapy modification	148 (66.7%)	57 (51.8%)	65 (54.2%)	108 (91.5%)	49 (41.9%)	339 (68.2%)	106 (46.7%)

[a] Treatment modification included dose interruption, dose delay, infusion rate decreased and dose modification.

Almost all patients in each group experienced at least one AE, of which almost all were assessed as treatment-related. The incidences of AEs and treatment-related AEs were comparable between treatment groups across the analysis populations. The majority of common AEs reflect the known safety profile of chemotherapy comprising haematological AEs (e.g., anaemia, neutropenia, thrombocytopenia, leukopenia), gastrointestinal AEs (e.g., nausea, constipation, vomiting, decreased appetite), alopecia, and asthenia. The common AE profile was generally consistent with the known safety profile of other PD-1/PD-L1 inhibitors when given in combination with chemotherapy. Similar AE profiles were observed in the squamous and non-squamous NSCLC populations.

In the NSCLC Combination Pool, the most commonly reported AEs and their incidences (T+Chemo vs Chemo) were anaemia (87.1% vs 78.9%), neutrophil count decreased (65.0% vs 54.2%), WBC count decreased (64.4% vs 54.6%), platelet count decreased (46.9% vs 33.0%), ALT increased (46.1% vs 33.9%), AST increased (42.3% vs 28.6%), nausea (41.5% vs 35.7%), decreased appetite (40.6% vs 32.2%), leukopenia (38.4% vs 39.2%), neutropenia (38.2% vs 41.9%), alopecia (37.8% vs 34.8%), thrombocytopenia (31.6% vs 29.1%), constipation (27.4% vs 23.4%), vomiting (24.4% vs 20.3%), asthenia (23.5% vs 18.1%),

hypoalbuminaemia (19.7% vs 13.2%), pyrexia (19.5% vs 13.7%), rash (19.3% vs 7.5%), hyponatraemia (17.9% vs 15.0%), malaise (17.7% vs 18.5%), blood lactate dehydrogenase (LDH) increased (16.7% vs 12.8%), blood bilirubin increased (16.1% vs 11.0%), pain in extremity (16.1% vs 15.4%), cough (15.3% vs 8.4%), and pneumonia (15.1% vs 11.9%).

Grade ≥3 AEs were reported in 79.3% of patients in the T+Chemo group and 70.9% of patients in the Chemo group. The most common Grade ≥3 AEs were neutrophil count decreased (38.8% vs 29.5%), neutropenia (25.4% vs 31.7%), WBC count decreased (19.3% vs 14.5%), anaemia (15.5% vs 12.3%), leukopenia (14.7% vs 15.0%), thrombocytopenia (9.9% vs 7.5%), platelet count decreased (9.1% vs 3.5%), pneumonia (5.0% vs 4.8%), ALT increased (3.2% vs 1.3%), pneumonitis (3.0% vs 0.4%), lymphocyte count decreased (2.8% vs 2.2%), febrile neutropenia (2.4% vs 1.3%), and haemoptysis (2.0% vs 0.0%).

The incidence of SAEs was higher for the T+Chemo group (40.0%) than for the Chemo group (23.8%). The most commonly reported SAEs were pneumonia (6.0% vs 4.8%), pneumonitis (5.6% vs 0.4%), and haemoptysis (2.4% vs 0.4%). The most common tislelizumab-related SAEs were pneumonitis (5.2%), pneumonia (1.2%), thrombocytopenia (1.0%), and AST increased (1.0%).

A total of 28.4% of patients in the T+Chemo group and 12.8% of patients in the Chemo group had AEs that led to treatment discontinuation. The most common AEs leading to treatment discontinuation were anaemia (5.0% vs 1.8%), pneumonitis (3.4% vs 0.0%), thrombocytopenia (2.6% vs 1.3%), and blood creatinine increased (2.4% vs 0.0%). The most common AEs leading to treatment discontinuation related to tislelizumab were pneumonitis (3.2%), pneumonia (0.8%), myocarditis (0.8%), and hypothyroidism (0.8%).

AEs leading to death were reported in 4.2% of patients in the T+Chemo group and 3.1% in the Chemo group. AEs leading to death reported in more than 1 patient were pneumonitis (0.6% vs 0.4%), death with no cause given (0.6% vs 0.9%), dyspnoea (0.4% vs 0.0%), haemoptysis (0.4% vs 0.0%), respiratory failure (0.4% vs 0.0%), myocarditis (0.4% vs 0.0%), and septic shock (0.0% vs 0.9%). AEs leading to death that were considered related to tislelizumab were reported for a total of 8 patients (1.6%), including 4 patients in the Study 304 T+PP group (3 with pneumonitis and 1 patient with myocarditis), 2 patients in the Study 307 T+nPC group (1 each with death with no cause given and hepatic failure), 1 patient in the Study 307 T+PC group (hydrocephalus) and 1 patient in the Study 206 T+Chemo group (dyspnoea and myocarditis). AEs leading to death that were considered related to chemotherapy were reported for 4 patients (0.8%) in the NSCLC T+Chemo group (1 patient each with death with no cause given, hepatic failure, hydrocephalus and pneumonitis) and 4 patients (1.8%) in the NSCLC Chemo group (2 patients with septic shock and 1 patient each with death with no cause given and pneumonitis).

A total of 24.3% of patients in the NSCLC T+Chemo group had immune-mediated AEs. Similar incidences of patients across treatment groups for both squamous and non-squamous NSCLC experienced immune-mediated AEs. The most commonly occurring immune-mediated AEs in the NSCLC Pool T+Chemo group were hypothyroidism (9.1%) and pneumonitis (9.1%). The profile of immune-mediated AEs with tislelizumab combination therapy in the first-line NSCLC population was comparable to that observed with tislelizumab monotherapy in the second/third-line NSCLC population (Study 303) and in the ESCC population (Study 302), and also generally consistent with that documented for other PD-1/PD-L1 inhibitors.

Summary of immune-mediated AEs

	Study 304 T+PP (N=222)	Study 307 T+PC (N=120)	Study 307 T+nPC (N=118)	NSCLC Pool T+Chemo (N=497)
Any immune-mediated AE	51 (23.0%)	36 (30.0%)	29 (24.6%)	121 (24.3%)
Grade ≥3 immune-mediated AE	19 (8.6%)	13 (10.8%)	12 (10.2%)	46 (9.3%)
Immune-mediated AE leading to treatment discontinuation of tislelizumab	17 (7.7%)	8 (6.7%)	8 (6.8%)	36 (7.2%)
Immune-mediated AE leading to treatment modification of tislelizumab	24 (10.8%)	14 (11.7%)	15 (12.7%)	56 (11.3%)
Immune-mediated AE leading to death	4 (1.8%)	0 (0.0%)	1 (0.8%)	5 (1.0%)
Immune-mediated AE treated with systemic steroids	36 (16.2%)	22 (18.3%)	21 (17.8%)	83 (16.7%)
Immune-mediated AE treated with immunosuppressants	1 (0.5%)	0 (0.0%)	0 (0.0%)	1 (0.2%)
Immune-mediated AE treated with hormone therapy	19 (8.6%)	18 (15.0%)	10 (8.5%)	49 (9.9%)

Immune-mediated AEs by category

	Study 304 T+PP (N=222)	Study 307 T+PC (N=120)	Study 307 T+nPC (N=118)	NSCLC Pool T+Chemo (N=497)
Any immune-mediated AE	51 (23.0%)	36 (30.0%)	29 (24.6%)	121 (24.3%)
Hypothyroidism	19 (8.6%)	15 (12.5%)	9 (7.6%)	45 (9.1%)
Pneumonitis	21 (9.5%)	9 (7.5%)	12 (10.2%)	45 (9.1%)
Skin adverse reaction	5 (2.3%)	7 (5.8%)	4 (3.4%)	16 (3.2%)
Colitis	4 (1.8%)	2 (1.7%)	1 (0.8%)	7 (1.4%)
Hepatitis	3 (1.4%)	1 (0.8%)	3 (2.5%)	7 (1.4%)
Myocarditis	3 (1.4%)	1 (0.8%)	2 (1.7%)	7 (1.4%)
Myositis/rhabdomyolysis	1 (0.5%)	1 (0.8%)	3 (2.5%)	6 (1.2%)
Nephritis and renal dysfunction	2 (0.9%)	0 (0.0%)	2 (1.7%)	4 (0.8%)
Hyperthyroidism	2 (0.9%)	0 (0.0%)	1 (0.8%)	3 (0.6%)
Nervous system disorder	1 (0.5%)	1 (0.8%)	0 (0.0%)	2 (0.4%)
Thyroiditis	0 (0.0%)	2 (1.7%)	0 (0.0%)	2 (0.4%)

Infusion-related reactions were reported with low and comparable incidences between the T+Chemo group and the Chemo group (2.8% vs 2.2%). The most commonly reported preferred term was infusion-related reaction (2.4% vs 2.2%), while the remaining were reported in 1 patient each in the T+Chemo group: flushing, palpitations, pruritus, and rash.

The safety profile of tislelizumab in combination with chemotherapy in the first-line treatment of patients with locally advanced or metastatic squamous or non-squamous NSCLC was overall considered acceptable and manageable. No new safety issues were identified and the safety of tislelizumab combination is consistent with that documented with other immune checkpoint inhibitors when used in combination with chemotherapy.

E ASSESSMENT OF BENEFIT-RISK PROFILE

ESCC

Locally advanced unresectable or metastatic esophageal squamous cell carcinoma (ESCC) is a serious, life-threatening disease with poor prognosis and dismal outcomes in patients who have progressed after prior therapy. Prior to the use of immune checkpoint inhibitors, the treatment approach for advanced ESCC after prior systemic therapy was based on single-

agent palliative chemotherapy (e.g., taxanes, irinotecan). There continues to be a place in therapy for alternative safe and effective options for previously treated ESCC patients.

In the pivotal Phase 3 Study 302, tislelizumab monotherapy was shown to provide a statistically significant and clinically meaningful improvement in OS over the chemotherapy control (ICC arm), with a median OS of 8.6 months in the tislelizumab arm vs 6.3 months in the ICC arm (stratified HR 0.70; 95% CI: 0.57, 0.85; one-sided p=0.0001). Although a PFS benefit was not shown (median 1.6 months vs 2.1 months; stratified HR 0.83; 95% CI: 0.67, 1.01), the confirmed ORR (15.2% vs 6.6%) and DOR (median 10.3 vs 6.3 months) showed improvements favouring the tislelizumab arm.

The safety profile of tislelizumab is characterised mainly by immune-mediated AEs, the most common of which were hypothyroidism (9.0%), pneumonitis (7.1%), and skin adverse reactions (2.0%). The types and incidences of immune-mediated AEs reported with tislelizumab generally fell within the profile known and documented for PD-1/PD-L1 inhibitors, and are acceptable and manageable in the target patient population.

Taking into consideration the clinically relevant OS improvement for tislelizumab compared to standard chemotherapy, and the acceptable safety profile that is consistent with that known for drugs of the PD-1/PD-L1 inhibitor class, the benefit-risk balance of tislelizumab monotherapy for the treatment of patients with unresectable, recurrent, locally advanced, or metastatic ESCC after prior chemotherapy is considered positive.

NSCLC

Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers, and is a serious and life-threatening condition. NSCLC is often diagnosed at a late stage, resulting in a poor prognosis. Prior to the approval of immune checkpoint inhibitors, the 5-year OS rate for patients with advanced NSCLC ranged from 19% in patients with Stage IIIb cancers to 6% with Stage IV disease. Despite progress in recent years in the treatment and personalisation of treatment options, there remains a medical need for more safe and effective treatment options for advanced NSCLC.

NSCLC after prior chemotherapy

The key benefits of tislelizumab monotherapy in the treatment of patients with advanced NSCLC after prior chemotherapy were demonstrated in the pivotal Phase 3 Study 303, in terms of a statistically significant and clinical meaningful improvement in OS for tislelizumab over docetaxel. The median OS was prolonged by 5 months at the final analysis (16.9 months in the tislelizumab arm vs 11.9 months in the docetaxel arm; stratified HR 0.66; 95% CI: 0.56, 0.79; one-sided p<0.0001).

These findings were supported by consistent improvements in terms of PFS (median 4.2 vs 2.6 months; stratified HR 0.63; 95% CI: 0.53, 0.75; one-sided p<0.0001), confirmed ORR (20.9% vs 3.7%) and DOR (median 14.7 vs 6.2 months).

