Tislelizumab
(NSCLC, second line or later)

Addendum to Project A24-128
(dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

Project: A25-63 Version: 1.0 Status: 28 May 2025 DOI: 10.60584/A25-63_en

[1] Translation of the addendum *Tislelizumab (NSCLC, ab Zweitlinie) – Addendum zum Projekt A24-128 (Dossierbewertung)*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Tislelizumab (NSCLC, second line or later) – Addendum to Project A24-128

Commissioning agency

Federal Joint Committee

Commission awarded on

6 May 2025

Internal Project No.

A25-63

https://doi.org/10.60584/A25-63_en

Address of publisher

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Recommended citation

Institute for Quality and Efficiency in Health Care. Tislelizumab (NSCLC, second line or later); Addendum to Project A24-128 (dossier assessment) [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-63_en.

Keywords

Tislelizumab, Carcinoma – Non-Small-Cell Lung, Benefit Assessment, NCT03358875

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Table of contents

Page

List of tables v
List of figures vi
List of abbreviations viii
1 Background 1
2 Assessment 2
2.1 Subsequently submitted analyses of patient-reported outcomes 2
2.2 Subsequently submitted information on missing values for the outcome of health status (EQ-5D VAS) 4
2.3 Subsequently submitted information on immune-related AEs 4
2.4 Risk of bias 6
2.5 Results 6
2.5.1 Subgroups and other effect modifiers 8
2.6 Probability and extent of added benefit 9
2.6.1 Assessment of added benefit at outcome level 9
2.7 Overall conclusion on added benefit 13
2.8 Summary 14
3 References 16
Appendix A Kaplan-Meier curves 17
A.1 Morbidity 17
A.1.1 Alopecia (EORTC QLQ-LC13) 17
Appendix B Kaplan-Meier curves presented as supplementary information 18
B.1 Morbidity 18
B.1.1 EORTC QLQ-C30 18
B.1.2 EORTC QLQ-LC13 22
B.1.3 Health status (EQ-5D VAS) 26
B.2 Health-related quality of life 27

List of tables

Page

Table 1: Results (morbidity, health-related quality of life, side effects) – RCT, direct comparison: tislelizumab vs. docetaxel 7
Table 2: Extent of added benefit at outcome level: tislelizumab vs. docetaxel 10
Table 3: Positive and negative effects from the assessment of tislelizumab in comparison with docetaxel 13
Table 4: Tislelizumab – probability and extent of added benefit 15

List of figures

Page

Figure 1: Kaplan-Meier curves for the outcome of alopecia (EORTC QLQ LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD L1 expression < 1%), 3rd data cut-off (18 January 2024) 17
Figure 2: Kaplan-Meier curves for the outcome of fatigue (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 18
Figure 3: Kaplan-Meier curves for the outcome of nausea and vomiting (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 18
Figure 4: Kaplan-Meier curves for the outcome of pain (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 19
Figure 5: Kaplan-Meier curves for the outcome of dyspnoea (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 19
Figure 6: Kaplan-Meier curves for the outcome of insomnia (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 20
Figure 7: Kaplan-Meier curves for the outcome of appetite loss (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 20
Figure 8: Kaplan-Meier curves for the outcome of constipation (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 21
Figure 9: Kaplan-Meier curves for the outcome of diarrhoea (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 21
Figure 10: Kaplan-Meier curves for the outcome of cough (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 22
Figure 11: Kaplan-Meier curves for the outcome of dysphagia (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 22
Figure 12: Kaplan-Meier curves for the outcome of dyspnoea (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 23

Figure 13: Kaplan-Meier curves for the outcome of haemoptysis (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 23
Figure 14: Kaplan-Meier curves for the outcome of pain (arm/shoulder) (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 24
Figure 15: Kaplan-Meier curves for the outcome of pain (chest) (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 24
Figure 16: Kaplan-Meier curves for the outcome of pain (other) (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 25
Figure 17: Kaplan-Meier curves for the outcome of peripheral neuropathy (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 25
Figure 18: Kaplan-Meier curves for the outcome of oral pain (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 26
Figure 19: Kaplan-Meier curves for the outcome of health status (EQ-5D VAS; time to first deterioration by ≥ 15 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 26
Figure 20: Kaplan-Meier curves for the outcome of global health status (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 27
Figure 21: Kaplan-Meier curves for the outcome of physical functioning (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 27
Figure 22: Kaplan-Meier curves for the outcome of role functioning (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 28
Figure 23: Kaplan-Meier curves for the outcome of emotional functioning (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 28
Figure 24: Kaplan-Meier curves for the outcome of cognitive functioning (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 29
Figure 25: Kaplan-Meier curves for the outcome of social functioning (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024) 29

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model with repeated measures
NSCLC	non-small cell lung cancer
PD-L1	programmed cell death ligand 1
PT	Preferred Term
QLQ-C30	Quality of Life Questionnaire-Core 30
QLQ-LC13	Quality of Life Questionnaire-Lung Cancer 13
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
VAS	visual analogue scale

1 Background

On 6 May 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-128 (Tislelizumab – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the information and analyses regarding the RATIONALE 303 study presented in the commenting procedure by the pharmaceutical company (hereinafter referred to as the "company") [2-4], taking into account the information in the dossier [5] on the following outcomes:

- European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) and EORTC Quality of Life Questionnaire-Lung Cancer 13 (QLQ-LC13): responder analyses on the time to first deterioration by ≥ 10 points
- EQ-5D visual analogue scale (VAS): responder analyses on the time to first deterioration by ≥ 15 points; information on missing values/low response rates at baseline
- Immune-related adverse events (AEs) (overall rate, severe immune-related AEs [Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3], serious immune-related AEs)

The responsibility for this assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The randomized controlled trial (RCT) RATIONALE 303 was used for the benefit assessment of tislelizumab as monotherapy in comparison with the appropriate comparator therapy (ACT) in adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after prior platinum-based therapy. A detailed description of the RCT RATIONALE 303 and the subpopulation with programmed cell death ligand 1 (PD-L1) expression ≤ 1%, which is the relevant subpopulation for the benefit assessment, can be found in dossier assessment A24-128 [1].

Based on the information in the company's dossier, no suitable data for the patient-reported outcomes of symptoms (assessed with EORTC QLQ-C30 and EORTC QLQ-LC13), health status (assessed with EQ-5D VAS) and health-related quality of life (assessed with EORTC QLQ-C30) were available for dossier assessment A24-128 [1]. This was due to the fact that the observation period for these outcomes was very much shortened and differed notably between the study arms, and the analyses presented by the company were not suitable against this background. There was also uncertainty as to how many patients had missing values for the outcome of health status (EQ-5D VAS), as the recording of this outcome was only later introduced with Protocol Amendment 1 dated 14 February 2018.

In addition, no suitable data on immune-related AEs were available in the company's dossier for dossier assessment A24-128, as only a selection of events were included that fulfil certain conditions (in particular, a need for treatment, or investigator's or other reviewers' assessment of an association with the study medication).

