UNIVERSITY OF COLOGNE

Immune Checkpoint Inhibitors for the Treatment of Adult Solid Cancer Patients in the Palliative 1st Line Setting

Proposal for Additions and Expansion of Indications
Application to the 2025 update of the WHO Model Lists of Essential Medicines

Julia Schroer, Marius Goldkuhle, Andreas Wender, Ina Monsef, Paul Bröckelmann, Nicole Skoetz and Mario Csenar

Addendum

Applicant
WHO Collaborating Center on Evidence Synthesis and Evaluation of Novel Cancer Therapies

Institute of Public Health, Medical Faculty and University Hospital Cologne
University of Cologne, Germany

Persons to contact
Mario Csenar, dr. med. M.Sc.
Email: mario.csenar@uk-koeln.de
Phone: +49 221 478 96650

Prof. Dr. Nicole Skoetz
Email: nicole.skoetz1@uk-koeln.de
Phone: +49 221 478 96651

WHO Collaborating Centre on Evidence Synthesis and Evaluation of Novel Cancer Therapies

Summary of findings

Tislelizumab-containing treatment regimens compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression

Patient or population: Oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression
Intervention: Tislelizumab-containing treatment regimens
Comparison: SoC (platinum-based doublet chemotherapy)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with SoC	**Risk with tislelizumab-containing treatment regimens**				
Overall survival (OS) follow-up: median 16.4 months[a]	**At 1 year**		**HR 0.80** (0.62 to 1.02) [death]	694 (2 RCTs)[c]	⊕⊕◯◯ Low[d,e]	Tislelizumab-containing treatment regimens may increase overall survival slightly. Considering the high crossover of participants in the control arms to subsequently receive immunotherapy upon progression, the effect might be underestimated.
	69 per 100[b]	**75 per 100** (69 to 80)				
	The median OS was **18.17** months	The median OS was **4.5 months more** (0.4 fewer to 11.1 more)[f,g]				
Progression-free survival (PFS) follow-up: median 16.4 months[a]	**At 1 year**		**HR 0.51** (0.40 to 0.66) [disease progression or death]	694 (2 RCTs)	⊕⊕⊕⊕ High	Tislelizumab-containing treatment regimens results in a large increase in progression-free survival.
	15 per 100[b]	**37 per 100** (28 to 46)				
Global Health Score/Quality of Life (GHS/QoL) assessed with: EORTC QLQ-C30 change score follow-up: 12 weeks from baseline		The mean difference was **3.7 higher** (0.06 lower to 7.46 higher)[h]	-	687 (2 RCTs)	⊕⊕⊕◯ Moderate[i]	Tislelizumab-containing treatment regimens likely results in little to no difference in global Health Score/Quality of Life (GHS/QoL).
Adverse events (CTCAE ≥ 3) irrespective of treatment attribution	71 per 100	**79 per 100** (66 to 95)	**RR 1.11** (0.93 to 1.34)	687 (2 RCTs)	⊕◯◯◯ Very low[i,j,k]	The addition of tislelizumab to a chemotherapeutic backbone in the first-line treatment of advanced or metastatic NSCLC may increase the number of people experiencing adverse events (CTCAE ≥ 3) irrespective of treatment attribution. However, the evidence is very uncertain.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HR:** hazard ratio; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Weight-adjusted median length of follow-up across studies
b. Weight-adjusted OS and PFS rates at 1 year across control arms of studies
c. RATIONALE-307 (NCT03594747) [1-3]; RATIONALE-304 (NCT03663205)[4-7]
d. Downgraded for indirectness due to subsequently received ICIs in control arms of included trials (56.2% in RATIONALE-307 and 36.0% in RATIONALE-304)

e. Downgraded for imprecision; the CI crosses both the lines of no effect and appreciable benefit (0.75)
f. The difference in median survival time was calculated using the directly reported median survival estimate from the trial's control arms and pooled HR and CIs, assuming proportional hazards throughout the trial's follow-up
g. The median survival and upper CI's in intervention arms were in part reported as not estimable
h. The mean difference between change scores from baseline did not cross the MID line at 10; therefore, we did not downgrade for imprecision
i. Downgraded for risk of detection and performance bias due to the open-label trial design and subjective nature of the outcome, at least in part
j. Downgraded for imprecision, with the CI crossing both the lines of no effect and appreciable harm (1.25)
k. Publication bias not applicable due to prespecified selection process