First-line treatment of non-squamous NSCLC

The pivotal Phase 3 Study 304 demonstrated a modest but statistically significant improvement in median PFS of 2.2 months for the use of tislelizumab in combination with chemotherapy (Arm T+PP) compared to chemotherapy alone (Arm PP) for the first-line treatment of patients

with non-squamous advanced NSCLC (median PFS 9.8 months in Arm T+PP vs 7.6 months in Arm PP; stratified HR 0.632; 95% CI: 0.467, 0.855; one-sided p=0.0013).

Subgroup analyses by PD-L1 expression status showed enhanced treatment effect in the PD-L1 ≥50%, whereas a potential detrimental effect in terms of OS in the PD-L1 <1% and 1-49% subgroups could not be ruled out, as the HRs exceeded 1 in these subgroups (OS HR 1.545 in the PD-L1 <1% group and HR 1.137 in the PD-L1 1-49% group). In the PD-L1 ≥50% subgroup, the median PFS was 14.6 months in Arm T+PP vs 4.6 months in Arm PP (stratified HR 0.313; 95% CI: 0.179, 0.547). The median OS was not reached in Arm T+PP vs 13.1 months in Arm PP (stratified HR 0.391; 95% CI: 0.215, 0.709), and the confirmed ORR was 70.3% in Arm T+PP vs 30.6% in Arm PP. Hence, the use of tislelizumab in combination with pemetrexed and platinum chemotherapy in the first-line treatment of locally advanced or metastatic non-squamous NSCLC indication is confined to patients whose tumours have PD-L1 expression on ≥50% of tumour cells.

First-line treatment of squamous NSCLC

The efficacy of tislelizumab in combination with chemotherapy for the first-line treatment of patients with squamous advanced NSCLC was demonstrated in the pivotal Phase 3 Study 307, in terms of a modest but statistically superior PFS for tislelizumab in combination with chemotherapy (Arm T+PC and Arm T+nPC) compared to chemotherapy alone (Arm PC). At the final analysis, the median PFS was 7.7 months in Arm T+PC vs 5.5 months in Arm PC (stratified HR 0.450; 95% CI: 0.326, 0.619; one-sided p<0.0001) and 9.6 months in Arm T+nPC vs 5.5 months in Arm PC (stratified HR 0.428; 95% CI: 0.308, 0.595; one-sided p<0.0001).

At the time of the final analysis, the median OS was 22.8 months in the T+PC arm and 20.2 months in the PC arm (stratified HR 0.678; 95% CI: 0.455, 1.010). The median OS was not reached in the T+nPC arm vs 20.2 months in the PC arm (stratified HR 0.752; 95% CI: 0.504, 1.120). The OS results might have been confounded by post-progression crossover and higher use of subsequent anti-cancer therapies in the control arm.

The secondary endpoints provided further supportive evidence of efficacy. The confirmed ORR was numerically higher in the tislelizumab arms (61.7% in Arm T+PC and 62.2% in Arm T+nPC) compared to the control arm (37.2% in Arm PC). The median DOR was also numerically longer in the tislelizumab arms (13.2 months in Arm T+PC and 10.4 months in Arm T+nPC) compared to Arm PC (4.8 months).

The safety profile of tislelizumab monotherapy and in combination with chemotherapy in patients with squamous or non-squamous NSCLC was generally consistent with that known and documented for other PD-1/PD-L1 inhibitors. The immune-mediated AEs reported in the NSCLC studies (comprising mostly hypothyroidism and pneumonitis) were similar to that observed in the ESCC study, and no new safety issues were identified.

Overall, considering the benefits demonstrated for tislelizumab monotherapy in terms of clinical relevant improvements in OS, ORR and DOR in the treatment of patients with advanced NSCLC after prior chemotherapy, and the improvements in PFS, ORR and DOR with tislelizumab in combination with chemotherapy in the first-line treatment of advanced squamous and non-squamous NSCLC, together with the acceptable safety profile that was consistent with the PD-1/PD-L1 inhibitor class of drugs, the benefit-risk profile of tislelizumab in the requested NSCLC patient populations is considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Tevimbra for the approved indications for ESCC and NSCLC was deemed favourable and approval of the product registration was granted on 19 September 2024.

APPROVED PACKAGE INSERT AT REGISTRATION

1. NAME OF THE MEDICINAL PRODUCT

TEVIMBRA (tislelizumab) concentrate for solution for infusion 100mg/ 10mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate for solution for infusion contains 10 mg tislelizumab.

Each vial of 10 ml contains 100 mg tislelizumab.

Tislelizumab is an Fc-engineered humanised immunoglobulin G4 (IgG4) variant monoclonal antibody produced in recombinant Chinese hamster ovary cells.

Excipient with known effect

Each ml of concentrate for solution for infusion contains 0.069 mmol (or 1.6 mg) sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Clear to slightly opalescent, colourless to slightly yellowish solution.

The solution has a pH of approximately 6.5 and an osmolality of approximately 270 to 330 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Non-small cell lung cancer (NSCLC)

TEVIMBRA in combination with pemetrexed and platinum-containing chemotherapy is indicated for the first-line treatment of adult patients with non-squamous NSCLC whose tumours have PD-L1 expression on ≥50% of tumour cells with no EGFR or ALK positive mutations and who have:

- locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or
- metastatic NSCLC.

TEVIMBRA in combination with carboplatin and either paclitaxel or nab-paclitaxel is indicated for the first-line treatment of adult patients with squamous NSCLC who have:

- locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or
- metastatic NSCLC.

TEVIMBRA as monotherapy is indicated for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy.

Esophageal squamous cell carcinoma (ESCC)

TEVIMBRA as monotherapy is indicated for the treatment of patients with unresectable, recurrent, locally advanced, or metastatic esophageal squamous cell carcinoma (ESCC) after prior chemotherapy

4.2 Posology and method of administration

Tevimbra treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

Posology

Tevimbra monotherapy
The recommended dose of Tevimbra is 200 mg administered by intravenous infusion once every 3 weeks.

Tevimbra combination therapy
The recommended dose of Tevimbra is 200 mg administered by intravenous infusion once every 3 weeks, in combination with chemotherapy.

When Tevimbra and chemotherapy are administered on the same day, Tevimbra should be administered before chemotherapy. The Package Leaflet for the chemotherapy product should be referred to for dosing as well as for recommendations on corticosteroid use as pre-medication for the prevention of chemotherapy-related adverse reactions.

Duration of treatment
Patients should be treated with Tevimbra until disease progression or unacceptable toxicity.

Dose delay or discontinuation (see also section 4.4)
No dose reductions of Tevimbra as monotherapy or in combination therapy are recommended. Tevimbra should be withheld or discontinued as described in Table 1.

Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4.

Table 1 Recommended treatment modifications for Tevimbra

Immune-related adverse reaction	**Severity[1]**	**Tevimbra treatment modification**
Pneumonitis	Grade 2	Withhold[2,3]
	Recurrent grade 2; grade 3 or 4	Permanently discontinue[3]
Hepatitis	ALT or AST >3 to 8 x ULN or total bilirubin >1.5 to 3 x ULN	Withhold[2,3]
	ALT or AST >8 x ULN or total bilirubin >3 x ULN	Permanently discontinue[3]

Rash	Grade 3	Withhold[2,3]
	Grade 4	Permanently discontinue[3]
Severe cutaneous adverse reactions (SCARs)	Suspected SCARs, including SJS or TEN	Withhold[2,3] For suspected SJS or TEN, do not resume unless SJS/TEN has been ruled out in consultation with appropriate specialist(s).
	Confirmed SCARs, including SJS or TEN	Permanently discontinue
Colitis	Grade 2 or 3	Withold[2,3]
	Recurrent grade 3; grade 4	Permanently discontinue[3]
Myositis/rhabdomyolysis	Grade 2 or 3	Withhold[2,3]
	Recurrent grade 3; grade 4	Permanently discontinue[3]
Hypothyroidism	Grade 2, 3 or 4	Hypothyroidism may be managed with replacement therapy without treatment interruption.
Hyperthyroidism	Grade 3 or 4	Withhold[2] For grade 3 or 4 that has improved to grade ≤2 and is controlled with anti-thyroid therapy, if indicated continuation of Tevimbra may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.
Adrenal insufficiency	Grade 2	Consider withholding treatment until controlled by HRT.
	Grade 3 or 4	Withhold[3] For grade 3 or 4 that has improved to grade ≤2 and is controlled with HRT, if indicated continuation of Tevimbra may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.[3]
Hypophysitis	Grade 2	Consider withholding treatment until controlled by HRT.
	Grade 3 or 4	Withhold[2,3] For grade 3 or 4 that has improved to grade ≤2 and is controlled with HRT, if indicated continuation of Tevimbra may be considered after corticosteroid taper. Otherwise, treatment should be discontinued.[3]
Type 1 diabetes mellitus	Type 1 diabetes mellitus associated with grade ≥3 hyperglycaemia (glucose >250 mg/dl or >13.9 mmol/l) or associated with ketoacidosis	Withhold For grade 3 or 4 that has improved to grade ≤2 with insulin therapy, if indicated continuation of Tevimbra may be considered once metabolic control is achieved. Otherwise, treatment should be discontinued.
Nephritis with renal dysfunction	Grade 2 (creatinine >1.5 to 3 x baseline or >1.5 to 3 x ULN)	Withhold[2,3]
	Grade 3 (creatinine >3 x baseline or >3 to 6 x ULN) or grade 4 (creatinine >6 x ULN)	Permanently discontinue[3]
Myocarditis	Grade 2, 3 or 4	Permanently discontinue[3]
Neurological toxicities	Grade 2	Withhold[2,3]
	Grade 3 or 4	Permanently discontinue[3]
Pancreatitis	Grade 3 pancreatitis or grade 3 or 4 serum amylase or lipase levels increased (>2 x ULN)	Withhold[2,3]
	Grade 4	Permanently discontinue[3]

Other immune-related adverse reactions	Grade 3	Withhold[2,3]
	Recurrent grade 3; grade 4	Permanently discontinue[3]
Other adverse drug reactions		
Infusion-related reactions	Grade 1	Consider pre-medication for prophylaxis of subsequent infusion reactions. Slow the rate of infusion by 50%.
	Grade 2	Interrupt infusion. Resume infusion if resolved or decreased to grade 1, and slow rate of infusion by 50%.
	Grade 3 or 4	Permanently discontinue

ALT = alanine aminotransferase, AST = aspartate aminotransferase, HRT= hormone replacement therapy, SJS = Stevens-Johnson syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit of normal

[1] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4.0). Hypophysitis grade is in accordance with NCI-CTCAE v5.0.

[2] Resume in patients with complete or partial resolution (grade 0 to 1) after corticosteroid taper over at least 1 month. Permanently discontinue if no complete or partial resolution within 12 weeks of initiating corticosteroids or inability to reduce prednisone to ≤10 mg/day (or equivalent) within 12 weeks of initiating corticosteroids.

[3] Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper to ≤10 mg/day (or equivalent) over at least 1 month is recommended, except for pneumonitis, where initial dose of 2 to 4 mg/kg/day is recommended.

Special populations

Paediatric population

The safety and efficacy of Tevimbra in patients aged below 18 years have not been established. No data are available.

Elderly

No dose adjustment is needed for patients aged ≥65 years (see section 4.8).

Renal impairment

No dose adjustment is needed for patients with mild or moderate renal impairment. Data from patients with severe renal impairment are too limited to make dosing recommendations for this population (see section 5.2).

Hepatic impairment

No dose adjustment is needed for patients with mild or moderate hepatic impairment. Data from patients with severe hepatic impairment are too limited to make dosing recommendations for this population (see section 5.2).

Method of administration

Tevimbra is for intravenous use only. It is to be administered as an infusion and must not be administered as an intravenous push or single bolus injection. For instructions on dilution of the medicinal product before administration, see section 6.6.

The first infusion should be administered over a period of 60 minutes. If this is well tolerated, the subsequent infusions may be administered over a period of 30 minutes. The infusion should be given via an intravenous line containing a sterile, non-pyrogenic, low-protein-binding 0.2 or 0.22 micron in-line or add-on filter.

Other medicinal products must not be mixed or co-administered through the same infusion line.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Patient Card

Patients treated with Tevimbra must be given the Patient Card to be informed about the risks of immune-related adverse reactions during Tevimbra therapy.

The prescriber must discuss the risks of immune-related adverse reactions during Tevimbra therapy with the patient.

Immune-related adverse reactions

Immune-related adverse reactions have been reported, including fatal cases, during treatment with tislelizumab (see section 4.8). The majority of these events improved with interruption of tislelizumab, administration of corticosteroids and/or supportive care. Immune-related adverse reactions have also been reported after the last dose of tislelizumab. Immune-related adverse reactions affecting more than one body system can occur simultaneously.