As part of the commenting procedure [2], the company subsequently submitted analyses on the patient-reported outcomes of symptoms, health status and health-related quality of life, and, for the outcome of health status, additional information on the proportion of patients with missing values due to the later introduction of the outcome [3].

Following the oral hearing [6], the company also presented information on the analyses of immune-related AEs presented in the dossier [4]. Further analyses on immune-related AEs were not submitted by the company following the oral hearing.

The analyses and data subsequently submitted by the company in the commenting procedure are assessed below, taking into account the information in the dossier.

2.1 Subsequently submitted analyses of patient-reported outcomes

As described in dossier assessment A24-128 [1], the linking of the observation period to the treatment duration resulted in systematically and very clearly shortened observation periods for the patient-reported outcomes compared with overall survival, as well as clearly different

observation periods between the treatment arms. The median observation period for symptom outcomes and health-related quality of life was 3.7 months in the intervention arm (1st to 3rd quartile: 1.9 to 9.9 months) and 2.1 months in the comparator arm (1st to 3rd quartile: 0.8 to 4.2 months). Observation periods were even shorter for health status (median 2.3 versus 1.4 months). Furthermore, the questionnaire response rates in the comparator arm fell sharply after just a few observation points (first 3 months) and differed greatly between the study arms. For example, after 12 weeks, around 69% of the patients in the intervention arm who were still alive at this time were still under observation, while only around 51% were still under observation in the comparator arm. These values fell to around 51% versus 23% by Week 24. For the patient-reported outcomes on the time to one-time-confirmed deterioration, the company's dossier presented responder analyses, as well as continuous analyses using a mixed-effects model with repeated measures (MMRM) on the change from baseline as supporting information. Due to the greatly shortened observation period and the differences between the treatment arms, these analyses were not used for the benefit assessment, and it was pointed out in the dossier assessment that analyses on the time to first deterioration should be presented. The company subsequently submitted these analyses with its comments.

Kaplan-Meier curves for the responder analyses subsequently submitted by the company for the time to first deterioration are presented in Appendix A and Appendix B. The data subsequently submitted shows that, at Month 6 (or Week 24), only ≤ 10 patients were still under observation for the majority of outcomes in the comparator arm. Furthermore, even when considering first deterioration, censoring occurred to a major extent already in the first 2.5 months after the start of observation. For most outcomes, however, differences between the treatment arms in the occurrence of events were only shown after Month 3, and were therefore potentially highly influenced by these censorings. This can be seen in particular in the Kaplan-Meier curves for health-related quality of life (see Figure 20 – Figure 25). Due to these great uncertainties, the responder analyses subsequently submitted by the company on the time to first deterioration of the patient-reported outcomes cannot be meaningfully interpreted in the given data situation. The results for the outcome of alopecia (EORTC QLQ-LC13), which are used for the benefit assessment, are an exception, as the Kaplan-Meier curves of this outcome split immediately after the start of the study and a clear difference in the course of the curves is seen (see Figure 1).

The results for the outcome of alopecia are presented in Section 2.5 and are used to derive the added benefit. For the reasons explained above, there are no suitable data for the other patient-reported outcomes of symptoms (assessed using the EORTC QLQ-C30 and EORTC QLQ-LC13), health status (assessed using the EQ-5D VAS) and health-related quality of life (assessed using the EORTC QLQ-C30) for the benefit assessment .

2.2 Subsequently submitted information on missing values for the outcome of health status (EQ-5D VAS)

As described in dossier assessment A24-128 [1], the response rates for the outcome of health status (EQ-5D VAS) were already low at study start (77% in the intervention arm and 67% in the comparator arm) and already < 70% in both study arms at the first subsequent recording. As described in the dossier assessment, this was partly due to the fact that the EQ-5D VAS was only recorded after the introduction of the outcome into the study per Protocol Amendment 1 of 14 February 2018. However, no information was available in the dossier on the proportion of patients in the relevant subpopulation of the RATIONALE 303 study for whom no recording at baseline was available for this reason. The company subsequently submitted information on this issue with its comments. This shows that the majority of patients without a value at baseline or post-baseline were randomized before Protocol Amendment 1 and were therefore not included in the analyses (46 of 49 patients in the intervention arm and 31 of 34 in the comparator arm). For the predominant share of patients (21.5% in the intervention arm and 30.1% in the comparator arm), the values can therefore be regarded as missing completely at random. Irrespective of this, however, due to the extremely shortened observation periods and the notable differences in observation periods between the study arms, the analyses subsequently submitted by the company for the outcome of health status are subject to the same uncertainties already described for the patient-reported outcomes overall. The analyses are therefore not suitable for use in the assessment, given the data situation (see Section 2.1 for an explanation).

2.3 Subsequently submitted information on immune-related AEs

In Module 4 D of the dossier [5], the company presented analyses of immune-related AEs, which were recorded as AEs of special interest in the study. In principle, the recording of immune-related AEs was predefined in the RATIONALE 303 study plans and was based on a collection of Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs), which, according to the study documents, was compiled on the basis of a search for known immune-related AEs of comparable drugs and a literature search. However, not all events were rated as immune-related AEs – just a selection if certain conditions were met. The conditions for considering the events as immune-related were the exclusion of alternative causes for the potentially immune-related event by the investigator, treatment with a specific therapy (e.g. with corticosteroids) and the final assessment within a “medical review” by 2 independent persons. This operationalization is unsuitable for fully representing immune-related AEs.

As described in the dossier assessment [1], the benefit assessment would require analyses based on a PT collection that not only includes a selection of PTs that fulfil certain conditions, but all PTs regardless of the investigator’s or other reviewers’ assessment of an association

with the study medication, or a need for treatment. However, such analyses were not available in the company's dossier and were also not presented by the company in its comments. In its comments, the company did not explain why these analyses were not submitted. Also during the oral hearing, when asked why it had not submitted analyses taking into account all potentially immune-related events, the company did not provide any reasons, but merely referred to various assessment approaches, some of which had been carried out in consultation with the European Medicines Agency (EMA) [6]. In addition, the company agreed to check after the oral hearing whether the relevant analyses could be conducted.

However, following the oral hearing, the company did not submit any analyses on immune-related AEs, but only further information on the analyses submitted within the approval procedure or in the dossier [4].

In this subsequent submission, the company described that the "adjudication method" originally envisaged in the study plans to record events for immune-related AEs was further developed in close consultation with the EMA. According to the company, this led to the use of a "programmatic methodology", which was approved by the EMA. According to the company, in this approach, a predefined list of potential immune-related PTs is divided into a narrow and a broad scope. For PTs in the narrow scope, the immune-related origin is clear and events in these PTs are therefore always classified as immune-related AEs, the company explained. It added that for PTs in the broad scope, the categorization of events as immune-related AEs is based on the following additional criteria: treatment with systemic steroids or other immunosuppressants; treatment of thyroid-related events with appropriate treatment; treatment of diabetes-related events with insulin; investigator assessment that an event is an immune-related AE; investigator assessment regarding a possible association with the study medication; measures such as interruption or discontinuation of the study medication.