Non-small cell lung cancer

Immunochemotherapy

This addendum pertains to the use of tislelizumab-based chemotherapy combinations in the palliative first-line setting for oncogenic-driver wild-type non-small cell lung carcinoma, following a request from the WHO EML secretariat in light of recent changes regarding the approval status of immune-checkpoint inhibitors, as outlined in the appendix of our initial application.

Search results

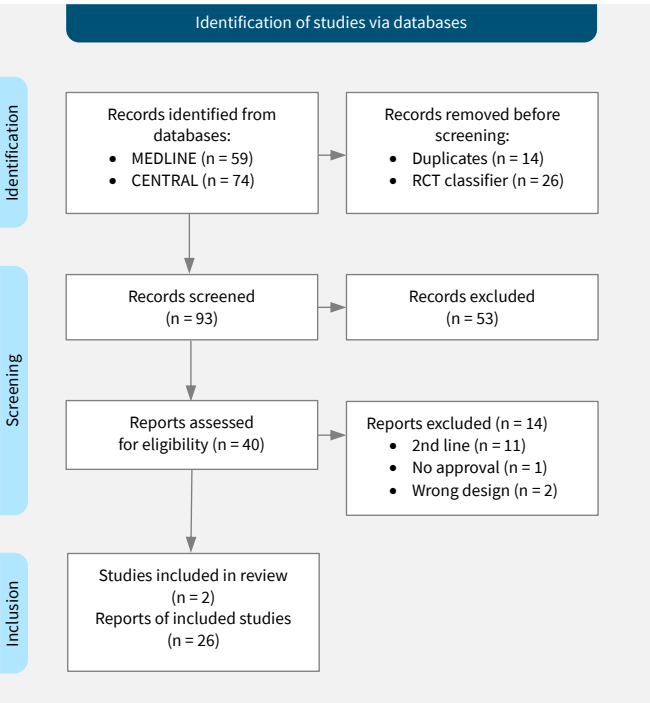


Figure 1. *PRISMA flow diagram. Search date: 15.04.25*

Included studies and participants

For a detailed description of the study, see the Characteristics of included studies. Here, we provide a brief overview.

We identified two studies comparing the combination of tislelizumab and a platinum-based chemotherapeutic doublet to platinum-chemotherapy alone. Both studies were multicentre, open-label, randomised-controlled trials performed in China. RATIONALE-304 (NCT03663205) [4, 5, 7] was a two-armed study that included only participants with non-small cell lung cancer (NSCLC) and a non-squamous cell histology (NSqC), while RATIONALE-307 (NCT03594747) [1-3] was conducted in NSCLC with squamous cell histology (SqC). In RATIONALE-307, participants were randomised into one of three arms. The two interventional arms, where participants received tislelizumab, differed in the composition of the chemotherapy doublet, either receiving paclitaxel or nab-paclitaxel in addition to carboplatin. Participants who were randomised into the control arm received the combination of carboplatin and paclitaxel. Key inclusion criteria for both studies were a good performance status, an age between 18 and 75 years, a good organ function, and relatively few comorbidities, particularly regarding autoimmune disease. Patients requiring corticosteroid therapy, apart from patients with known adrenal insufficiency, receiving supplemental corticosteroids at low doses, immunosuppressive therapy or patients with a history of HIV, active hepatitis B, C or tuberculosis were excluded. PD-L1 positivity was not an eligibility criterion.