For suspected immune-related adverse reactions, adequate evaluation to confirm aetiology or exclude alternative aetiologies, including infection, should be ensured. Based on the severity of the adverse reaction, tislelizumab should be withheld and corticosteroids administered (see section 4.2). Based on limited data from clinical studies, administration of other systemic immunosuppressants can be considered in patients whose immune-related adverse reactions are not controlled with corticosteroid use (see sections 4.2 and 4.8). Upon improvement to grade ≤1, corticosteroid taper should be initiated and continued over at least 1 month.

Immune-related pneumonitis
Immune-related pneumonitis, including fatal cases, has been reported in patients receiving tislelizumab. Patients should be monitored for signs and symptoms of pneumonitis. Patients with suspected pneumonitis should be evaluated with radiographic imaging and infectious or disease-related aetiologies should be ruled out.

Patients with immune-related pneumonitis should be managed according to the treatment modifications as recommended in Table 1 (see section 4.2).

Immune-related hepatitis
Immune-related hepatitis, including fatal cases, has been reported in patients treated with tislelizumab. Patients should be monitored for signs and symptoms of hepatitis and changes in liver function. Liver function tests should be performed at baseline and periodically during treatment.

Patients with immune-related hepatitis should be managed according to the treatment modifications as recommended in Table 1 (see section 4.2).

Immune-related skin reactions
Immune-related skin rash or dermatitis have been reported in patients receiving tislelizumab. Patients should be monitored for suspected skin reactions and other causes should be excluded. Based on the severity of the skin adverse reactions, tislelizumab should be withheld or permanently discontinued as recommended in Table 1 (see section 4.2).

Cases of severe cutaneous adverse reactions (SCARs) including erythema multiforme (EM), Stevens-Johnson Syndrome (SJS) and Toxic epidermal necrolysis (TEN), some of them with fatal outcome, have been reported in patients receiving tislelizumab (see section 4.8). Patients should be monitored for signs or symptoms of SCARs (e.g. a prodrome of fever, flu-like symptoms, mucosal lesions or progressive skin rash) and other causes should be excluded. For suspected SCAR, tislelizumab should be withheld and the patient should be referred to specialised care for assessment and treatment. If SCAR, is confirmed, tislelizumab should be permanently discontinued (see section 4.2).

Immune-related colitis
Immune-related colitis, frequently associated with diarrhoea, has been reported in patients treated with tislelizumab. Patients should be monitored for signs and symptoms of colitis. Infectious and disease-related aetiologies should be ruled out.

Patients with immune-related colitis should be managed according to the treatment modifications as recommended in Table 1 (see section 4.2).

Immune-related endocrinopathies
Immune-related endocrinopathies, including thyroid disorders, adrenal insufficiency, hypophysitis and type 1 diabetes mellitus, have been reported in patients treated with tislelizumab. These may require supportive treatment depending on the specific endocrine disorder. Long-term hormone replacement therapy (HRT) may be necessary in cases of immune-related endocrinopathies.

Patients with immune-related endocrinopathies should be managed according to the treatment modifications as recommended in Table 1 (see section 4.2).

Thyroid disorders
Thyroid disorders, including thyroiditis, hypothyroidism and hyperthyroidism, have been reported in patients treated with tislelizumab. Patients should be monitored (at the start of treatment, periodically during treatment and as indicated based on clinical evaluation) for changes in thyroid function and clinical signs and symptoms of thyroid disorders. Hypothyroidism may be managed with HRT without treatment interruption and without corticosteroids. Hyperthyroidism may be managed symptomatically (see section 4.2).

Adrenal insufficiency
Adrenal insufficiency has been reported in patients treated with tislelizumab. Patients should be monitored for signs and symptoms of adrenal insufficiency. Monitoring of adrenal function and hormone levels should be considered. Corticosteroids and HRT should be administered as clinically indicated (see section 4.2).

Hypophysitis
Hypophysitis has been reported in patients treated with tislelizumab. Patients should be monitored for signs and symptoms of hypophysitis/hypopituitarism. Monitoring of pituitary function and hormone levels should be considered. Corticosteroids and HRT should be administered as clinically indicated (see section 4.2).

Type 1 diabetes mellitus
Type 1 diabetes mellitus, including diabetic ketoacidosis, has been reported in patients treated with tislelizumab. Patients should be monitored for hyperglycaemia and other signs and symptoms of diabetes. Insulin should be administered for type 1 diabetes. In patients with severe hyperglycaemia or ketoacidosis (grade ≥3), tislelizumab should be withheld and anti-hyperglycaemic treatment should be administered (see section 4.2). Treatment with tislelizumab may be resumed when metabolic control is achieved.

Immune-related nephritis with renal dysfunction
Immune-related nephritis with renal dysfunction has been reported in patients treated with tislelizumab. Patients should be monitored for changes in renal function (elevated serum creatinine), and other causes of renal dysfunction should be excluded.

Patients with immune-related nephritis with renal dysfunction should be managed according to the treatment modifications as recommended in Table 1 (see section 4.2).

Other immune-related adverse reactions
Other clinically important immune-related adverse reactions were reported with tislelizumab: myositis, myocarditis, arthritis, polymyalgia rheumatica, pericarditis, Guillain-Barré syndrome and aplastic anaemia (see section 4.8).

Patients with other immune-related adverse reactions should be managed according to the treatment modifications as recommended in Table 1 (see section 4.2).

Solid organ transplant rejection
Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with tislelizumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with tislelizumab versus the risk of possible organ rejection should be considered in these patients.

Infusion-related reactions

Severe infusion-related reactions (grade 3 or higher) have been reported in patients receiving tislelizumab (see section 4.8). Patients should be monitored for signs and symptoms of infusion-related reactions.

Infusion-related reactions should be managed as recommended in Table 1 (see section 4.2).

Patients excluded from clinical studies

Patients with any of the following conditions were excluded from clinical studies: baseline ECOG performance score greater than or equal to 2; active brain or leptomeningeal metastases; active autoimmune disease or history of autoimmune disease that may relapse; any condition requiring systemic treatment with either corticosteroids (>10 mg/day prednisone or equivalent) or other immunosuppressants within the 14 days prior to study treatment; active or untreated HIV; untreated hepatitis B or hepatitis C carriers; history of interstitial lung disease; administration of live vaccine within the 14 days prior to study treatment; infection requiring systemic therapy within the 14 days prior to study treatment; history of severe hypersensitivity to another monoclonal antibody. In the absence of data, tislelizumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Patients on controlled sodium diet

Each ml of this medicinal product contains 0.069 mmol (or 1.6 mg) sodium. This medicinal product contains 16 mg sodium per 10 ml vial, equivalent to 0.8% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

Tislelizumab is a humanised monoclonal antibody, cleared from the circulation through catabolism. As such, formal pharmacokinetic interaction studies have not been conducted. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug-metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of tislelizumab.

The use of systemic corticosteroids and other immunosuppressants at baseline, before starting tislelizumab, except for physiological doses of systemic corticosteroid (10 mg/day prednisone or equivalent), should be avoided because of their potential interference with the pharmacodynamic activity and efficacy. However, systemic corticosteroids and other immunosuppressants can be used after starting tislelizumab to treat immune-related adverse reactions (see section 4.4). Corticosteroids can also be used as pre-medication when tislelizumab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Tislelizumab should not be used in women of childbearing potential not using effective contraception unless the clinical condition of the woman requires treatment with tislelizumab. Women of childbearing potential should use effective contraception (methods that result in less than 1% pregnancy rates) during treatment and for at least 4 months following the last dose of tislelizumab.

Pregnancy

There are no available data on the use of tislelizumab in pregnant women. Based on its mechanism of action, tislelizumab can cause foetal harm when administered to a pregnant woman.

Animal reproduction studies have not been conducted with tislelizumab. However, in murine models of pregnancy, blockade of PD-1/PD-L1 signalling has been shown to disrupt tolerance to the foetus and to result in increased foetal loss.

Human IgG4 (immunoglobulins) are known to cross the placental barrier. Therefore, tislelizumab, being an IgG4 variant, has the potential to be transmitted from the mother to the developing foetus. Women should be advised of the potential risk to a foetus.

Tislelizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with tislelizumab.

Breast-feeding

It is unknown whether tislelizumab is excreted in human milk. Its effects on breast-fed newborns/infants and on milk production are also unknown.

Because of the potential for serious adverse drug reactions in breast-fed newborns/infants from Tevimbra, women should be advised not to breast-feed during treatment and for at least 4 months after the last dose of Tevimbra.

Fertility

No clinical data are available on the possible effects of tislelizumab on fertility. No reproductive and development toxicity studies have been conducted with tislelizumab. Based on a 3-month repeat-dose toxicity study, there were no notable effects in the male and female reproductive organs in cynomolgus monkeys when tislelizumab was given at doses of 3, 10 or 30 mg/kg every 2 weeks for 13 weeks (7 dose administrations) (see section 5.3).

4.7 Effects on ability to drive and use machines

Tevimbra has minor influence on the ability to drive and use machines. In some patients, fatigue has been reported following administration of tislelizumab (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety of tislelizumab as monotherapy is based on pooled data in 1 534 patients across multiple tumour types who received 200 mg tislelizumab every 3 weeks. The most common adverse reactions were anaemia (29.2%), fatigue (22.9%) and aspartate aminotransferase (20.9%) increased. The most common grade 3/4 adverse reactions were anaemia (5.0%), pneumonia (4.2%), hyponatraemia (2.7%), aspartate aminotransferase increased (2.6%), blood bilirubin increased (2.0%), pneumonitis (2.0%) and fatigue (2.0%). 1.2% of patients experienced adverse reactions leading to death. The adverse

reactions leading to death were pneumonia (0.78%), hepatitis (0.13%), pneumonitis (0.07%), dyspnoea (0.07%), decreased appetite (0.07%) and thrombocytopenia (0.07%). Among the 1 534 patients, 40.1% were exposed to tislelizumab for longer than 6 months, and 22.2% were exposed for longer than 12 months.

The safety of tislelizumab given in combination with chemotherapy is based on data in 497 patients with NSCLC. The most common adverse reactions were anaemia (88.3%), neutropenia (86.5%), thrombocytopenia (67.0%), alanine aminotransferase increased (46.1%), fatigue (43.1%), aspartate aminotransferase increased (42.3%), nausea (41.4%), decreased appetite (40.6%) and rash (26.4%). The most common grade 3/4 adverse reactions were neutropenia (58.6%), thrombocytopenia (18.3%), anaemia (15.7%), pneumonia (5.0%), pneumonitis (3.4%), alanine aminotransferase increased (3.2%), lymphopenia (2.8%), rash (2.6%) and fatigue (2.2%). 1.6% of patients experienced adverse reactions leading to death. The adverse reactions leading to death were pneumonitis (0.60%), dyspnoea (0.40%), myocarditis (0.40%), pneumonia (0.20%) and hypokalaemia (0.20%). Among the 497 patients, 65.8% were exposed to tislelizumab for longer than 6 months, and 37.8% were exposed for longer than 12 months.