In the subsequent submission, the company stated that the analyses on immune-related AEs presented in the dossier were not based on the "adjudication method" originally intended according to the study plans, but on the "programmatic methodology" described above. From the perspective of the company, these analyses are an appropriate reflection of the available data. According to the company, it is not currently possible to make further post hoc analyses available to the G-BA.

The analyses of immune-related AEs based on the "programmatic methodology" described by the company, just like the analyses based on the "adjudication method", do not take into account all potentially immune-related events regardless of the investigator's assessment of an association with the study medication, or a need for treatment. Particularly against the background that it is apparently possible to conduct analyses of the recorded data using different assessment approaches, it remains unclear why the company was unable to provide

suitable analyses based on post hoc analyses for all potentially immune-related AEs without prior selection steps for this benefit assessment.

Since the company did not submit any analyses taking into account all potentially immune-related events, there are still no suitable data on immune-related AEs, including severe immune-related AEs (CTCAE grade ≥ 3) and serious immune-related AEs, available for the benefit assessment.

2.4 Risk of bias

In dossier assessment A24-128 [1], the risk of bias across outcomes was rated as low.

The risk of bias of the results for the outcome of alopecia (EORTC QLQ-LC13) was initially rated as high. This assessment was based, on the one hand, on a lack of blinding in the subjective recording of outcomes, and, on the other hand, on incomplete observation for potentially informative reasons with different lengths of follow-up observation and a sharp decline in questionnaire response rates, which differed greatly between the treatment arms. However, despite a high risk of bias, a high certainty of results is assumed for the results of this outcome due to the size of the effects and the early occurrence of the events over time (see Figure 1 in Appendix A.1.1).

No suitable data are available for the other outcomes of symptoms (EORTC QLQ-C30, EORTC QLQ-LC13), health status (EQ-5D VAS), health-related quality of life (EORTC QLQ-C30), and immune-related AEs. Therefore, the risk of bias for the corresponding results is not assessed.

2.5 Results

The results for the outcomes of symptoms (recorded using EORTC QLQ-C30, EORTC QLQ-LC13), health status (recorded using EQ-5D VAS), health-related quality of life (recorded using EORTC QLQ-C30) and immune-related AEs from the RATIONALE 303 study are presented in Table 1 below.

The Kaplan-Meier curves for the time-to-event analyses of the outcome of alopecia (EORTC QLQ-LC13) are shown in Appendix A. The Kaplan-Meier curves for all other outcomes in the morbidity and health-related quality of life categories are shown in Appendix B as supplementary information.

Table 1: Results (morbidity, health-related quality of life, side effects) – RCT, direct comparison: tislelizumab vs. docetaxel

Study Outcome category Outcome	Tislelizumab N	Tislelizumab Median time to event in months [95% CI] Patients with event n (%)	Docetaxel N	Docetaxel Median time to event in months [95% CI] Patients with event n (%)	Tislelizumab vs. docetaxel HR [95% CI]; p-value[a]
RATIONALE 303					
Morbidity					
Symptoms (time to first deterioration[b])					
EORTC QLQ-C30			No suitable data[c]		
EORTC QLQ-LC13					
Alopecia	214	NA [33.1; NC] 34 (15.9)	103	0.8 [0.8; 1.4] 67 (65.0)	0.09 [0.06; 0.14]; < 0.001
Cough, dysphagia, dyspnoea, haemoptysis, pain (arm/shoulder; chest; other), peripheral neuropathy, oral pain			No suitable data[c]		
Health status (time to first deterioration[d])					
EQ-5D VAS			No suitable data[c]		
Health-related quality of life					
EORTC QLQ-C30 – time to first deterioration[e]			No suitable data[c]		
Side effects					
Immune-related AEs			No suitable data[f]		

a. Cox proportional hazards model and log-rank test; each stratified by histology (squamous cell carcinoma vs. non-squamous cell carcinoma), and line of treatment (second vs. third line of treatment).
b. An increase by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
c. See Section 2.1 for an explanation.
d. A decrease by ≥ 15 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
e. A decrease by ≥ 10 points from baseline is considered a clinically relevant deterioration (scale range: 0 to 100).
f. See Section 2.3 for an explanation.

AE: adverse event; CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung 13; RCT: randomized controlled trial; VAS: visual analogue scale

Based on the available data, at most an indication, e.g. of an added benefit, can be determined for the alopecia outcome of the EORTC QLQ-LC13.

Morbidity

Symptoms (EORTC QLQ-C30) and health status (EQ-5D VAS)

No suitable data are available for the outcomes of symptoms (recorded using EORTC QLQ-C30) and health status (recorded using EQ-5D VAS) (for justification, see Section 2.1). In each case, there is no hint of an added benefit of tislelizumab in comparison with docetaxel; an added benefit is therefore not proven.

Symptoms (EORTC QLQ-LC13)

Alopecia

A statistically significant difference in favour of tislelizumab compared with docetaxel was shown for the outcome of alopecia (EORTC QLQ-LC13). There is an indication of an added benefit from tislelizumab in comparison with docetaxel.

Cough, dysphagia, dyspnoea, haemoptysis, pain (arm/shoulder) pain (chest), pain (other), peripheral neuropathy, and oral pain

No suitable data are available for the outcomes of cough, dysphagia, dyspnoea, haemoptysis, pain (arm/shoulder) pain (chest), pain (other), peripheral neuropathy, and oral pain (EORTC QLQ-LC13) (for justification, see Section 2.1). In each case, there is no hint of an added benefit of tislelizumab in comparison with docetaxel; an added benefit is therefore not proven.

Health-related quality of life (EORTC QLQ-C30)

No suitable data are available for health-related quality of life (recorded using the EORTC QLQ-C30) (for justification, see Section 2.1). There is no hint of an added benefit of tislelizumab in comparison with docetaxel; an added benefit is therefore not proven.

Side effects

Immune-related AEs

No suitable data are available for immune-related AEs (for justification, see Section 2.3). There is no hint of greater or lesser harm from tislelizumab in comparison with docetaxel; greater or lesser harm is therefore not proven.

2.5.1 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for this benefit assessment (see dossier assessment A24-128 [1])

- age (< 65/≥ 65)
- sex (female versus male)
- brain metastases at baseline (yes versus no)

Subgroup analyses for these characteristics were prespecified for overall survival according to the study plans.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there have to be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup results do not reveal any effect modifications.

Regarding the prior therapies, the G-BA additionally pointed out that in the context of the specification of the ACT for dossier assessment A24-128 [1], subgroup analyses according to the number of prior therapies should be presented, so that a potential effect in patients with a different number of prior therapies can be investigated. For the RATIONALE 303 study, subgroup analyses were available for patients who were in the second or third line of treatment during the study. When applying the methods described above, no effect modifications were revealed for this characteristic either.

2.6 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [7].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Section 2.5 (see Table 2).