Across studies, 694 participants underwent randomisation, with 462 allocated to tislelizumab-based treatment arms and 232 receiving the comparator treatments. The median age of participants was 61-62 years. The female proportion of participants differed between studies: in RATIONALE-304, 26% were female, and in RATIONALE-307, the proportion ranged between 5.9% and 10.8% across arms. Discrepancies in baseline criteria could be noted concerning the proportion of participants who were never-smokers, particularly in RATIONALE-307, ranging from 5.9% in the intervention arm receiving the nab-paclitaxel chemotherapy doublet to 19% and 20% in the comparator arm and paclitaxel chemotherapy arm, respectively. Participants in both studies who received the control treatment were allowed to crossover and receive tislelizumab monotherapy or another immunotherapy upon progression. In RATIONALE-307, 56.2% of participants receiving the control subsequently received tislelizumab monotherapy. In RATIONALE-304, the rate of participants with the comparator treatment switching over to receive tislelizumab monotherapy was at 36.0%, and 50.5% overall received immunotherapy.

The median follow-up across the two studies was 16.4 months.

BeiGene funded both studies.

Interventions and comparisons

The dose, frequency and route of administration of tislelizumab, as well as the duration of treatment, were the same across studies, with participants receiving 200 mg every three weeks as an intravenous infusion until disease progression, loss of clinical benefit or intolerable toxicity. The partnering chemotherapeutic regimen in RATIONALE-307 was composed of carboplatin AUC 5 mg/ml/min given every three weeks together with either paclitaxel 175 mg/m^2 every three weeks or nab-paclitaxel 100 mg/m^2 given on day one, eight and 15 of every 3-week cycle. The chemotherapeutic backbone was administered for a total of four to six cycles. Thereafter, participants in the intervention arms continued to receive tislelizumab as maintenance. Participants in the comparator arm received the carboplatin and paclitaxel combination for four to six cycles. RATIONALE-304 differed in that the chemotherapy doublet allowed for the use of either carboplatin AIC 5 mg/ml/min or cisplatin 75 mg/m^2, based on the investigator's choice, combined with pemetrexed 500 mg/m^2 for a total of four to six cycles. After completing chemotherapy, participants in the interventional arm who received tislelizumab in addition to the chemotherapy backbone received tislelizumab along with pemetrexed as maintenance. In contrast, patients in the comparator arm received only pemetrexed.

Outcomes of interventions

In both studies, progression-free survival (PFS) by independent central review was selected as the primary outcome, with overall survival, safety assessment by CTCAE v5.0 and patient-reported outcome assessment via EORTC QLQ-C30 and the lung cancer module LC13 evaluated as secondary outcomes. Analysis of PD-L1 expression as a predictive biomarker for response was reported only for PFS in both included studies, and additionally for overall survival in RATIONALE-304.

Risk of bias

Allocation (selection bias)

Using an Interactive Response Technology (IRT) system, the randomisation method was adequate in both studies. Participant stratification in both trials was by tumour stage IIIB vs IV and PD-L1 expression into TC < 1%, 1-49% and ≥ 50%. Baseline characteristics could be noted in RATIONALE-307 regarding female patient proportion and smoking status. Thus, we rated selection bias as unclear in RATIONALE-307 and low in RATIONALE-304.

Blinding (performance bias and detection bias)

Both studies had an open-label design, with patients and participants aware of the group allocation. For the objective outcomes of overall survival and progression-free survival, where outcome assessment was conducted by an independent review committee using RECIST v1.1 criteria, we judged the risk of bias to be low. For the outcomes of quality of life and adverse events, we judged the risk of bias to be high, considering their subjective nature, at least in part.

Incomplete outcome reporting (attrition bias)

In both studies, an intention-to-treat analysis was performed; thus, we judged the risk of attrition bias low for OS, PFS and safety analysis. Data missingness for the safety outcome, resulting from the exclusion of participants who were excluded from the as-treated population, was not significant. While both studies reported a high compliance rate regarding quality-of-life assessments from baseline through week 36, in RATIONALE-307, quality of life outcome data were missing from week 18 onward, leading to a high risk of bias judgment.

Selective reporting (reporting bias)

The trial protocols of both studies were accessible through clinicaltrials.gov, and the outcomes of interest were adequately reported in both studies. Thus, we judged the risk of reporting bias as low.

Effects of interventions

See the summary of findings table for all assessed outcomes. Herein, we only summarise the results for the overall survival outcome.