Tabulated list of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with Tevimbra monotherapy (N= 1 534) and in combination with chemotherapy (N = 497) are presented in Table 2. Adverse reactions are listed according to system organ class in MedDRA. Within each system organ class, the adverse reactions are presented in decreasing frequency. The corresponding frequency category for each adverse reaction is defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 Adverse reactions with Tevimbra as monotherapy (N = 1 534) and in combination with chemotherapy (N = 497)

	Tislelizumab monotherapy N = 1 534	**Tislelizumab plus chemotherapy N = 497**
Adverse reactions	**Frequency category (All grades)**	**Frequency category (All grades)**
Infections and infestations		
Pneumonia[1]	Common*	Very common*
Blood and lymphatic system disorders		
Anaemia[2]	Very common	Very common
Thrombocytopenia[3]	Common*	Very common
Neutropenia[4]	Common	Very common
Lymphopenia[5]	Common	Very common
Endocrine disorders		
Hypothyroidism[6]	Very common	Very common
Hyperthyroidism[7]	Common	Very common
Thyroiditis[8]	Common	Uncommon
Adrenal insufficiency[9]	Uncommon	-
Hypophysitis[10]	Rare	-

Metabolism and nutrition disorders		
Hyperglycaemia[11]	Common	Very common
Hyponatraemia[12]	Common	Very common
Hypokalaemia[13]	Common	Very common*
Diabetes mellitus[14]	Uncommon	Common
Nervous system disorders		
GuillainBarré syndrome	-	Uncommon
Eye disorders		
Uveitis[15]	Uncommon	-
Cardiac disorders		
Myocarditis[16]	Uncommon	Common*
Pericarditis	Rare	-
Vascular disorders		
Hypertension[17]	Common	Common
Respiratory, thoracic and mediastinal disorders		
Cough	Very common	Very common
Dyspnoea	Common*	Very common*
Pneumonitis[18]	Common*	Very common*
Gastrointestinal disorders		
Nausea	Common	Very common
Diarrhoea[19]	Common	Very common
Stomatitis[20]	Common	Common
Pancreatitis[21]	Uncommon	Uncommon
Colitis[22]	Uncommon	Common
Hepatobiliary disorders		
Hepatitis[23]	Common*	Common
Skin and subcutaneous tissue disorders		
Rash[24]	Very common	Very common
Pruritus	Very common	Common
Severe skin reactions[25]	Rare	-
Musculoskeletal and connective tissue disorders		
Arthralgia	Common	Very common
Myalgia	Common	Common
Myositis[26]	Uncommon	Uncommon
Arthritis[27]	Uncommon	Common
Renal and urinary disorders		
Nephritis[28]	Uncommon	Uncommon
General disorders and administration site conditions		
Fatigue[29]	Very common	Very common
Decreased appetite	Very common*	Very common
Investigations		
Aspartate aminotransferase increased	Very common	Very common
Alanine aminotransferase increased	Very common	Very common
Blood bilirubin increased[30]	Very common	Very common
Blood alkaline phosphatase increased	Common	Very common
Blood creatinine increased	Common	Very common

Injury, poisoning and procedural complications		
Infusion-related reaction[31]	Uncommon	Common

[1] Pneumonia includes preferred terms (PTs) of pneumonia, lower respiratory tract infection, lower respiratory tract infection bacterial, pneumonia bacterial, pneumonia fungal and pneumocystis jirovecii pneumonia.
[2] Anaemia includes PTs of anaemia and haemoglobin decreased.
[3] Thrombocytopenia includes PTs of thrombocytopenia and platelet count decreased.
[4] Neutropenia includes PTs of neutropenia and neutrophil count decreased.
[5] Lymphopenia includes PTs of lymphopenia, lymphocyte count decreased and lymphocyte percentage decreased.
[6] Hypothyroidism includes preferred terms (PTs) of hypothyroidism, thyroxine free decreased, tri-iodothyronine free decreased, tri-iodothyronine decreased, primary hypothyroidism and thyroxine decreased.
[7] Hyperthyroidism includes PTs of hyperthyroidism, blood thyroid stimulating hormone decreased, tri-iodothyronine free increased, thyroxine free increased, thyroxine increased and tri-iodothyronine increased.
[8] Thyroiditis includes PTs of thyroiditis, autoimmune thyroiditis and thyroiditis subacute.
[9] Adrenal insufficiency includes PTs of adrenal insufficiency and secondary adrenocortical insufficiency.
[10] Hypophysitis includes PTs of hypophysitis and hypopituitarism.
[11] Hyperglycaemia includes PTs of hyperglycaemia and blood glucose increased.
[12] Hyponatraemia includes PTs of hyponatraemia and blood sodium decreased.
[13] Hypokalaemia includes PTs of hypokalaemia and blood potassium decreased.
[14] Diabetes mellitus includes PTs of diabetes mellitus, type 1 diabetes mellitus and latent autoimmune diabetes in adults.
[15] Uveitis includes PTs of uveitis and iritis.
[16] Myocarditis includes PTs of myocarditis, immune-mediated myocarditis and autoimmune myocarditis.
[17] Hypertension includes PTs of hypertension, blood pressure increased and essential hypertension.
[18] Pneumonitis includes PTs of pneumonitis, immune-mediated lung disease, interstitial lung disease and organising pneumonia.
[19] Diarrhoea includes PTs of diarrhoea and frequent bowel movements.
[20] Stomatitis includes PTs of stomatitis, mouth ulceration and aphthous ulcer.
[21] Pancreatitis includes PTs of amylase increased, lipase increased, and pancreatitis acute.
[22] Colitis includes PTs of colitis and immune-mediated enterocolitis.
[23] Hepatitis includes PTs of hepatitis, hepatic function abnormal, immune-mediated hepatitis and liver injury and autoimmune hepatitis.
[24] Rash includes PTs of rash, rash maculo-papular, eczema, rash erythematous, dermatitis, dermatitis allergic, rash papular, urticaria, erythema, skin exfoliation, drug eruption, rash macular, psoriasis, rash pustular, dermatitis acneiform, rash pruritic, lichenoid keratosis, hand dermatitis, immune-mediated dermatitis, rash follicular, acute febrile neutrophilic dermatosis, erythema nodosum and pemphigoid.
[25] Severe skin reaction includes erythema multiforme.
[26] Myositis includes PTs of myositis and immune-mediated myositis.
[27] Arthritis includes PTs of arthritis and immune-mediated arthritis.
[28] Nephritis includes PTs of nephritis, focal segmental glomerulosclerosis and immune-mediated nephritis.
[29] Fatigue includes PTs of fatigue, asthenia, malaise and lethargy.
[30] Blood bilirubin increased includes PTs of blood bilirubin increased, bilirubin conjugated increased, blood bilirubin unconjugated increased and hyperbilirubinaemia.
[31] Infusion-related reaction includes PTs of infusion-related reaction and infusion-related hypersensitivity reaction.

*including fatal outcomes

Description of selected adverse reactions

The data below reflect information for significant adverse drug reactions for tislelizumab as monotherapy in clinical studies. Details for the significant adverse reactions for tislelizumab when given in combination with chemotherapy are presented if clinically relevant differences were noted in comparison to tislelizumab monotherapy.

Immune-related pneumonitis
In patients treated with tislelizumab as monotherapy, immune-related pneumonitis occurred in 4.3% of patients, including grade 1 (0.3%), grade 2 (2.0%), grade 3 (1.5%), grade 4 (0.3%) and grade 5 (0.2%) events.

The median time from first dose to onset of the event was 3.2 months (range: 1.0 day to 16.5 months), and the median duration from onset to resolution was 6.1 months (range: 1.0+ day to 22.8+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 1.8% of patients and tislelizumab treatment was interrupted in 1.8% of patients. Pneumonitis resolved in 45.5% of patients.

In patients treated with tislelizumab as monotherapy, pneumonitis occurred more frequently in patients with a history of prior thoracic radiation (6.3%) than in patients who did not receive prior thoracic radiation (2.8%).

Pneumonitis occurred in 9.1% of patients with NSCLC treated with tislelizumab in combination with chemotherapy. In patients with NSCLC treated with tislelizumab as monotherapy, pneumonitis occurred in 6.0% of patients.

Immune-related hepatitis
In patients treated with tislelizumab as monotherapy, immune-related hepatitis occurred in 1.7% of patients, including grade 1 (0.1%), grade 2 (0.5%), grade 3 (0.9%), grade 4 (0.1%) and grade 5 (0.1%) events.

The median time from first dose to onset of the event was 31.0 days (range: 8.0 days to 13.1 months), and the median duration from onset to resolution was 2.0 months (range: 1.0+ day to 37.9+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.4% of patients and tislelizumab treatment was interrupted in 1.0% of patients for immune-related hepatitis. Hepatitis resolved in 50.0% of patients.

Immune-related skin adverse reactions
In patients treated with tislelizumab as monotherapy, immune-related skin adverse reactions occurred in 1.8% of patients, including grade 1 (0.4%), grade 2 (0.8%), grade 3 (0.3%) and grade 4 (0.3%) events.

The median time from first dose to onset of the event was 2.5 months (range: 7.0 days to 11.6 months). The median duration from onset to resolution was 11.2 months (range: 4.0 days to 34.0+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.3% of patients, and tislelizumab treatment was interrupted in 0.5% of patients. Skin adverse reactions resolved in 51.9% of patients.

Cases of SJS and TEN have been reported from post-marketing experience, some with fatal outcome (see section 4.2 and 4.4).

Immune-related colitis
In patients treated with tislelizumab as monotherapy, immune-related colitis occurred in 0.7% of patients, including grade 2 (0.6%) and grade 3 (0.1%) events.

The median time from first dose to onset of the event was 6.0 months (range: 12.0 days to 14.4 months), and the median duration from onset to resolution was 28.0 days (range: 9.0 days to 3.6 months). Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.6% of patients. Colitis resolved in 81.8% of patients.

Immune-related myositis/rhabdomyolysis
In patients treated with tislelizumab as monotherapy, immune-related myositis/rhabdomyolysis occurred in 0.9% of patients, including grade 1 (0.2%), grade 2 (0.3%), grade 3 (0.3%) and grade 4 (0.1%) events.

The median time from first dose to onset of the event was 1.8 months (range: 15.0 days to 17.6 months), and the median duration from onset to resolution was 2.1 months (range: 5.0 days to 11.2+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.2% of patients and tislelizumab treatment was interrupted in 0.7% of patients. Myositis/rhabdomyolysis resolved in 57.1% of patients.

Immune-related endocrinopathies
Thyroid disorders
Hypothyroidism:
In patients treated with tislelizumab as monotherapy, hypothyroidism occurred in 7.6% of patients, including grade 1 (1.4%), grade 2 (6.1%) and grade 4 (0.1%) events.

The median time from first dose to onset of the event was 3.7 months (range: 0 days to 16.6 months). The median duration from onset to resolution was 15.2 months (range: 12.0 days to 28.6+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.4% of patients. Hypothyroidism resolved in 31.9% of patients.

Hyperthyroidism:
In patients treated with tislelizumab as monotherapy, hyperthyroidism occurred in 0.3% of patients, including grade 1 (0.1%) and grade 2 (0.3%) events.

The median time from first dose to onset of the event was 31.0 days (range: 19.0 days to 14.5 months). The median duration from onset to resolution was 1.4 months (range: 22.0 days to 4.0+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was not interrupted in any patient. Hyperthyroidism resolved in 80.0% of patients.

Thyroiditis:
In patients treated with tislelizumab as monotherapy, thyroiditis occurred in 0.8% of patients, including grade 1 (0.2%) and grade 2 (0.6%) events.

The median time from first dose to onset of the event was 2.0 months (range: 20.0 days to 20.6 months). The median duration from onset to resolution was not evaluable based on currently available data (range: 22.0 days to 23.1+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.1% of patients. Thyroiditis resolved in 16.7% of patients.

Adrenal insufficiency
In patients treated with tislelizumab as monotherapy, adrenal insufficiency occurred in 0.3% of patients, including grade 2 (0.1%), grade 3 (0.1%) and grade 4 (0.1%) events.

The median time from first dose to onset of the event was 3.1 months (range: 1.3 months to 11.6 months). The median duration from onset to resolution was not evaluable based on currently available data (range: 1.0 month to 6.5+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was not permanently discontinued in any patient and tislelizumab treatment was interrupted in 0.2% of patients. Adrenal insufficiency resolved in 25.0% of patients.

Hypophysitis
In patients treated with tislelizumab as monotherapy, hypopituitarism (grade 2) occurred in 0.1% of patients.

Type 1 diabetes mellitus
In patients treated with tislelizumab as monotherapy, type 1 diabetes mellitus occurred in 0.4% of patients, including grade 1 (0.1%) and grade 3 (0.3%) events.

The median time from first dose to onset of the event was 2.5 months (range: 33.0 days to 13.8 months). The median duration from onset to resolution was not evaluable based on currently available data (range: 4.0 days to 19.9+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.1% of patients. Type 1 diabetes mellitus resolved in 16.7% of patients.

Immune-related nephritis and renal dysfunction
In patients treated with tislelizumab as monotherapy, immune-related nephritis and renal dysfunction occurred in 0.7% of patients, including grade 2 (0.3%), grade 3 (0.2%), grade 4 (0.1%) and grade 5 (0.1%) events.

The median time from first dose to onset of the event was 1.2 months (range: 3.0 days to 5.7 months). The median duration from onset to resolution was 1.9 months (range: 3.0+ days to 16.2+ months). + denotes a censored observation, with ongoing events at the time of the analysis. Tislelizumab was permanently discontinued in 0.3% of patients and tislelizumab treatment was interrupted in 0.3% of patients. Immune-related nephritis and renal dysfunction resolved in 50.0% of patients.

Immune-related myocarditis
In patients treated with tislelizumab as monotherapy, immune-related myocarditis occurred in 0.5% of patients, including grade 1 (0.1%), grade 2 (0.1%), grade 3 (0.2%) and grade 4 (0.1%) events.

The median time from first dose to onset of the event was 1.6 months (range: 14.0 days to 6.1 months), and the median duration from onset to resolution was 5.1 months (range: 4.0 days to 7.6 months). Tislelizumab was permanently discontinued in 0.3% of patients and tislelizumab treatment was interrupted in 0.2% of patients. Myocarditis resolved in 57.1% of patients.

Myocarditis occurred in 1.4% of patients treated with tislelizumab in combination with chemotherapy, including grade 5 (0.4%).