Determination of the outcome category for symptom outcomes

For the outcome of alopecia, recorded using the EORTC QLQ-LC13, insufficient severity data are available which would allow a classification as serious/severe. The outcome is therefore assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 2: Extent of added benefit at outcome level: tislelizumab vs. docetaxel (multipage table)

Observation period **Outcome category** **Outcome**	**Tislelizumab vs. docetaxel** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	15.4 vs. 11.7 months HR: 0.79 [0.61; 1.03]; p = 0.084	Lesser/added benefit not proven
Outcomes with shortened observation period		
Morbidity		
Symptoms (EORTC QLQ-C30)	No suitable data[c]	Lesser/added benefit not proven
Symptoms (EORTC QLQ-LC13)		
Alopecia	NA vs. 0.8 months HR: 0.09 [0.06; 0.14]; p < 0.001 Probability: “indication”	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 Added benefit, extent: “considerable”
Cough, dysphagia, dyspnoea, haemoptysis, pain (arm/shoulder; chest; other), peripheral neuropathy, oral pain	No suitable data[c]	Lesser/added benefit not proven
Health status (EQ-5D VAS)	No suitable data[c]	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30	No suitable data[c]	Lesser/added benefit not proven
Side effects		
SAEs	22.4 vs. NA months HR: 0.87 [0.55; 1.37]; p = 0.549	Greater/lesser harm not proven
Severe AEs	16.4 vs. 0.3 months HR: 0.25 [0.18; 0.35]; p < 0.001 Probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Lesser harm, extent: “major”
Discontinuation due to AEs	NA vs. NA HR: 0.59 [0.29; 1.19]; p = 0.134	Greater/lesser harm not proven
Immune-related AEs	No suitable data[d]	Greater/lesser harm not proven

Table 2: Extent of added benefit at outcome level: tislelizumab vs. docetaxel (multipage table)

Observation period **Outcome category** **Outcome**	**Tislelizumab vs. docetaxel** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Gastrointestinal disorders (AEs)	14.5 vs. 2.1 months HR: 0.46 [0.32; 0.66]; p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm, extent: "considerable"
Asthenia (AEs)	NA vs. NA HR: 0.50 [0.28; 0.87]; p = 0.012 Probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ Lesser harm, extent: "minor"
Insomnia (AEs)	NA vs. NA HR: 0.36 [0.15; 0.83]; p = 0.013 Probability: "hint"	Outcome category: non-serious/non-severe side effects $0.80 \leq CI_u < 0.90$ Lesser harm, extent: "minor"
Alopecia (AEs)	NA vs. 1.6 months HR: 0.01 [0.003; 0.05]; p < 0.001 Probability: "indication"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Lesser harm, extent: "considerable"
Respiratory, thoracic and mediastinal disorders (SAEs)	NA vs. NA HR: 2.87 [1.00; 8.21] HR: 0.34 [0.12; 1.00][e]; p = 0.040 Probability: "hint"	Outcome category: serious/severe side effects Greater harm[f]; extent: minor[g]
Blood and lymphatic system disorders (severe AEs) Including: Neutropenia (severe AEs)	NA vs. 4.6 months HR: 0.09 [0.05; 0.17]; p < 0.001 Probability: "indication" NA vs. NA HR: 0.03 [0.01; 0.12]; p < 0.001	Outcome category: serious/severe side effects $CI_u < 0.75$; risk ≥ 5% Lesser harm, extent: "major"
Leukopenia (severe AEs) Febrile neutropenia (severe AEs)	NA vs. NA RR: 0.03 [0.004; 0.20]; p < 0.001 NA vs. NA RR: 0.01 [0.001; 0.23]; p < 0.001	

Table 2: Extent of added benefit at outcome level: tislelizumab vs. docetaxel (multipage table)

Observation period **Outcome category** **Outcome**	**Tislelizumab vs. docetaxel** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Investigations (severe AEs)	NA vs. NA HR: 0.13 [0.07; 0.24]; p < 0.001 Probability: “indication”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Lesser harm, extent: “major”
Including:		
Neutrophil count decreased (severe AEs)	NA vs. NA HR: 0.01 [0.002; 0.10]; p < 0.001	
White blood cell count decreased (severe AEs)	NA vs. NA HR: 0.02 [0.002; 0.11]; p < 0.001	
Infections and infestations (severe AEs)	NA vs. NA HR: 0.37 [0.19; 0.74]; p = 0.004 Probability: “hint”	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Lesser harm, extent: “major”
Metabolism and nutrition disorders (severe AEs)	NA vs. NA HR: 0.45 [0.21; 0.96]; p = 0.034 Probability: “hint”	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 Lesser harm, extent: “minor”

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. See Section 2.1 for reasons.
d. See Section 2.3 for reasons.
e. Institute’s calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
f. The result of the statistical test is decisive for the derivation of added benefit.
g. Discrepancy between CI and p-value due to different calculation methods; the extent is rated as minor.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; NA: not achieved; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

2.7 Overall conclusion on added benefit

Table 3 summarizes the results taken into account for the overall conclusion on the extent of added benefit.

Table 3: Positive and negative effects from the assessment of tislelizumab in comparison with docetaxel

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
–	–
Outcomes with shortened observation period	
Non-serious/non-severe symptoms/late complications ▪ Alopecia (EORTC QLQ-LC13): indication of an added benefit – extent: “considerable”	–
Serious/severe side effects ▪ Severe AEs: hint of lesser harm – extent: “major” ▫ Blood and lymphatic system disorders (severe AEs, including: neutropenia [severe AEs], leukopenia [severe AEs], febrile neutropenia [severe AEs]): indication of lesser harm – extent: “major” ▫ Investigations (severe AEs, including: neutrophil count decreased [severe AEs], white blood cell count decreased [severe AEs]): indication of lesser harm – extent: “major” ▫ Infections and infestations (severe AEs): hint of lesser harm – extent: “major” ▫ Metabolism and nutrition disorders (severe AEs): hint of lesser harm – extent: “minor”	Serious/severe side effects ▪ Respiratory, thoracic and mediastinal disorders (SAEs): hint of greater harm – extent: “minor”
Non-serious/non-severe side effects ▪ Gastrointestinal disorders (AEs): hint of lesser harm – extent: “considerable” ▪ Asthenia (AEs): hint of lesser harm – extent: “minor” ▪ Insomnia (AEs): hint of lesser harm – extent: “minor” ▪ Alopecia (AEs): indication of lesser harm – extent: “considerable”	–
No suitable data are available for the outcomes of symptoms, health status and health-related quality of life, as well as immune-related AEs.	
AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-LC13: Quality of Life Questionnaire-Lung Cancer 13; SAE: serious adverse event	

Overall, there are several positive and one negative effect of tislelizumab compared with docetaxel for outcomes in the morbidity and side effects categories. There are advantages particularly in the case of severe AEs, in some cases to a major extent. In addition, advantages in alopecia were shown both in non-serious/non-severe symptoms/late complications and in non-serious/non-severe side effects. However, there are still no suitable data for the outcomes in the categories of morbidity and health-related quality of life. Furthermore, there is still a lack of suitable data on immune-related AEs. Although no disadvantages are expected

to an extent that would completely call into question the positive effects, the extent of added benefit cannot be quantified due to the uncertainties or the lack of data on other outcomes.