Overall survival

Treatment with a tislelizumab-based regimen compared to chemotherapy in NSCLC, irrespective of PD-L1 expression, may increase overall survival slightly in the palliative first-line setting (HR 0.80 [95% CI, 0.62 to 1.02], two studies, 694 participants; low-certainty evidence). In absolute terms, this translates to a 5.3% higher overall survival (0.5% less to 12.7% more) at one year. The median overall survival (OS) calculated based on the pooled hazard ratio and confidence interval, and the baseline risk of 18.2 months median OS with the comparator treatment, leads to a 4.5 months higher median OS (0.4 less to 11.1 months more) with a tislelizumab-based treatment regimen than relying solely on chemotherapy. However, considering the short follow-up for OS, the high rate of treatment switching with participants receiving immunotherapy upon progression in the comparator arms and imprecision of the effect estimate, including both appreciable benefit and null effect, the certainty of evidence was rated as low. Uncertainty regarding the estimate of the median OS gain results from the relatively short follow-up period, which was shorter than the calculated median OS in comparator arms, with median OS and upper CIs in intervention arms in part being reported as not estimable. Underestimation of the effect might stem from the significant rate of treatment crossover upon progression in comparator arms, assuming ICIs are not readily available as a second-line treatment.

Evidence discussion

Summary of main results

Tislelizumab combined with chemotherapy in the palliative first-line setting of NSCLC may increase overall survival slightly compared to standard of care treatment with chemotherapy only, while potentially increasing the number of people experiencing higher-grade adverse events (CTCAE ≥ 3) with little to no difference regarding quality of life.

Quality of evidence

The certainty of evidence across outcomes was rated very low to high. Reasons for downgrading were concerns regarding risk of bias resulting from potential detection and performance bias, imprecision, particularly in the case of higher-grade adverse events and indirectness in the case of overall survival, which resulted from crossover to receive checkpoint inhibitor therapy in control arms upon disease progression.

Overall completeness and applicability of evidence

PD-L1 expression and mutational dependence

Both studies addressed the PD-L1's predictive value for treatment response. However, differences in outcomes by PD-L1 expression levels regarding OS were only reported for RATIONALE-304. In RATIONALE-307, findings across PD-L1 expression levels for PFS were consistent across subgroups.

In case of NSqC NSCLC (RATIONALE-304), a difference was noted between different PD-L1 expression subgroups, indicating that the benefit of adding tislelizumab to the treatment regimen might mainly be driven by patients with PD-L1 TC > 50% for both PFS and OS outcomes, pointing to its ineffectiveness in patients with lower PD-L1 expression. Despite subgroup analyses' shortcomings that limit their interpretability, like the risk of type II error, considering the stratification of the randomisation by PD-L1 expression levels and preplanning of the analysis, concerns regarding PD-L1 dependence of the beneficial effect of tislelizumab-based treatment in NSqC NSCLC are justified. This is also reflected in the EMA's approval of the tislelizumab-chemotherapy combination only for NSqC NSCLC with high PD-L1 expression (TC ≥ 50%).

Generalizability of data for other patient populations or settings

In addition to tislelizumab's approval in the palliative first-line setting in combination with a platinum-based doublet chemotherapy, approval was granted in the palliative second-line treatment as monotherapy based on results from RATIONALE-303 (NCT03358875) [8]. The generalizability of data to patient populations that do not meet the included trials' eligibility criteria is limited. Thus, the evidence presented only applies to patients with good performance status, without oncogenic driver mutations, relatively few comorbidities, and no autoimmune disease requiring immunosuppression or chronic infectious disease (HIV, hepatitis B/C, TBC). Of note, patients over 75 years were not eligible for inclusion; thus, the applicability of the presented evidence to elderly patients is questionable.

AGREEMENTS AND DISAGREEMENTS WITH OTHER STUDIES

Other ICIs and contradictory findings

Please refer to the 'Agreements and Disagreements with other studies' section in the initial ICI application on p. 37.