Immune checkpoint inhibitor class effects
There have been cases of the following adverse reactions reported during treatment with other immune checkpoint inhibitors which might also occur during treatment with tislelizumab: pancreatic exocrine insufficiency.

Infusion-related reactions
In patients treated with tislelizumab as monotherapy, infusion-related reactions occurred in 3.5% of patients, including grade 3 (0.3%) events. Tislelizumab was permanently discontinued in 0.1% of patients and tislelizumab treatment was interrupted in 0.5% of patients.

Laboratory abnormalities
In patients treated with tislelizumab monotherapy, the proportion of patients who experienced a shift from baseline to a grade 3 or 4 laboratory abnormality was as follows: 0.1% for increased haemoglobin, 4.4% for decreased haemoglobin, 0.9% for decreased leukocytes, 8.5% for decreased lymphocytes, 0.07% for increased lymphocytes, 1.7% for decreased neutrophils, 1.1% for decreased platelets, 2.0% for increased alanine aminotransferase, 0.4% for decreased albumin, 2.3% for increased alkaline phosphatase, 3.2% for increased aspartate aminotransferase, 2.2% for increased bilirubin, 2.0% for increased creatine kinase, 0.9% for increased creatinine, 0.9% for increased potassium, 2.2% for decreased potassium, 0.1% for increased sodium, 5.7% for decreased sodium.

In patients treated with tislelizumab in combination with chemotherapy, the proportion of patients who experienced a shift from baseline to a grade 3 or 4 laboratory abnormality was as follows: 14.2% for

decreased haemoglobin, 17.3% for decreased leukocytes, 41.2% for decreased neutrophils, 4.6% for decreased platelets, 3.1% for increased alanine aminotransferase, 0.9% for increased alkaline phosphatase, 3.4% for increased aspartate aminotransferase, 0.6% for increased bilirubin, 1.6% for increased creatine kinase, 2.5% for increased creatinine, 2.8% for increased potassium, 10.2% for decreased potassium, 0.6% for increased sodium, 18.9% for decreased sodium.

Immunogenicity
Of 1 916 antidrug antibodies (ADA)-evaluable patients treated at the recommended dose of 200 mg once every 3 weeks, 18.3% of patients tested positive for treatment-emergent ADA, and neutralising antibodies (NAbs) were detected in 0.9% of patients. Population pharmacokinetic analysis showed that ADA status was a statistically significant covariate on clearance; however, the presence of treatment-emergent ADA against tislelizumab appears to have no clinically relevant impact on pharmacokinetics or efficacy.

Among ADA-evaluable patients, the following rates of adverse events (AEs) have been observed for the ADA-positive population compared to the ADA-negative population, respectively: grade ≥3 AEs 50.9% vs. 39.3%, serious adverse events (SAEs) 37.1% vs. 29.7%, AEs leading to treatment discontinuation 10.8% vs 10.2% (for monotherapy); grade ≥ 3 AEs 85.6% vs. 78.2%, SAEs 45.9% vs. 38.2%, AEs leading to treatment withdrawal 13.5% vs. 13.3% (for combination therapy). Patients who developed treatment-emergent ADAs tended to have overall poorer health and disease characteristics at baseline which can confound the interpretation of the safety analysis. Available data do not allow firm conclusions to be drawn on possible patterns of adverse drug reactions.

Elderly
No overall differences in safety were observed with tislelizumab monotherapy between patients aged <65 years and patients aged between 65 and 74 years. Data for patients aged 75 years and above are too limited to draw conclusions on this population.

4.9 Overdose

There is no information on overdose with tislelizumab. In case of overdose, patients should be closely monitored for signs or symptoms of adverse drug reactions, and appropriate symptomatic treatment instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Monoclonal antibodies and antibody drug conjugates, ATC code: L01FF09

Mechanism of action

Tislelizumab is a humanised immunoglobulin G4 (IgG4) variant monoclonal antibody against PD-1, binding to the extracellular domain of human PD-1. It competitively blocks the binding of both PD-L1 and PD-L2, inhibiting PD-1-mediated negative signalling and enhancing the functional activity in T cells in *in vitro* cell-based assays.

Clinical efficacy and safety

Non-small cell lung cancer
First-line treatment of non-squamous NSCLC: BGB-A317-304
BGB-A317-304 was a randomised, open-label, multicentre phase III study to investigate the efficacy and safety of tislelizumab in combination with platinum-pemetrexed versus platinum-pemetrexed alone as first-line treatment for chemotherapy-naïve patients with locally advanced non-squamous

NSCLC who were not candidates for surgical resection or platinum-based chemoradiation, or metastatic non-squamous NSCLC.

The study excluded patients with active brain or leptomeningeal metastases, known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, active autoimmune disease, or any condition requiring systemic treatment with either corticosteroids (>10 mg daily of prednisone or equivalent) or other immunosuppressants.

A total of 334 patients were randomised (2:1) to receive tislelizumab 200 mg combined with pemetrexed 500 mg/m^2 and carboplatin AUC 5 mg/ml/min or cisplatin 75 mg/m^2 (T+PP arm, N = 223) or pemetrexed 500 mg/m^2 and carboplatin AUC 5 mg/ml/min or cisplatin 75 mg/m^2 (PP arm, N = 111). The choice of platinum (cisplatin or carboplatin) was at the investigator's discretion.

The treatment was administered on a 3-week cycle. After the administration of 4, 5 or 6 cycles of chemotherapy or tislelizumab combined with chemotherapy at the investigator's discretion, patients in the T+PP arm received tislelizumab 200 mg combined with pemetrexed 500 mg/m^2 on a 3-week cycle until disease progression or unacceptable toxicity; patients in the PP arm received pemetrexed 500 mg/m^2 alone until disease progression or unacceptable toxicity, and those with disease progression confirmed by Independent Review Committee (IRC) were given the option to cross over to receive tislelizumab monotherapy on a 3-week cycle.

Randomisation was stratified by PD-L1 expression in tumour cells (TC) (<1% versus 1% to 49% versus ≥50%) and disease stage (IIIB versus IV), as classified according to American Joint Committee on Cancer (AJCC), 7th edition of Cancer Staging Manual. PD-L1 expression was evaluated at a central laboratory using the Ventana PD-L1 (SP263) assay that identified PD-L1 staining on tumour cells. Tumour assessments were conducted every 6 weeks for the first 6 months, then every 9 weeks for the second 6 months, then every 12 weeks.

The baseline characteristics for patients in study BGB-A317-304 were: median age 61 years (range: 25 to 75), 29% age 65 years or older; 74% male; 100% Asian (all enrolled in China); 23.4% with ECOG PS of 0 and 76.6% with ECOG PS of 1; 18.3% with disease stage IIIB; 26.6% with unknown status for ALK rearrangement and 73.4% with negative ALK rearrangement; 36.2% never-smokers; 5.4% with brain metastases. The characteristics of age, sex, ECOG PS, stage, smoking status, PD-L1 TC score and prior anticancer treatments were balanced between the treatment arms.

The primary efficacy endpoint was progression-free survival (PFS) per RECIST v1.1 by IRC in the intent-to-treat (ITT) analysis. The secondary efficacy endpoints included overall survival (OS), objective response rate (ORR) and duration of response (DoR) per IRC and per investigator.

The study met its primary endpoint at the interim analysis (data cut-off date of 23-Jan-2020 and a median duration of study follow-up of 9.0 months), showing a statistically significant improvement in PFS with T+PP compared with PP. The stratified hazard ratio was 0.65 (95% CI: 0.47, 0.91; p = 0.0054) with a median PFS of 9.7 months with T+PP and 7.6 months with PP.

The efficacy results of the final analysis (data cut-off date of 26-Oct-2020 and a median duration of study follow-up of 16.1 months) were consistent with those of the interim analysis.

Amongst the 334 patients in study BGB-A317-304, 110 (33%) patients had tumour cell PD-L1 expression ≥50%. Of these, 74 patients were in the tislelizumab plus chemotherapy group and 36 patients were in the placebo plus chemotherapy group. Efficacy results of the patients with tumour cell PD-L1 expression ≥50% from the final analysis are shown in Table 3 and the Kaplan-Meier curve for PFS and OS is presented in Figures 1 and 2, respectively.

Table 3 Efficacy results in BGB-A317-304 in patients with PD-L1 expression ≥50%

Endpoint	Tislelizumab + Pemetrexed + Platinum (N = 74)	Pemetrexed + Platinum (N = 36)
PFS		
Events, n (%)	33 (44.6)	22 (61.1)
Median PFS (months) (95% CI)	14.6 (11.5, NE)	4.6 (3.5, 9.7)
Stratified hazard ratio[a] (95% CI)	0.31 (0.18, 0.55)	
OS		
Deaths, n (%)	24 (32.4)	20 (55.6)
Median OS (months) (95% CI)	NE (NE, NE)	13.1 (5.6, NE)
Stratified hazard ratio[a] (95% CI)	0.39 (0.22, 0.71)	
Best overall response, n (%)[b]		
ORR[b], n (%)	52 (70.3)	11 (30.6)
95% CI[c]	(58.5, 80.3)	(16.3, 48.1)
CR, n (%)	7 (9.5)	0 (0.0)
PR, n (%)	45 (60.8)	11 (30.6)
DoR[b]		
Median DoR (months) (95% CI)	NE (13.2, NE)	8.5 (3.3 NE)

PFS = progression-free survival; CI = confidence interval; OS = overall survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; NE = not estimable. Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

[a] Hazard ratio was estimated from stratified Cox model with pemetrexed+platinum group as reference group and stratified by disease stage (IIIB versus IV).

[b] PFS was based on IRC assessment, and ORR/DoR was based on the confirmed response by IRC.

[c] 95% CI was calculated using Clopper-Pearson method.

Figure 1 Kaplan-Meier plot of PFS in BGB-A317-304 in patients with PD-L1 ≥50%

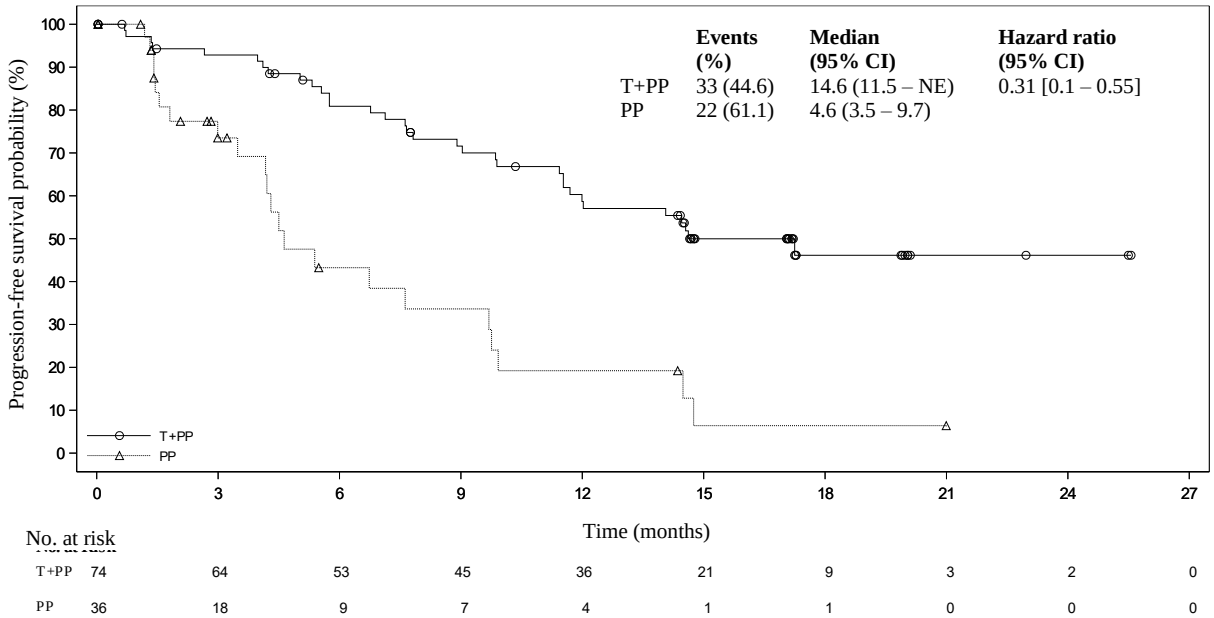
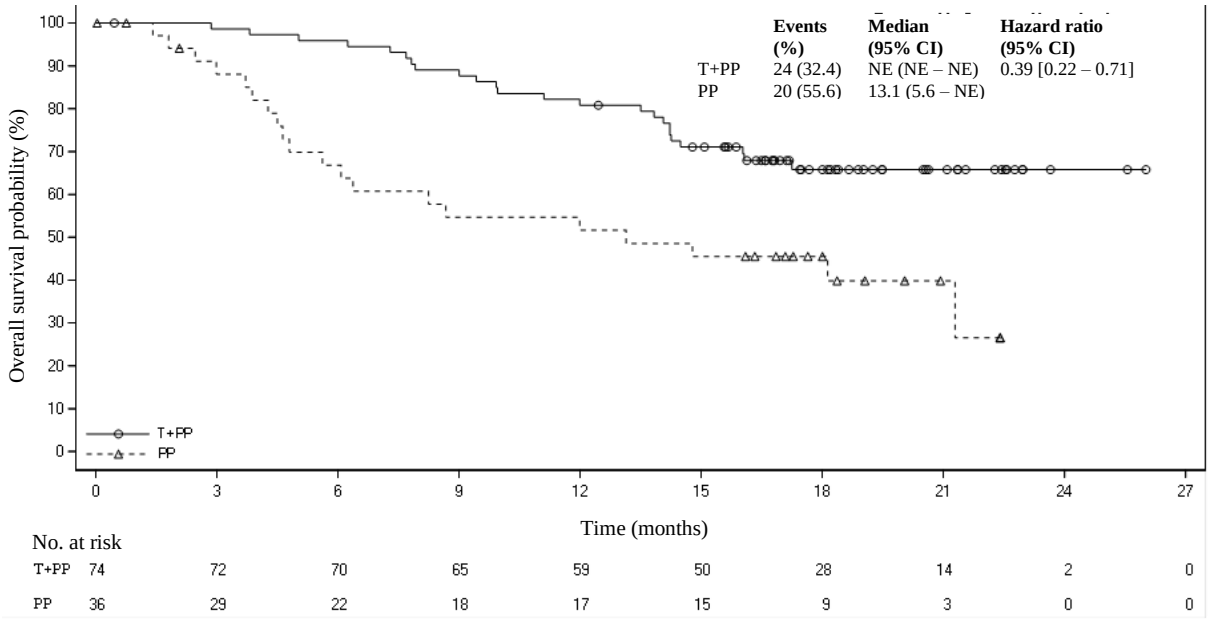