In summary, there is a hint of a non-quantifiable added benefit of tislelizumab compared with the ACT for adult patients with locally advanced or metastatic NSCLC after prior platinum-based therapy, with PD-L1-negative tumours (PD-L1 expression < 1%).

No data are available to assess the added benefit of tislelizumab in comparison with the ACT specified by the G-BA for adult patients with locally advanced or metastatic NSCLC after prior platinum-based therapy with PD-L1-positive tumours (PD-L1 expression ≥ 1%). An added benefit of tislelizumab in comparison with the ACT is not proven for patients with PD-L1-positive tumours (PD-L1 expression ≥ 1%).

2.8 Summary

The data subsequently submitted by the company within the commenting procedure do not change the conclusion drawn in dossier assessment A24-128 on the added benefit of tislelizumab.

Table 4 below shows the result of the benefit assessment of tislelizumab, taking into account both dossier assessment A24-128 and this addendum.

Table 4: Tislelizumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with locally advanced or metastatic NSCLC after prior treatment with platinum-based chemotherapy; in addition, patients with EGFR-mutant or ALK-positive NSCLC should also have received targeted therapies before receiving tislelizumab[b]	▪ docetaxel (only for patients with PD-L1-negative tumours) or ▪ pemetrexed (only for patients with PD-L1-negative tumours and except in mainly squamous histology) or ▪ nivolumab or ▪ pembrolizumab (only for patients with PD-L1 expressing tumours, [TPS ≥ 1%]) or ▪ atezolizumab or ▪ docetaxel in combination with nintedanib (only for patients with PD-L1-negative tumours and adenocarcinoma histology)	▪ Patients with PD-L1-negative tumours[c]: hint of non-quantifiable added benefit[d] ▪ Patients with PD-L1-positive tumours[e]: added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. In accordance with the G-BA, it is assumed for the present therapeutic indication that patients have no medical indication for definitive local therapy. In addition, it is assumed that no (other) molecularly stratified therapy (directed against ALK, BRAF, EGFR, exon 20, HER2, KRAS G12C, METex14, RET or ROS1) is an option for the patients at the time of treatment with tislelizumab.
c. PD-L1 expression < 1%.
d. The RATIONALE 303 study included only patients with an ECOG-PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2. In addition, the study only included patients in the second or third line of treatment and patients who had not received targeted therapies against EGFR-mutant or ALK-positive NSCLC. Therefore, it also remains unclear whether the observed effects are transferable to patients in the fourth or later lines of treatment and patients who have already received targeted therapies against EGFR-mutant or ALK-positive NSCLC.
e. PD-L1 expression ≥ 1%.

ACT: appropriate comparator therapy; ALK: anaplastic lymphoma kinase; BRAF: rapidly accelerated fibrosarcoma – isoform B; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; KRAS: Kirsten rat sarcoma viral oncogene homologue; METex14: mesenchymal-epithelial transition factor gene exon 14; NSCLC: non-small cell lung cancer; PD-L1: programmed cell death ligand 1; RET: rearranged during transfection; ROS1: proto-oncogene tyrosine-protein kinase 1; TPS: Tumour Proportion Score

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Tislelizumab (NSCLC, ab Zweitlinie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2025 [Accessed: 07.05.2025]. URL: https://doi.org/10.60584/A24-128.

2. BeiGene Germany. Stellungnahme zum IQWiG-Bericht Nr. 1968: Tislelizumab (NSCLC, ab Zweitlinie); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1118/#beschluesse in the document "Zusammenfassende Dokumentation"].

3. BeiGene Germany. Anlage zur Stellungnahme zum IQWiG-Bericht Nr. 1968: Tislelizumab (NSCLC, ab Zweitlinie) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [unpublished]. 2025.

4. BeiGene Germany. Anlage zur Stellungnahme (Nachreichung nach mündlicher Anhörung) zum IQWiG-Bericht Nr. 1968: Tislelizumab (NSCLC, ab Zweitlinie) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/1118/#beschluesse in the document "Zusammenfassende Dokumentation"].

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6. Gemeinsamer Bundesausschuss. Tislelizumab (D-1126, D-1127, D-1128): mündliche Anhörung gemäß § 35 a Abs. 2 SGB V - stenografisches Wortprotokoll [online]. 2025 [Accessed: 20.05.2025]. URL: https://www.g-ba.de/downloads/91-1031-1118/2025-05-05_Wortprotokoll_Tislelizumab_D-1128.pdf.

7. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 02.09.2024]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

Appendix A Kaplan-Meier curves

A.1 Morbidity

A.1.1 Alopecia (EORTC QLQ-LC13)

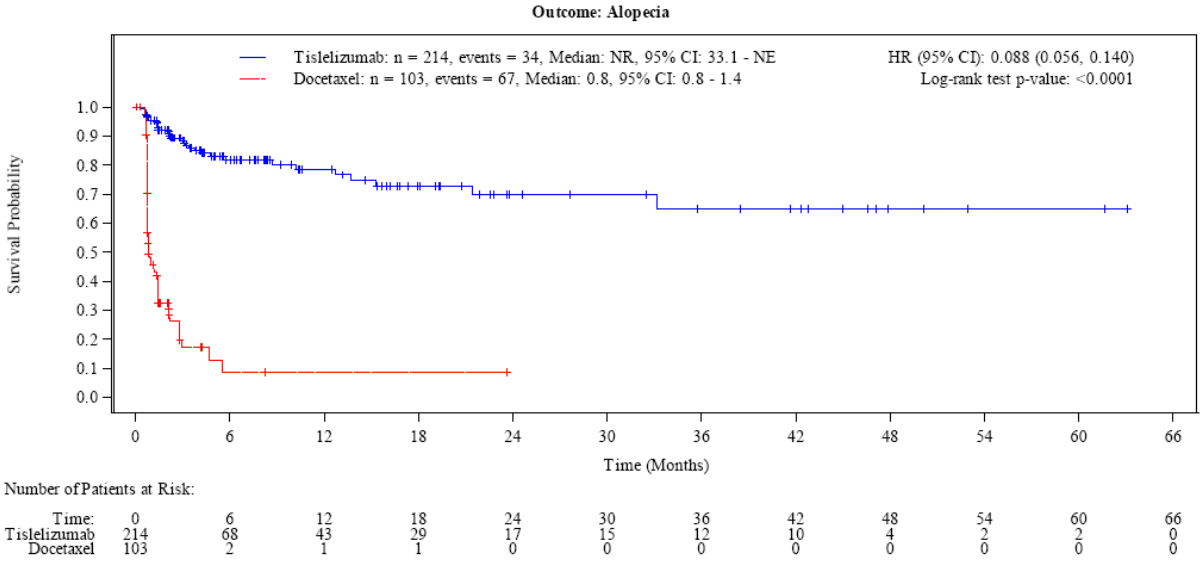

Figure 1: Kaplan-Meier curves for the outcome of alopecia (EORTC QLQ LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD L1 expression < 1%), 3rd data cut-off (18 January 2024)