Data summary

Characteristics of included studies

Non-small cell lung cancer – Immunochemotherapy

RATIONALE-307

Methods	**Phase:** 3 **Study design:** RCT, open-label, multicentre, 3-arm, active-controlled **Locations:** China (43 sites)
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: SqC - Pathomolecular determinants: EGFR-, ALK- - PD-L1 status: not required - ECOG: 0-1 - Adequate organ function (incl. CrCl ≥ 45 ml/min) - Age: 18-75 years • **Key exclusion criteria** - Treatment in neoadjuvant/adjuvant setting completed at least 6 months before enrollment (i.e. disease-free survival of ≥ 6 months) - Treatment with systemic steroid therapy of > 10 mg prednisone equivalent per day or immunosuppressive medication ≤ 14 days before randomisation - Clinically significant pericardial effusion or uncontrolled pleural or peritoneal effusion requiring frequent centesis - Untreated CNS metastases; if treated, radiologically stable, no ongoing requirement for corticosteroids as therapy, anticonvulsants at a stable dose allowed - Active autoimmune disease or history of autoimmune disease that may relapse - Active infection requiring therapy (incl. antibacterial, antifungal or antiviral) - Known history of HIV, active Hepatitis B or C, TBC - History of interstitial lung disease or non-infectious pneumonitis or uncontrolled systemic diseases, incl. diabetes, hypertension, pulmonary fibrosis, acute lung diseases - Participants who received a live-virus vaccine ≤ 4 weeks before randomisation - Cardiovascular comorbidities (incl. symptomatic pulmonary embolism ≤ 28 days before randomisation, any history of acute myocardial infarction ≤ 6 months before randomisation, any history of heart failure NYHA III or IV ≤ 6 months before randomisation, cerebrovascular event ≤ 6 months before randomisation) **Number of participants:** • **Randomised** - Intervention group A (I-P): 120 - Intervention group B (I-nP): 119 - Comparator group (C): 121 • **Evaluated (efficacy analysis)** - I-P: 120 - I-nP: 119 - C: 121 • **Evaluated (safety analysis)** - I-P: 120 - I-nP: 118 - C: 117 **Median age:** 62 years (range: 34-74) (across arms) **Female:** I-P: 10.8%, I-nP: 5.9%, C: 8.3% **Never-smoker:** I-P: 20.0%, I-nP: 5.9%, C: 19.0% **Brain metastases (at baseline):** 1.7% (across arms)
Interventions	**Immune checkpoint inhibitor(s):** Tislelizumab **Treatment regimen:** Tislelizumab + carboplatin + paclitaxel or nab-paclitaxel **Intervention details:** • Route of administration: - Tislelizumab: IV - Carboplatin/paclitaxel or nab-paclitaxel: IV • Dosage: - Tislelizumab: 200 mg - Carboplatin: AUC 5 mg/mL/min - Paclitaxel: 175 mg/m^2 - Nab-paclitaxel: 100 mg/m^2 • Length of treatment cycles and day(s) of application: d1 q3w - Tislelizumab: d1 q3w until disease progression, loss of clinical benefit, intolerable toxicity - Carboplatin and paclitaxel: d1 q3w for 4-6 cycles - Nab-paclitaxel: d1/8/15 q3w for 4-6 cycles **Comparator treatment(s):** Carboplatin/paclitaxel (same dosage, length of treatment cycles and application as in intervention group A) **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** allowed, effective crossover-rate of 56.2% (received tislelizumab monotherapy upon PD)

Outcomes according to the trial protocol	**Primary outcome(s):** • PFS – by IRC **Relevant secondary or exploratory outcome(s):** • OS • ORR – by IRC • DoR – by IRC • PD-L1 expression by IHC as predicitive biomarker for response • Safety and tolerability • PFS by investigators • PROs: QLQ-C30 and LC13 **Longest median follow-up for survival outcomes:** 16.7 months
Notes	**ClinicalTrials.gov ID:** NCT03594747 **Trial status:** completed **Sponsors and collaborators:** BeiGene, Ltd.