Figure 2 Kaplan-Meier plot of OS in BGB-A317-304 in patients with PD-L1 ≥50%



First-line treatment of squamous NSCLC: BGB-A317-307
BGB-A317-307 was a randomised, open-label, multicentre phase III study to compare the efficacy and safety of tislelizumab in combination with paclitaxel plus carboplatin or nab-paclitaxel plus carboplatin with that of paclitaxel plus carboplatin alone as first-line treatment for chemotherapy-naïve patients with locally advanced squamous NSCLC who were not candidates for surgical resection or platinum-based chemoradiation or metastatic squamous NSCLC.

The study excluded patients with active brain or leptomeningeal metastases, known EGFR mutations or ALK translocations sensitive to available targeted inhibitor therapy, active autoimmune disease, or any condition requiring systemic treatment with either corticosteroids (>10 mg daily of prednisone or equivalent) or other immunosuppressive treatments.

A total of 360 patients were randomised (1:1:1) to receive tislelizumab 200 mg combined with paclitaxel 175 mg/m^2 and carboplatin AUC 5 mg/ml/min (T+PC arm, N= 120), or tislelizumab 200 mg combined with nab-paclitaxel 100 mg/m^2 and carboplatin AUC 5 mg/ml/min (T+nPC arm, N = 119), or paclitaxel 175 mg/m^2 and carboplatin AUC 5 mg/ml/min (PC arm, N = 121).

The treatment was administered on a 3-week cycle, until the patient completed administration of 4 to 6 cycles of chemotherapy or tislelizumab combined with chemotherapy at the investigator's discretion. Patients in the T+nPC and T+PC arms received tislelizumab until disease progression or unacceptable toxicity. Patients in the PC arm with disease progression were given the option to cross over to receive tislelizumab monotherapy on a 3-week cycle.

Randomisation was stratified by PD-L1 expression in tumour cells (TC) (<1% versus 1% to 49% versus ≥50%) and tumour staging (IIIB versus IV), as classified according to American Joint Committee on Cancer (AJCC), 7th edition of Cancer Staging Manual. PD-L1 expression was evaluated at a central laboratory using the Ventana PD-L1(SP263) assay that identified PD-L1 staining on tumour cells. Tumour assessments were conducted every 6 weeks for the first 6 months, then every 9 weeks for the remainder of the first year, then every 12 weeks until disease progression.

The baseline characteristics for the study population were: median age 62.0 years (range: 34 to 74), 35.3% age 65 years or older; 91.7% male; 100% Asian (all enrolled in China), 23.6% with ECOG PS of 0 and 76.4% with ECOG PS of 1; 33.9% diagnosed with stage IIIB and 66.1% with stage IV at baseline; 16.4% never-smokers; 38.3% with PD-L1 TC score <1%, 25.3% with PD-L1 TC score ≥1% and ≤49%, 34.7% with PD-L1 TC score ≥50%. The characteristics of age, sex, ECOG PS, stage,

smoking status, PD-L1 TC score and prior anticancer treatments were balanced between the treatment arms.

The primary efficacy endpoint was progression-free survival (PFS) as assessed by IRC per RECIST v1.1 in the ITT analysis which was to be tested sequentially in arms T+PC versus PC and arms T+nPC versus PC. The secondary efficacy endpoints included overall survival (OS), objective response rate (ORR) and duration of response (DoR) per IRC and per investigator.

The study met its primary endpoint at the interim analysis (data cut-off date of 06-Dec-2019 and a median duration of study follow-up of 8.4 months), showing statistically significant improvements in PFS with tislelizumab in combination with paclitaxel and carboplatin (T+PC arm) and tislelizumab in combination with nab-paclitaxel and carboplatin (T+nPC arm) compared with paclitaxel and carboplatin alone (PC arm). The stratified HR (T+PC arm versus PC arm) was 0.48 (95% CI: 0.34, 0.69; p <0.0001). The stratified HR (T+nPC arm versus PC arm) was 0.45 (95% CI: 0.32, 0.64; p <0.0001). Median PFS was 7.6 months in the T+PC arm, 7.6 months in the T+nPC arm and 5.4 months in the PC arm.

The final analysis (data cut-off date of 30-Sep-2020 and a median duration of study follow-up of 16.7 months) showed the consistent results from the interim analysis.

Efficacy results for the final analysis are shown in Table 4, Figure 3 and Figure 4.

Table 4 Efficacy results in BGB-A317-307

Endpoint	Tislelizumab + Paclitaxel + Carboplatin (N = 120)	Tislelizumab + nab-Paclitaxel + Carboplatin (N = 119)	Paclitaxel + Carboplatin (N = 121)
PFS			
Events, n (%)	80 (66.7)	79 (66.4)	86 (71.1)
Median PFS (months) (95% CI)	7.7 (6.7, 10.4)	9.6 (7.4, 10.8)	5.5 (4.2, 5.6)
Stratified hazard ratio[a] (95% CI)	0.45 (0.33, 0.62)	0.43 (0.31, 0.60)	-
OS			
Deaths, n (%)	48 (40.0)	47 (39.5)	52 (43.0)
Median OS (months) (95% CI)	22.8 (19.1, NE)	NE (18.6, NE)	20.2 (16.0, NE)
Stratified hazard ratio (95% CI)	0.68 (0.45, 1.01)	0.752 (0.50, 1.12)	-
ORR[b]			
ORR, n (%)	74 (61.7)	74 (62.2)	45 (37.2)
95% CI	(52.4, 70.4)	(52.8, 70.9)	(28.6, 46.4)
CR, n (%)	7 (5.8)	6 (5.0)	1 (0.8)
PR, n (%)	67 (55.8)	68 (57.1)	44 (36.4)
DoR[b]			
Median DoR (months) (95% CI)	13.2 (7.85, 18.79)	10.4 (8.34, 17.15)	4.8 (4.04, 5.72)

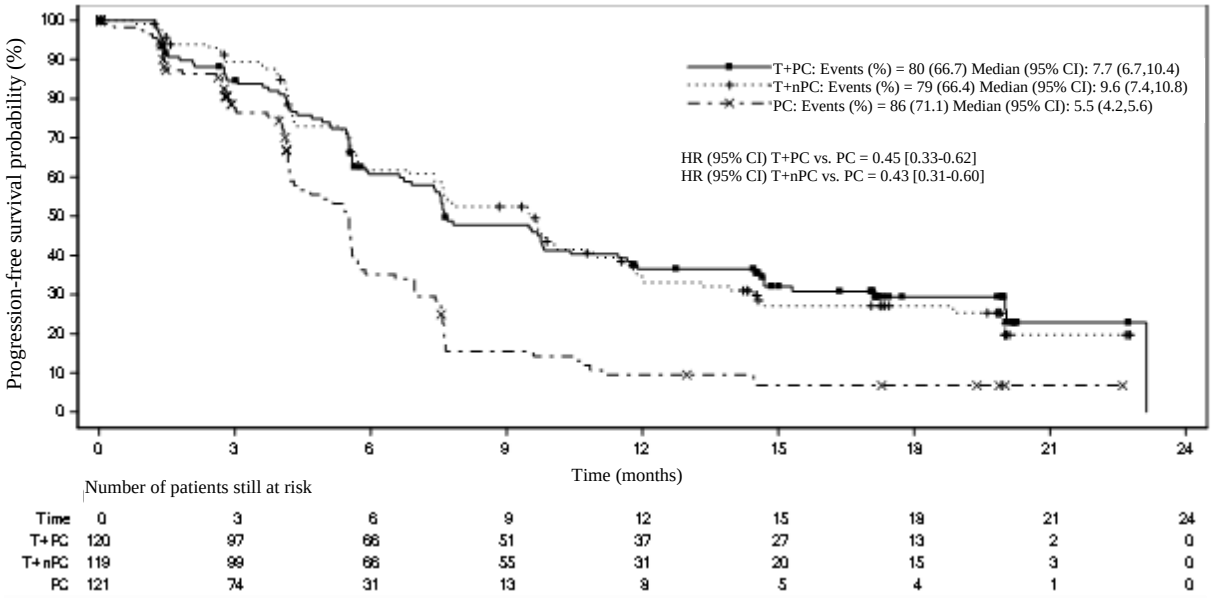
PFS = progression-free survival; CI = confidence interval; OS = overall survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response; NE = not estimable.

[a] Stratified by stratification factors: disease stage (IIIB versus IV) and PD-L1 expression in tumour cell (≥50% TC versus 1% to 49% TC versus <1% TC).

[b] PFS was based on IRC assessment, and ORR/DoR was based on the confirmed response by IRC.

Figure 3 Kaplan-Meier plot of PFS in BGB-A317-307 by IRC

T+PC arm versus T+nPC arm versus PC arm



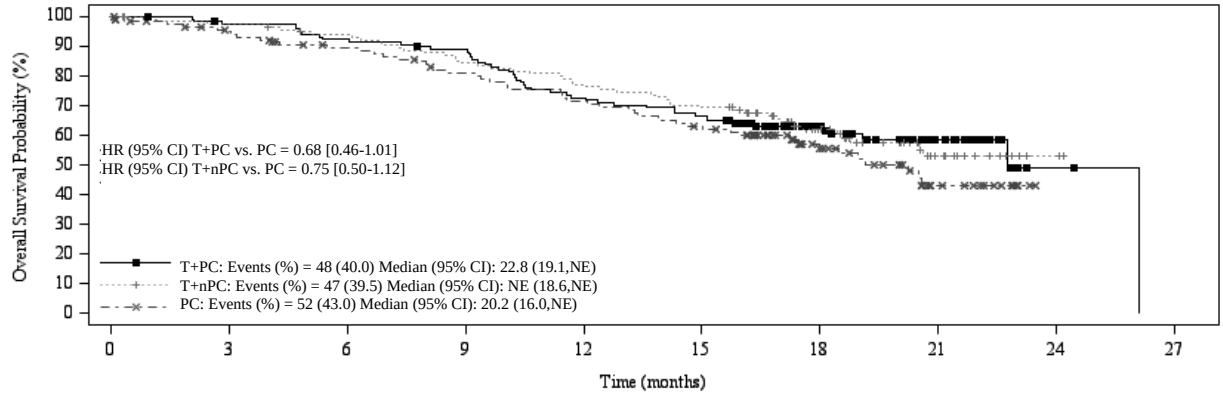
Number of patients still at risk

Time	0	3	6	9	12	15	18	21	24
T+PC	120	97	68	51	37	27	13	2	0
T+nPC	119	99	68	55	31	20	15	3	0
PC	121	74	31	13	9	5	4	1	0

CI = Confidence interval; T+PC = tislelizumab+paclitaxel+carboplatin; T+nPC = tislelizumab+nab-paclitaxel+carboplatin; PC = paclitaxel+carboplatin.