Appendix B Kaplan-Meier curves presented as supplementary information

B.1 Morbidity

B.1.1 EORTC QLQ-C30

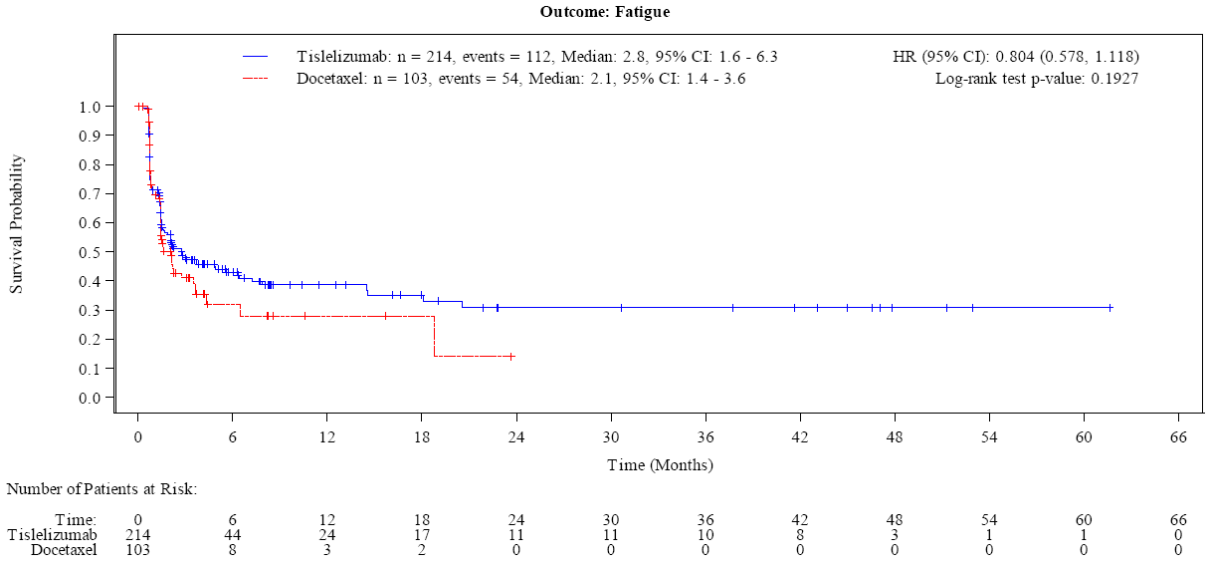

Figure 2: Kaplan-Meier curves for the outcome of fatigue (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

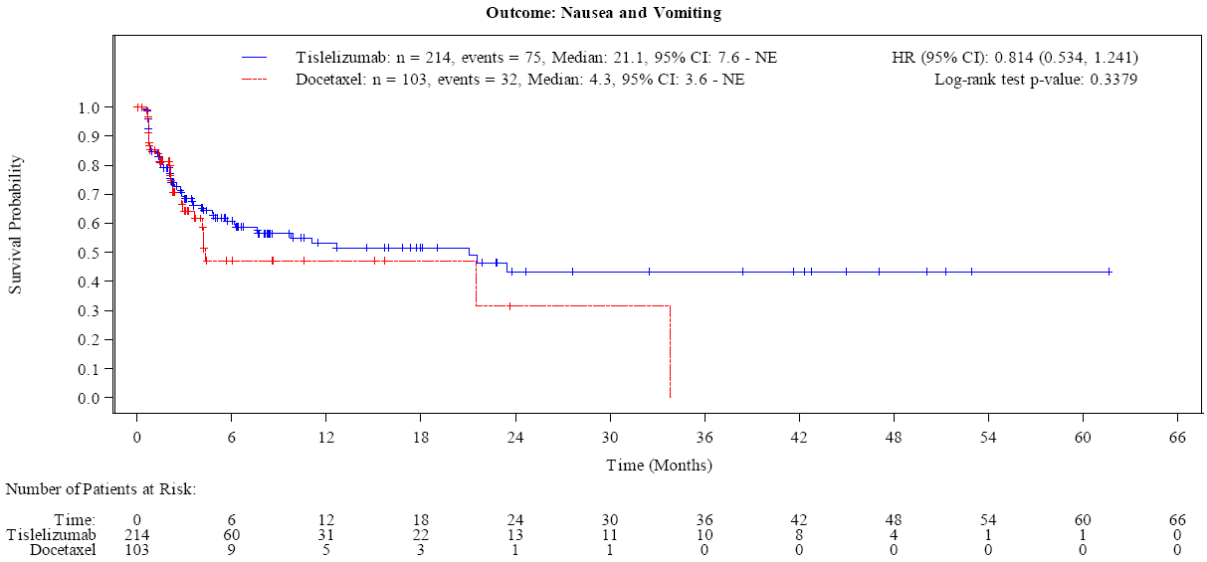

Figure 3: Kaplan-Meier curves for the outcome of nausea and vomiting (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

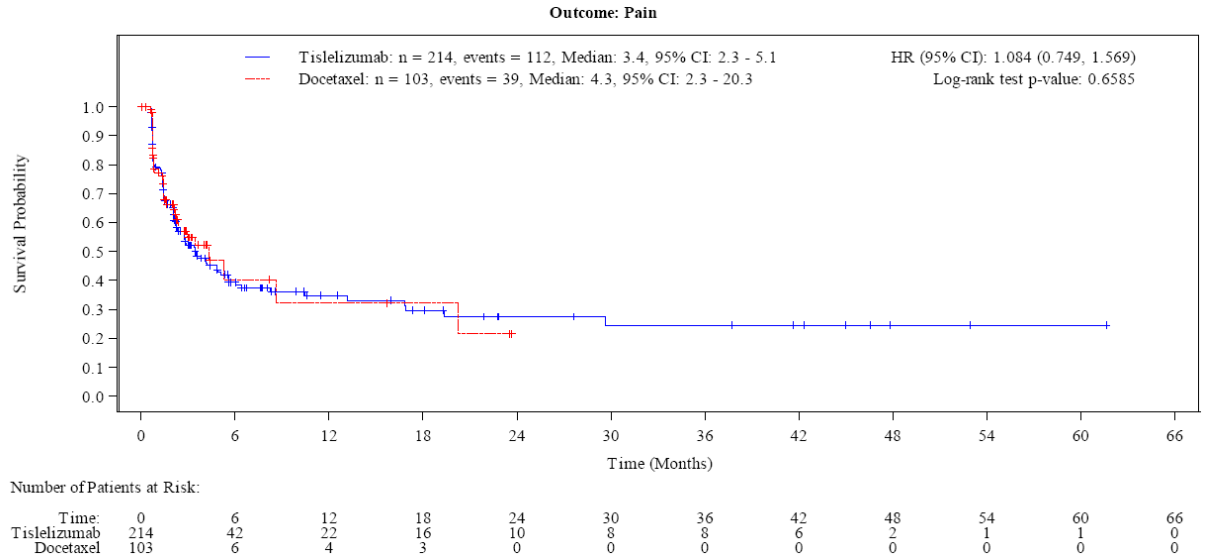

Figure 4: Kaplan-Meier curves for the outcome of pain (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