RATIONALE-304

Methods	**Phase:** 3 **Study design:** RCT, open-label, multicentre, 2-arm, active-controlled **Locations:** China (47 sites)
Participants	**Eligibility criteria** • **Key inclusion criteria** - Histologic subtype: NSqC - Pathomolecular determinants: EGFR-, ALK- - PD-L1 status: not required - ECOG: 0-1 - Adequate organ function - Age: 18-75 years • **Key exclusion criteria** - Treatment in neoadjuvant/adjuvant setting completed at least 6 months prior to enrollment (i.e. disease-free survival of ≥ 6 months) - Treatment with systemic steroid therapy of > 10 mg prednisone equivalent per day or immunosuppressive medication ≤ 14 days before randomisation - RT to lung > 30 Gy within 6 mts. Prior to the first dose of trial treatment - Clinically significant pericardial effusion or uncontrolled pleural or peritoneal effusion requiring frequent centesis - Untreated CNS metastases; if treated, radiologically stable, no ongoing requirement for corticosteroids as therapy, anticonvulsants at a stable dose allowed - Active autoimmune disease or history of autoimmune disease that may relapse - Active infection requiring therapy (incl. antibacterial, antifungal or antiviral) - Known history of HIV, active Hepatitis B or C, TBC - History of interstitial lung disease or non-infectious pneumonitis or uncontrolled systemic diseases, incl. diabetes, hypertension, pulmonary fibrosis, acute lung diseases - Participants who received a live-virus vaccine ≤ 4 weeks before randomisation - Cardiovascular comorbidities (incl. symptomatic pulmonary embolism ≤ 28 days before randomisation, any history of acute myocardial infarction ≤ 6 months before randomisation, any history of heart failure NYHA III or IV ≤ 6 months before randomisation, cerebrovascular event ≤ 6 months before randomisation) **Number of participants:** 334 • **Randomised** - Intervention group (I): 223 (PD-L1 in TC ≥ 50%: 74) - Comparator group (C): 111 (PD-L1 in TC ≥ 50%: 36) • **Evaluated (efficacy analysis)** - I: 223 - C: 111 • **Evaluated (safety analysis)** - I: 222 - C: 110 **Median age:** median 61 years (range: 25–75) **Female:** 26% **Never-smoker:** I: 76 (34.1%), C: 45 (40.5%) **Brain metastases (at baseline):** I: 11 (4.9%), C: 7 (6.3%)
Interventions	**Immune checkpoint inhibitor(s):** Tislelizumab **Treatment regimen:** Tislelizumab + carboplatin or cisplatin + pemetrexed **Intervention details:** • Route of administration: - Tislelizumab: IV - Pemetrexed/carboplatin or cisplatin: IV • Dosage: - Tislelizumab: 200 mg - Carboplatin: AUC 5 mg/mL/min - Cisplatin: 75 mg/m^2 - Pemetrexed: 500 mg/m^2 • Length of treatment cycles and day(s) of application: d1 q3w

	- Tislelizumab: d1 q3w until disease progression, loss of clinical benefit, or intolerable toxicity - Pemetrexed: d1 q3w until disease progression, loss of clinical benefit, or intolerable toxicity - Cisplatin or carboplatin: d1 q3w for 4-6 cycles **Comparator treatment(s):** Pemetrexed/carboplatin or cisplatin (same dosage, length of treatment cycles and application as in intervention group with pemetrexed maintenance until disease progression, loss of clinical benefit, or intolerable toxicity) **Treatment switching in comparator arm (crossover to receive ICIs upon progression):** allowed, effective crossover-rate of 36.0% (received tislelizumab monotherapy upon PD)
Outcomes according to the trial protocol	**Primary outcome(s):** • PFS – by IRC **Relevant secondary or exploratory outcome(s):** • OS • PFS – investigator assessed • DoR – by IRC • ORR – by IRC • Safety assessment • HR-QoL by EORTC QLQ-C30 and QLQ LC13 • PD-L1 expression by IHC as a predictive biomarker for response **Longest median follow-up for survival outcomes:** 16.1 months
Notes	**ClinicalTrials.gov ID:** NCT03663205 **Trial status:** completed **Sponsors and collaborators:** BeiGene, Ltd.