Figure 4 Kaplan-Meier plot of OS in BGB-A317-307

T+PC arm versus T+nPC arm versus PC arm



Number of patients still at risk

Time	0	3	6	9	12	15	18	21	24	27
T+PC	120	115	109	104	85	78	46	17	2	0
T+nPC	119	113	107	96	88	79	46	20	2	0
PC	121	108	96	85	75	65	35	13	0	0

CI = Confidence interval; T+PC = tislelizumab+paclitaxel+carboplatin; T+nPC = tislelizumab+nab-paclitaxel+carboplatin; PC = paclitaxel+carboplatin; NE = not estimable.

Subgroup analyses demonstrated consistent PFS treatment effect across major demographic and prognostic subgroups, including PD-L1 expression <1%, 1 to 49% and ≥50% and disease stages IIIB and IV:

- for T+PC, with PFS HR of 0.57 (95% CI, HR = 0.34, 0.94) for PD-L1 <1%, 0.40 (95% CI, HR = 0.21, 0.76) for 1 to 49% and 0.44 (95% CI, HR = 0.26, 0.75)) for ≥50%
- for T+nPC, with PFS HR of 0.65 (95% CI, HR = 0.40, 1.06) for PD-L1 <1%, 0.40 (95% CI, HR = 0.22, 0.74) for 1 to 49% and 0.33 (95% CI, HR = 0.18, 0.59)) for ≥50%

Second-line treatment of NSCLC: BGB-A317-303
BGB-A317-303 was a randomised, open-label, multicentre phase III study to investigate the efficacy and safety of tislelizumab compared with docetaxel in patients with locally advanced or metastatic NSCLC (squamous or non-squamous), who had experienced disease progression on or after a prior platinum-based regimen.

The study excluded patients with known EGFR mutation or ALK rearrangement, prior PD-(L)1 inhibitor or CTLA-4 inhibitor treatment, active autoimmune disease, or any condition requiring systemic treatment with either corticosteroids (>10 mg daily of prednisone or equivalent) or other immunosuppressive treatments.

A total of 805 patients were randomised (2:1) ratio to receive tislelizumab 200 mg intravenously every 3 weeks (N = 535) or docetaxel 75 mg/m^2 intravenously every 3 weeks (N = 270). Randomisation was stratified by histology (squamous versus non-squamous), lines of therapy (second- versus third-line), and PD-L1 expression in tumour cells (TC) (≥25% versus <25%). Administration of docetaxel and tislelizumab continued until disease progression, as assessed by investigator per RECIST v1.1, or unacceptable toxicity. PD-L1 expression was evaluated at a central laboratory using the Ventana PD-L1 (SP263) assay that identified PD-L1 staining on tumour cells. Tumour assessments were conducted every 9 weeks for 52 weeks after randomisation and continued every 12 weeks thereafter. Survival status was followed every 3 months after discontinuation of the study treatment.

The baseline characteristics for the study population were: median age 61 years (range: 28 to 88), 32.4% age 65 years or older, 3.2% age 75 years or older; 77.3% male; 17.0% White and 79.9% Asian; 20.6% with ECOG PS of 0 and 79.4% with ECOG PS of 1; 85.5% with metastatic disease; 30.3% never-smokers; 46.0% with squamous and 54.0% non-squamous histology; 65.8% with wild-type and 34% with unknown EGFR status; 46.1% with wild-type and 53.9% with unknown ALK status; 7.1% with previously treated brain metastases.

57.0% of the patients had a PD-L1 TC score <25% and 42.5% had a PD-L1 TC score ≥25%. All patients had received prior therapy with a platinum-doublet regimen: 84.7% patients received one prior therapy, 15.3% had received two prior therapies.

The dual-primary efficacy endpoints were OS in the ITT and PD-L1 TC score ≥25% analysis sets. Additional efficacy endpoints included investigator-assessed PFS, ORR and DoR.

BGB-A317-303 met both dual-primary endpoints of OS in the ITT analysis and PD-L1 ≥25% analysis sets. At the prespecified interim analysis (data cut-off date 10-Aug-2020 with a median duration of follow-up time of 11.7 months), a statistically significant improvement in OS was observed in the ITT population. Results favoured the tislelizumab arm (HR = 0.64; 95% CI: 0.53, 0.78; p < 0.0001). Median OS was 17.2 months for the tislelizumab arm and 11.9 months for the docetaxel arm. At the final analysis (data cutoff date 15-Jul-2021 with a median duration of follow-up of 14.2 months), a statistically significant improvement in OS was observed in the PD-L1 ≥25% analysis set favouring the tislelizumab arm (startified HR = 0.53; 95% CI: 0.41, 0.70; p < 0.0001) with median OS being 19.3 months for the tislelizumab arm and 11.5 months for the docetaxel arm.

The final analysis (data cut-off date 15-Jul-2021 and a median duration of follow-up of 14.2 months) showed consistent efficacy results in the ITT population compared to the interim analysis.

Table 5 and Figure 5 summarise the efficacy results for BGB-A317-303 (ITT analysis set) at the final analysis.

Table 5 Efficacy results in BGB-A317-303

Endpoint	Tislelizumab (N = 535)	Docetaxel (N = 270)
OS		
Deaths, n (%)	365 (68.2)	206 (76.3)
Median OS (months) (95% CI)	16.9 (15.24, 19.09)	11.9 (9.63, 13.54)
Hazard ratio (95% CI)[a, b]	0.66 (0.56, 0.79)	
PFS		
Events, n (%)	451 (84.3)	208 (77.0)
Median PFS (months) (95% CI)	4.2 (3.88, 5.52)	2.6 (2.17, 3.78)
Hazard ratio[a] (95% CI)	0.63 (0.53, 0.75)	
ORR (%) (95% CI)[c]	20.9 (17.56, 24.63)	3.7 (1.79, 6.71)
Best overall response[c]		
CR (%)	1.7	0.4
PR (%)	19.3	3.3
DoR[c]		
Median DoR (months) (95% CI)	14.7 (10.55, 21.78)	6.2 (4.11, 8.31)

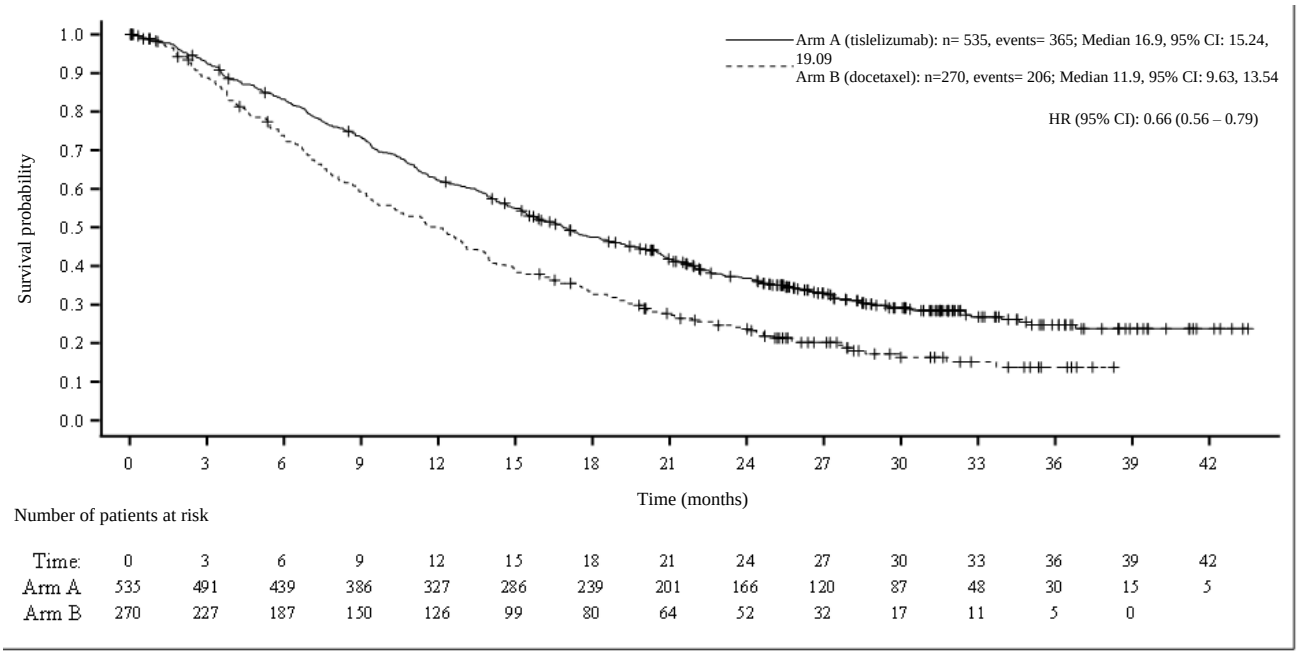
OS = overall survival; CI = confidence interval; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; DoR = duration of response.
Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley.

[a] Hazard ratio was estimated from stratified Cox model with docetaxel group as reference group.

[b] Stratified by stratification factors: histology (squamous versus non-squamous), lines of therapy (second versus third), and PD-L1 expression in tumour cells (≥25% PD-L1 score versus <25% PD-L1 score).

[c] Confirmed by investigator.

Figure 5 Kaplan-Meier plot of OS in BGB-A317-303 (ITT Analysis Set)



Prespecified subgroup analyses demonstrated a consistent OS treatment effect in favour of tislelizumab across major demographic and prognostic subgroups.

Table 6 summarises efficacy results of OS by tumour PD-L1 (<25% TC, ≥25% TC) expression in prespecified subgroup analyses.

Table 6 Efficacy results of OS by tumour PD-L1 expression (<25% TC, ≥25% TC) in BGB-A317-303

	Tislelizumab arm	Docetaxel arm
	N = 535	**N = 270**
PD-L1 expression in tumour cells <25%, n	307	152
Events, n (%)	223 (72.6)	117 (77.0)
Median OS (months) (95% CI)	15.2 (13.4, 17.6)	12.3 (9.3, 14.3)
Hazard ratio [a] (95% CI)	0.79 (0.64, 0.99)	
PD-L1 expression in tumour cells ≥25%, n	227	115
Events, n (%)	141 (62.1)	86 (74.8)
Median OS (months) (95% CI)	19.3 (16.5, 22.6)	11.5 (8.2, 13.5)
Hazard ratio [a] (95% CI)	0.54 (0.41, 0.71)	

[a] Hazard ratio and its 95% CI were estimated from unstratified Cox model.

Oesophageal squamous cell carcinoma (OSCC)

BGB-A317-302

BGB-A317-302 was a randomised, controlled, open-label, global phase III study to compare the efficacy of tislelizumab versus chemotherapy in patients with unresectable, recurrent, locally advanced or metastatic OSCC who progressed on or after prior systemic treatment. Patients were enrolled regardless of their tumour PD-L1 expression level. Where available, the archival/fresh tumour tissue specimens taken were retrospectively tested for PD-L1 expression status. PD-L1 expression was evaluated at a central laboratory using the Ventana PD-L1 (SP263) assay that identified PD-L1 staining on both tumour and tumour-associated immune cells.

The study excluded patients with prior anti-PD-1 inhibitor treatment and tumour invasion into organs located adjacent to the oesophageal disease site (e.g. aorta or respiratory tract).

Randomisation was stratified by geographic region (Asia [excluding Japan] versus Japan versus USA/EU), ECOG PS (0 versus 1) and investigator choice of chemotherapy (ICC) option (paclitaxel versus docetaxel versus irinotecan). The choice of ICC was determined by the investigator before randomisation.

Patients were randomised (1:1) to receive tislelizumab 200 mg every 3 weeks or investigator's choice of chemotherapy (ICC), selected from the following, all given intravenously:

- paclitaxel 135 to 175 mg/m² on day 1, given every 3 weeks (also at doses of 80 to 100 mg/m^2 on a weekly schedule according to local and/or country-specific guidelines for standard of care), or
- docetaxel 75 mg/m^2 on day 1, given every 3 weeks, or
- irinotecan 125 mg/m^2 on days 1 and 8, given every 3 weeks.

Patients were treated with Tevimbra or one of the ICC until disease progression as assessed by the investigator per RECIST version 1.1 or unacceptable toxicity.

The tumour assessments were conducted every 6 weeks for the first 6 months, and every 9 weeks thereafter.