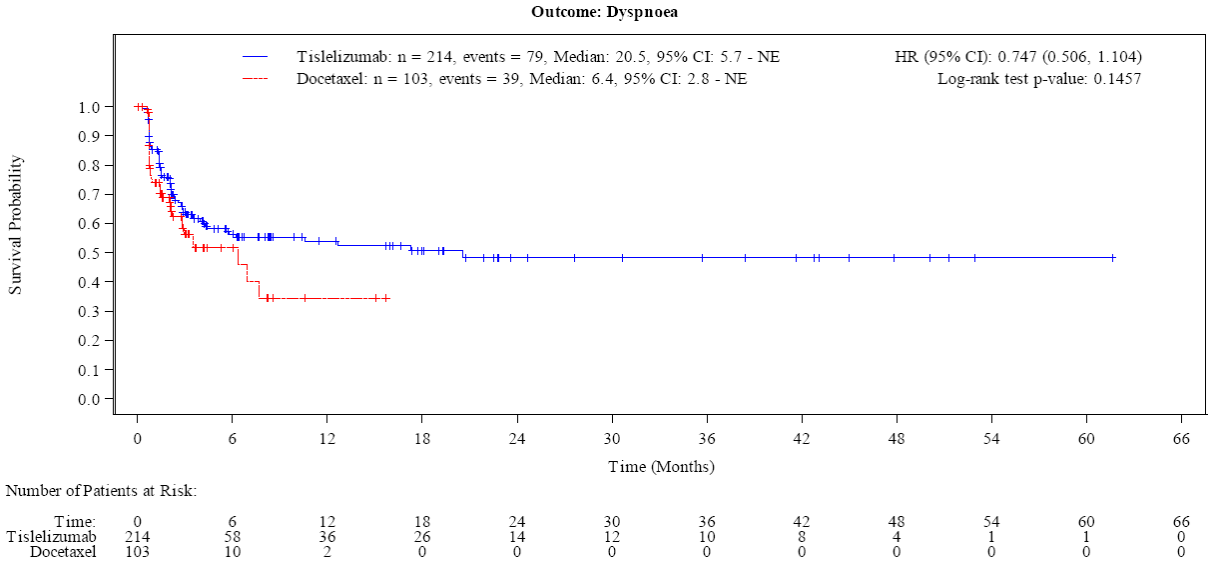

Figure 5: Kaplan-Meier curves for the outcome of dyspnoea (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

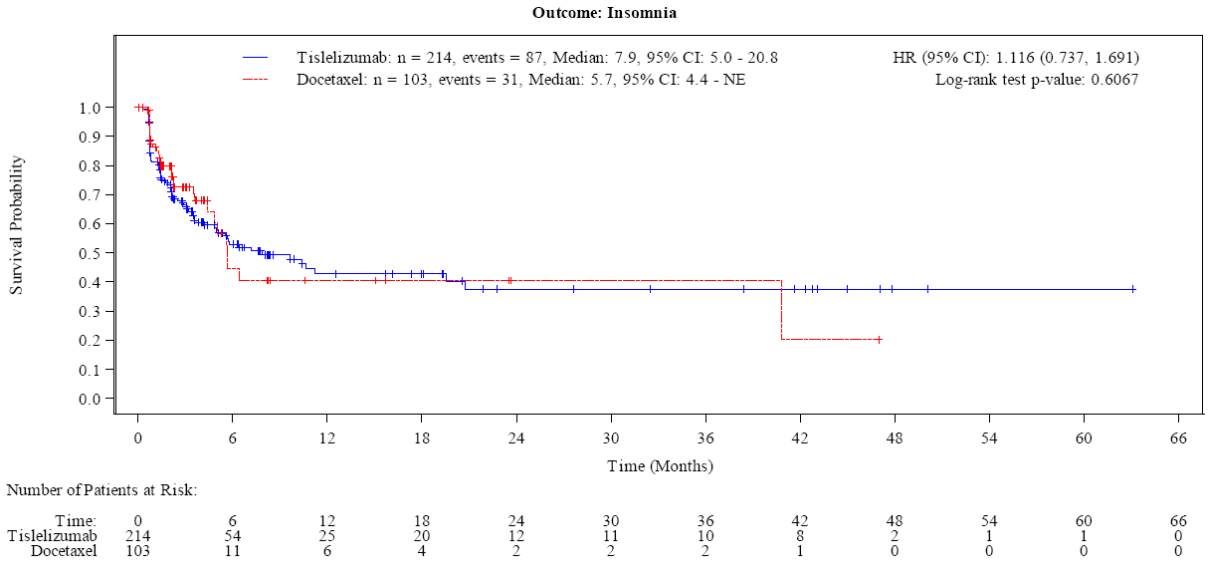

Figure 6: Kaplan-Meier curves for the outcome of insomnia (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

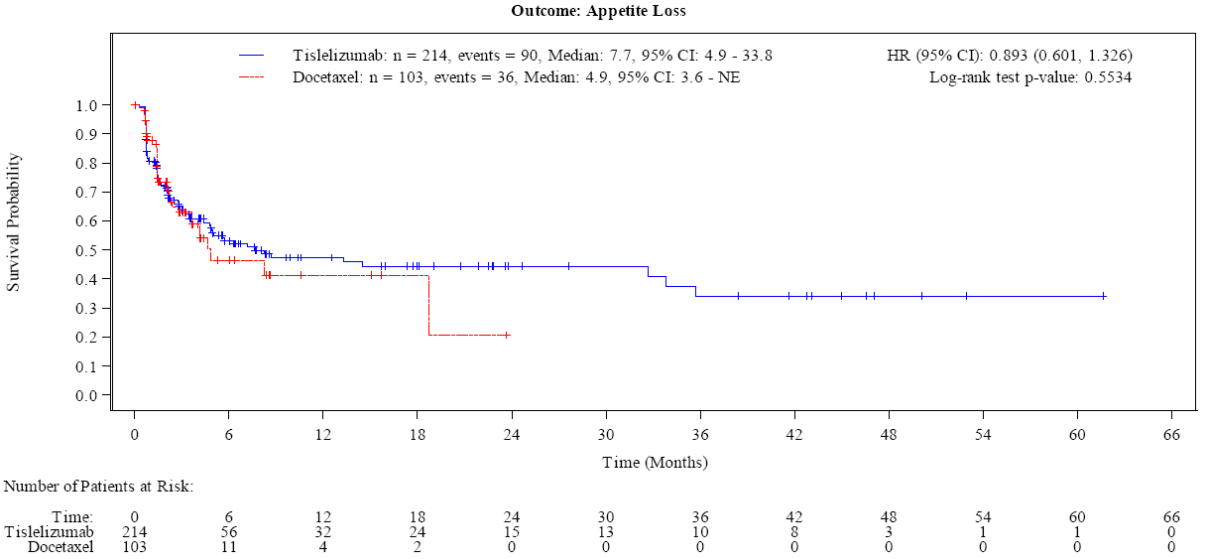

Figure 7: Kaplan-Meier curves for the outcome of appetite loss (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