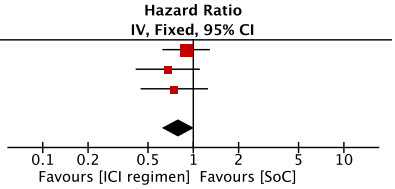
Analyses

Non-small cell lung cancer – Immunochemotherapy

Tislelizumab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: OS

Study or Subgroup	log[Hazard Ratio]	SE	ICI regimen Total	SoC Total	Weight	Hazard Ratio IV, Fixed, 95% CI
RATIONALE-304	-0.11	0.18	223	111	49.3%	0.90 [0.63, 1.27]
RATIONALE-307 (A)	-0.39	0.245	120	61	26.6%	0.68 [0.42, 1.09]
RATIONALE-307 (B)	-0.29	0.25725	119	60	24.1%	0.75 [0.45, 1.24]
Total (95% CI)			**462**	**232**	**100.0%**	**0.80 [0.62, 1.02]**

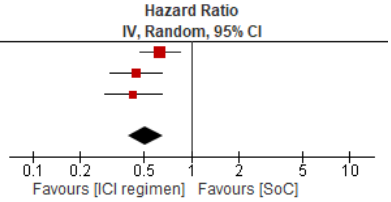
Heterogeneity: $Chi^2 = 0.93$, df = 2 (P = 0.63); $I^2 = 0\%$
Test for overall effect: Z = 1.80 (P = 0.07)



Tislelizumab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: PFS

Study or Subgroup	log[Hazard Ratio]	SE	ICI regimen Total	SoC Total	Weight	Hazard Ratio IV, Random, 95% CI
RATIONALE-304	-0.46	0.15	223	111	42.2%	0.63 [0.47, 0.85]
RATIONALE-307 (A)	-0.8	0.196	120	61	30.1%	0.45 [0.31, 0.66]
RATIONALE-307 (B)	-0.84	0.20825	119	60	27.7%	0.43 [0.29, 0.65]
Total (95% CI)			**462**	**232**	**100.0%**	**0.51 [0.40, 0.66]**

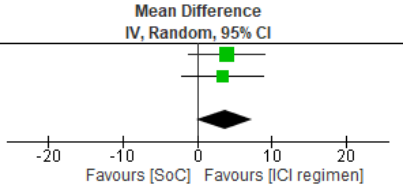
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 3.02$, df = 2 (P = 0.22); $I^2 = 34\%$
Test for overall effect: Z = 5.16 (P < 0.00001)



Tislelizumab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: Global Health Score/Quality of Life (GHS/QoL; measured by EORTC QLQ-C30)

Study or Subgroup	ICI regimen Mean	SD	Total	SoC Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
RATIONALE-304	0.9	21.29	222	-3.05	22.74	110	54.5%	3.95 [-1.14, 9.04]
RATIONALE-307	3.8	22.22	238	0.4	26.49	117	45.5%	3.40 [-2.17, 8.97]
Total (95% CI)			**460**			**227**	**100.0%**	**3.70 [-0.06, 7.46]**

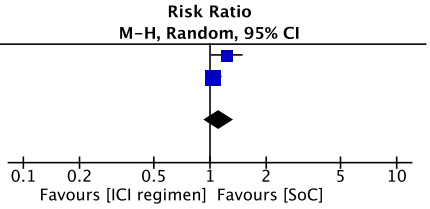
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 (P = 0.89); $I^2 = 0\%$
Test for overall effect: Z = 1.93 (P = 0.05)



Tislelizumab-based treatment regimen compared to SoC in oncogenic driver wild-type NSCLC, irrespective of PD-L1 expression, Outcome: Adverse events (CTCAE ≥ 3) irrespective of treatment attribution

Study or Subgroup	ICI regimen Events	Total	SoC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
RATIONALE-304	154	222	62	110	40.3%	1.23 [1.02, 1.48]
RATIONALE-307	210	238	99	117	59.7%	1.04 [0.95, 1.14]
Total (95% CI)		**460**		**227**	**100.0%**	**1.11 [0.93, 1.34]**
Total events	364		161			

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 3.20$, df = 1 (P = 0.07); $I^2 = 69\%$
Test for overall effect: Z = 1.17 (P = 0.24)