The primary efficacy endpoint was overall survival (OS) in the intent-to-treat (ITT) population. Secondary efficacy endpoints were OS in PD-L1 Positive Analysis Set (PD-L1 score of visually-estimated Combined Positive Score, now known as Tumour Area Positivity score [TAP] [PD-L1 score] ≥10%), objective response rate (ORR), progression-free survival (PFS) and duration of response (DoR), as assessed by the investigator per RECIST v1.1.

A total of 512 patients were enrolled and randomised to tislelizumab (N = 256) or ICC (N = 256; paclitaxel [N = 85], docetaxel [N = 53] or irinotecan [N = 118]). Of the 512 patients, 142 (27.7%) had

PD-L1 score ≥10%, 222 (43.4%) had PD-L1 score <10%, and 148 (28.9%) had unknown baseline PD-L1 status.

The baseline characteristics for the study population were median age 62 years (range: 35 to 86), 37.9% age 65 years or older; 84% male; 19% White and 80% Asian; 25% with ECOG PS of 0 and 75% with ECOG PS of 1. Ninety-five percent of the study population had metastatic disease at study entry. All patients had received at least one prior anti-cancer chemotherapy, which was a platinum-based combination chemotherapy for 97% of patients.

BGB-A317-302 showed a statistically significant improvement in OS for patients randomised to the tislelizumab arm as compared to the ICC arm. The median follow-up times by reverse Kaplan-Meier methodology were 20.8 months in the tislelizumab arm and 21.1 months in the ICC arm.

Efficacy results are shown in Table 7 and Figure 6.

Table 7 Efficacy results in BGB-A317-302

Endpoint	**Tevimbra (N = 256)**	**Chemotherapy (N = 256)**
OS		
Deaths, n (%)	197 (77.0)	213 (83.2)
Median (months)[a] (95% CI)	8.6 (7.5, 10.4)	6.3 (5.3, 7.0)
Hazard ratio (95% CI)[b]	0.70 (0.57, 0.85)	
p-value[c]	p = 0.0001	
PFS assessed by investigator[d]		
Disease progression or death, n (%)	223 (87.1)	180 (70.3)
Median (months) (95% CI)	1.6 (1.4, 2.7)	2.1 (1.5, 2.7)
Hazard ratio (95% CI)	0.83 (0.67, 1.01)	
ORR with confirmation by investigator[d]		
ORR (%) (95% CI)	15.2 (11.1, 20.2)	6.6 (3.9, 10.4)
CR, n (%)	5 (2.0)	1 (0.4)
PR, n (%)	34 (13.3)	16 (6.3)
SD, n (%)	81 (31.6)	90 (35.2)
Median duration of response with confirmation by investigator (months) (95% CI)	10.3 (6.5, 13.2)	6.3 (2.8, 8.5)

OS = overall survival; CI = confidence interval; PFS = progression-free survival; ORR = objective response rate; CR = complete response; PR = partial response; SD = stable disease

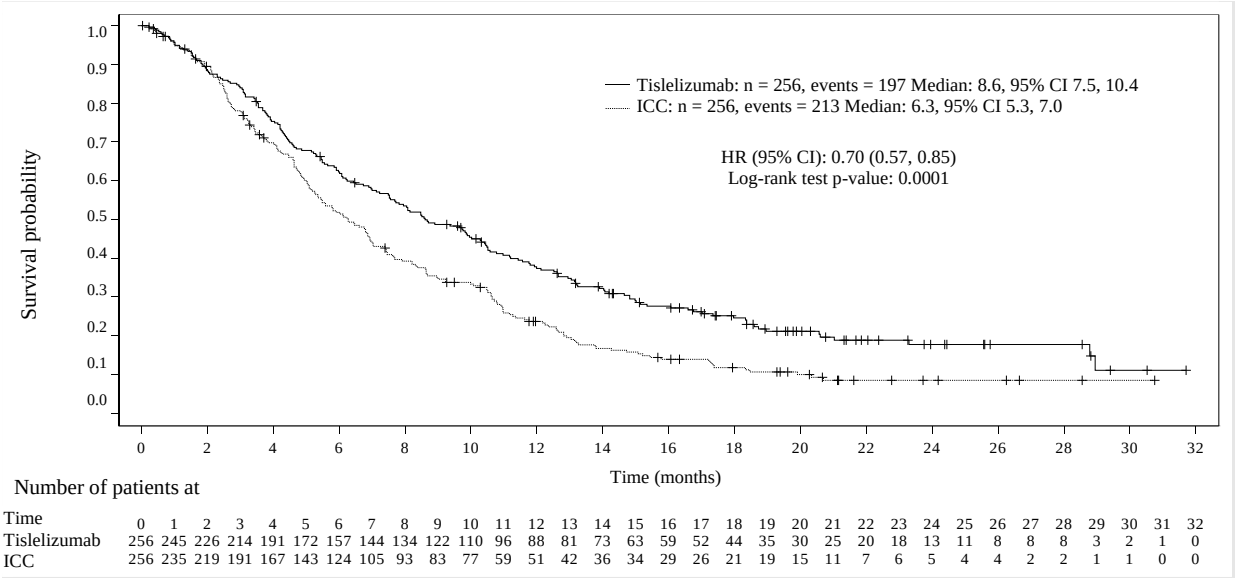
[a] Estimated using Kaplan-Meier method.

[b] Based on Cox regression model including treatment as covariate, and stratified by baseline ECOG status and investigator's choice of chemotherapy.

[c] Based on a one-sided log-rank test stratified by ECOG performance status and investigator's choice of chemotherapy.

[d] Based on ad hoc analysis.

Figure 6 Kaplan-Meier plot of OS in BGB-A317-302 (ITT analysis set)



Efficacy and PD-L1 subgroups:
In a pre-specified analysis of OS in the PD-L1 positive subgroup (PD-L1 score ≥10%), the stratified hazard ratio (HR) for OS was 0.49 (95% CI: 0.33 to 0.74), with a 1-sided stratified log-rank test p-value of 0.0003. The median survival was 10.0 months (95% CI: 8.5 to 15.1 months) and 5.1 months (95% CI: 3.8 to 8.2 months) for the tislelizumab and ICC arms, respectively.

In the PD-L1 negative subgroup (PD-L1 score <10%), the stratified HR for OS was 0.83 (95% CI: 0.62 to 1.12), with median overall survival of 7.5 months (95% CI: 5.5 to 8.9 months) and 5.8 months (95% CI: 4.8 to 6.9 months) for the tislelizumab and ICC arms, respectively.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of tislelizumab were assessed for Tevimbra both as monotherapy and in combination with chemotherapy.

The PK of tislelizumab were characterised using population PK analysis with concentration data from 2 596 patients with advanced malignancies who received tislelizumab doses of 0.5 to 10 mg/kg every 2 weeks, 2.0 and 5.0 mg/kg every 3 weeks, and 200 mg every 3 weeks.

The time to reach 90% steady-state level is approximately 84 days (12 weeks) after 200 mg doses once every 3 weeks, and the steady-state accumulation ratio of tislelizumab PK exposure is approximately 2-fold.

Absorption

Tislelizumab is administered intravenously and therefore is immediately and completely bioavailable.

Distribution

A population pharmacokinetic analysis indicates that the steady-state volume of distribution is 6.42 l, which is typical of monoclonal antibodies with limited distribution.

Biotransformation

Tislelizumab is expected to be degraded into small peptides and amino acids via catabolic pathways.

Elimination

Based on population PK analysis, the clearance of tislelizumab was 0.153 l/day with an inter-individual variability of 26.3% and the geometrical mean terminal half-life was approximately 23.8 days with a coefficient variation (CV) of 31%.

Linearity/non-linearity

At the dosing regimens of 0.5 mg/kg to 10 mg/kg once every 2 or 3 weeks (including 200 mg once every 3 weeks), the PK of tislelizumab were observed to be linear and the exposure was dose proportional.

Special populations

The effects of various covariates on tislelizumab PK were assessed in population PK analyses. The following factors had no clinically relevant effect on the exposure of tislelizumab: age (range 18 to 90 years), weight (range 32 to 130 kg), gender, race (White, Asian and other), mild to moderate renal impairment (creatinine clearance [CL_{Cr}] ≥30 ml/min), mild to moderate hepatic impairment (total bilirubin ≤3 times ULN and any AST), and tumour burden.

Renal impairment
No dedicated studies of tislelizumab have been conducted in patients with renal impairment. In the population PK analyses of tislelizumab, no clinically relevant differences in the clearance of tislelizumab were found between patients with mild renal impairment (CL_{Cr} 60 to 89 ml/min, N = 1 046) or moderate renal impairment (CL_{Cr} 30 to 59 ml/min, n = 320) and patients with normal renal function (CL_{Cr} ≥90 ml/min, n = 1 223). Mild and moderate renal impairment had no effect on the exposure of tislelizumab (see section 4.2). Based on the limited number of patients with severe renal impairment (n = 5), the effect of severe renal impairment on the pharmacokinetics of tislelizumab is not conclusive.

Hepatic impairment
No dedicated studies of tislelizumab have been conducted in patients with hepatic impairment. In the population PK analyses of tislelizumab, no clinically relevant differences in the clearance of tislelizumab were found between patients with mild hepatic impairment (bilirubin ≤ ULN and AST >ULN or bilirubin >1.0 to 1.5 x ULN and any AST, n = 396) or moderate hepatic impairment (bilirubin >1.5 to 3 x ULN and any AST; n = 12), compared to patients with normal hepatic function (bilirubin ≤ ULN and AST = ULN, n = 2 182) (see section 4.2). Based on the limited number of patients with severe hepatic impairment (bilirubin >3 x ULN and any AST, n = 2), the effect of severe hepatic impairment on the pharmacokinetics of tislelizumab is unknown.

5.3 Preclinical safety data

In repeat-dose toxicology studies in cynomolgus monkeys with intravenous dose administration at doses of 3, 10, 30 or 60 mg/kg every 2 weeks for 13 weeks (7 dose administrations), no apparent treatment-related toxicity or histopathological changes were observed at doses up to 30 mg/kg every 2 weeks, corresponding to 4.3 to 6.6 times the exposure in humans with the clinical dose of 200 mg.

No developmental and reproductive toxicity studies or animal fertility studies have been conducted with tislelizumab.

No studies have been performed to assess the potential of tislelizumab for carcinogenicity or genotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium citrate dihydrate
Citric acid monohydrate
L-histidine hydrochloride monohydrate
L-histidine
Trehalose dihydrate
Polysorbate 20
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

3 years.

After opening

Once opened, the medicinal product should be diluted and infused immediately (see section 6.6 for instructions on dilution of the medicinal product before administration).

After preparation of solution for infusion

Tevimbra does not contain a preservative. Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C. The 24 hours include storage of the diluted solution under refrigeration (2°C to 8°C) for no more than 20 hours, time required for returning to room temperature (25°C or below) and time to complete the infusion within 4 hours.

From a microbiological point of view, unless the method of dilution precludes the risk of microbial contamination, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user. The diluted solution must not be frozen.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Store in the original carton in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 ml of Tevimbra concentrate is provided in a clear Type 1 glass vial, with a grey chlorobutyl stopper with FluroTec coating and seal cap with a flip-off button.

Tevimbra is available in unit packs containing 1 vial.

6.6 Special precautions for disposal and other handling

The diluted solution for infusion should be prepared by a healthcare professional using aseptic technique.

Preparation of solution for infusion

- Two Tevimbra vials are required for each dose.
- Remove the vials from the refrigerator, taking care not to shake them.
- Inspect each vial visually for particulate matter and discolouration prior to administration. The concentrate is a clear to slightly opalescent, colourless to slightly yellowish solution. Do not use a vial if the solution is cloudy, or if visible particles or discolouration are observed.
- Invert the vials gently without shaking. Withdraw the solution from the two vials (a total of 200 mg in 20 ml) into a syringe and transfer into an intravenous infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for injection, to prepare a diluted solution with a final concentration ranging from 2 to 5 mg/ml. Mix diluted solution by gentle inversion to avoid foaming or excessive shearing of the solution.

Administration

- Administer the diluted Tevimbra solution by infusion through an intravenous administration line with a sterile, non-pyrogenic, low-protein-binding 0.2 micron or 0.22 micron in-line or add-on filter with a surface area of approximately 10 cm^2.
- The first infusion should be delivered over 60 minutes. If well tolerated, subsequent infusions may be administered over 30 minutes.
- Other medicinal products should not be co-administered through the same infusion line.
- Tevimbra must not be administered as an intravenous push or single bolus injection.
- The intravenous line must be flushed at the end of the infusion.
- Discard any unused portion left in the vial.
- Tevimbra vials are for single use only.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

BeiGene Switzerland GmbH
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8. DATE OF REVISION OF THE TEXT

8 August 2024