Appendix

Search strategy

Tislelizumab	
Ovid MEDLINE(R) ALL 1946 to April 15, 2025	
#	Searches
1	Carcinoma, Non-Small-Cell Lung/
2	(non small cell* or nonsmall cell* or NSCL*).ti,ab,kf.
3	or/1-2
4	(Tislelizumab* or BGBA317* or BGB A317* or JHL-2108* or JHL2108* or Tevimbra*).ti,ab,kf,nm.
5	3 and 4
6	exp randomized controlled trial/
7	controlled clinical trial.pt.
8	drug therapy.fs.
9	(randomi?ed or placebo or randomly or trial or groups).ab.
10	or/6-9
11	exp animals/ not humans.sh.
12	10 not 11
13	5 and 12
14	limit 13 to yr="2010 -Current"
Cochrane Central Register of Controlled Trials (Central, 2024, Issue 07) (via Cochrane Library)	
ID	Search
#1	[mh ^"Carcinoma, Non-Small-Cell Lung"]
#2	("non small cell" OR "nonsmall cell" OR NSCL*):TI,AB,KW
#3	#1 OR #2
#4	(Tislelizumab* OR BGBA317* OR "BGB A317" OR JHL2108* OR "JHL 2108" OR Tevimbra*):TI,AB,KW
#5	#3 AND #4 with Cochrane Library publication date from Jan 2010 to present
#6	ctgov:AN
#7	ictrp:AN
#8	#5 NOT (#6 OR #7)

References

1. Wang J, Lu S, Yu X, Hu Y, Zhao J, Sun M, et al. Tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for advanced squamous non-small-cell lung cancer: final analysis of the randomized, phase III RATIONALE-307 trial. ESMO open. 2024;9(10):103727.
2. Wang J, Yu X, Barnes G, Leaw S, Bao Y, Tang B. The effects of tislelizumab plus chemotherapy as first-line treatment on health-related quality of life of patients with advanced squamous non-small cell lung cancer: Results from a phase 3 randomized clinical trial. Cancer Treat Res Commun. 2022;30:100501.
3. Wang J, Lu S, Yu X, Hu Y, Sun Y, Wang Z, et al. Tislelizumab Plus Chemotherapy vs Chemotherapy Alone as First-line Treatment for Advanced Squamous Non-Small-Cell Lung Cancer: A Phase 3 Randomized Clinical Trial. JAMA Oncol. 2021;7(5):709-17.
4. Lu S, Wang J, Yu Y, Yu X, Hu Y, Ma Z, et al. Tislelizumab plus chemotherapy as first-line treatment of locally advanced or metastatic nonsquamous non-small-cell lung cancer (final analysis of RATIONALE-304: a randomized phase III trial). ESMO open. 2024;9(10):103728.
5. Lu S, Yu Y, Barnes G, Qiu X, Bao Y, Tang B. Examining the Impact of Tislelizumab Added to Chemotherapy on Health-Related Quality-of-Life Outcomes in Previously Untreated Patients With Nonsquamous Non-Small Cell Lung Cancer. Cancer J. 2022;28(2):96-104.
6. Lu S, Wang J, Yu Y, Yu X, Hu Y, Ma Z, et al. Randomized phase III study of tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for advanced non-squamous non-small cell lung cancer (nsq-NSCLC): RATIONALE-304 updated analysis. Immuno-oncology and technology. 2022;16.
7. Lu S, Wang J, Yu Y, Yu X, Hu Y, Ai X, et al. Tislelizumab Plus Chemotherapy as First-Line Treatment for Locally Advanced or Metastatic Nonsquamous NSCLC (RATIONALE 304): A Randomized Phase 3 Trial. J Thorac Oncol. 2021;16(9):1512-22.
8. Zhou C, Huang D, Fan Y, Yu X, Liu Y, Shu Y, et al. Tislelizumab Versus Docetaxel in Patients With Previously Treated Advanced NSCLC (RATIONALE-303): A Phase 3, Open-Label, Randomized Controlled Trial. J Thorac Oncol. 2023;18(1):93-105.