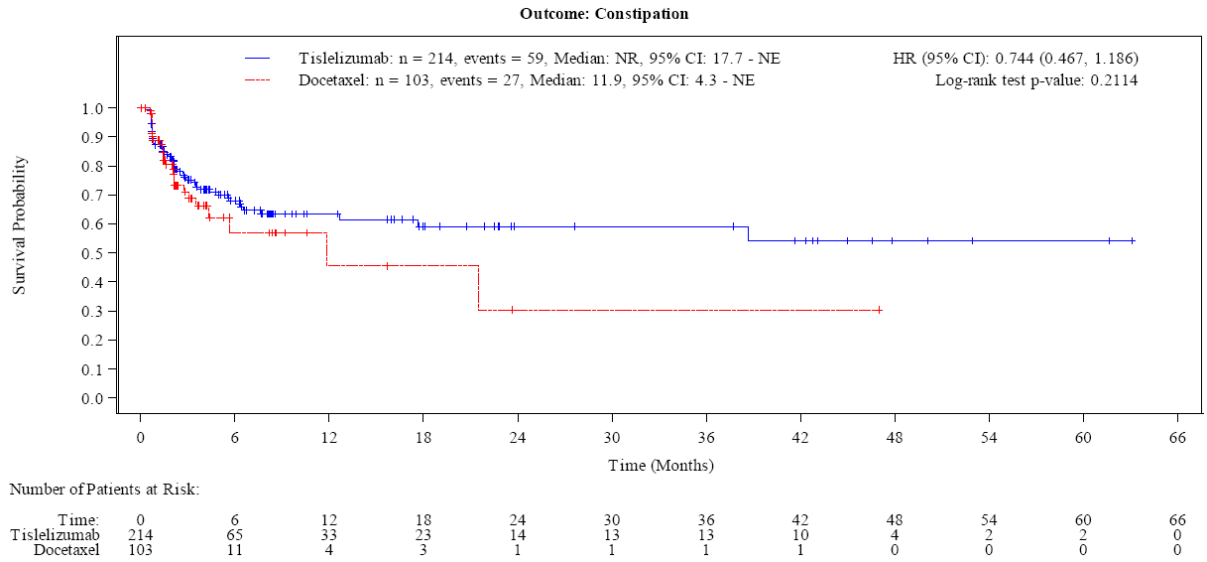

Figure 8: Kaplan-Meier curves for the outcome of constipation (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

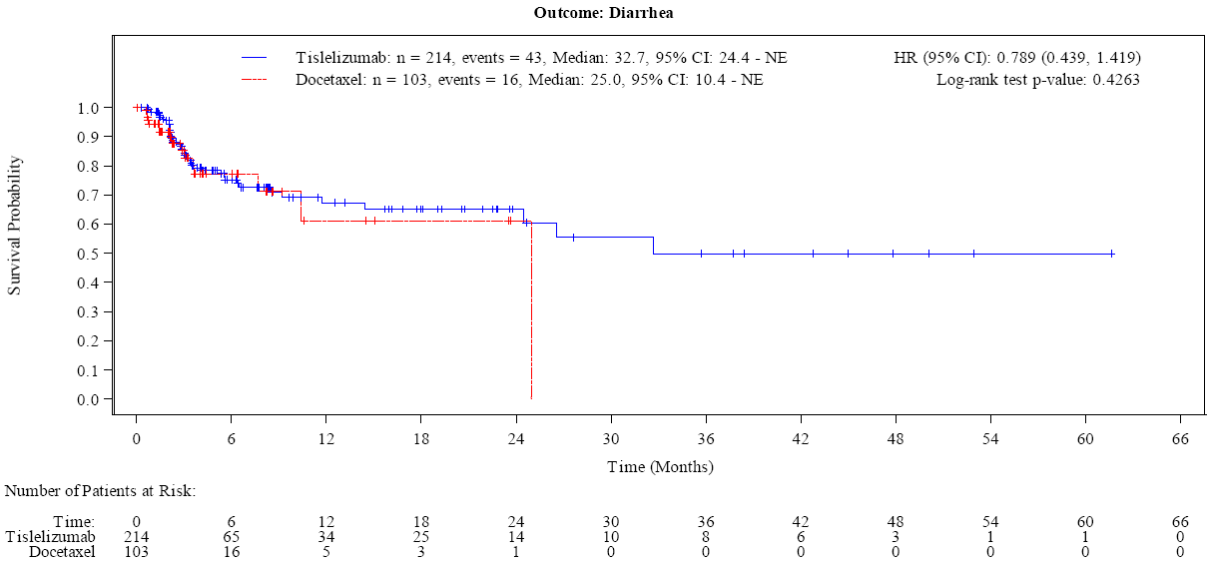

Figure 9: Kaplan-Meier curves for the outcome of diarrhoea (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

B.1.2 EORTC QLQ-LC13

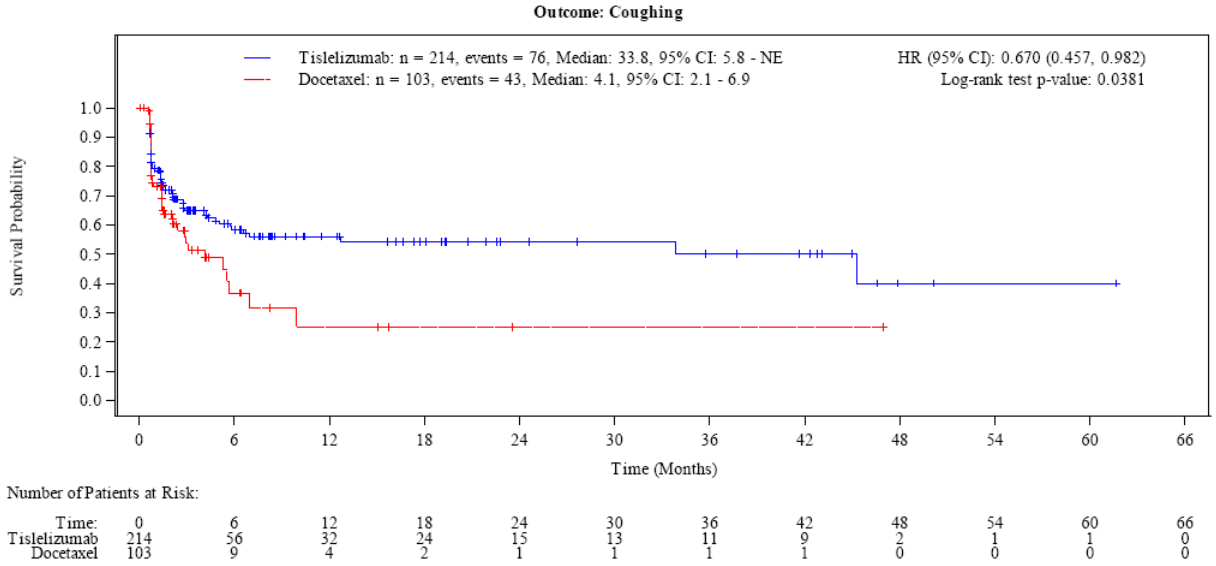

Figure 10: Kaplan-Meier curves for the outcome of cough (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

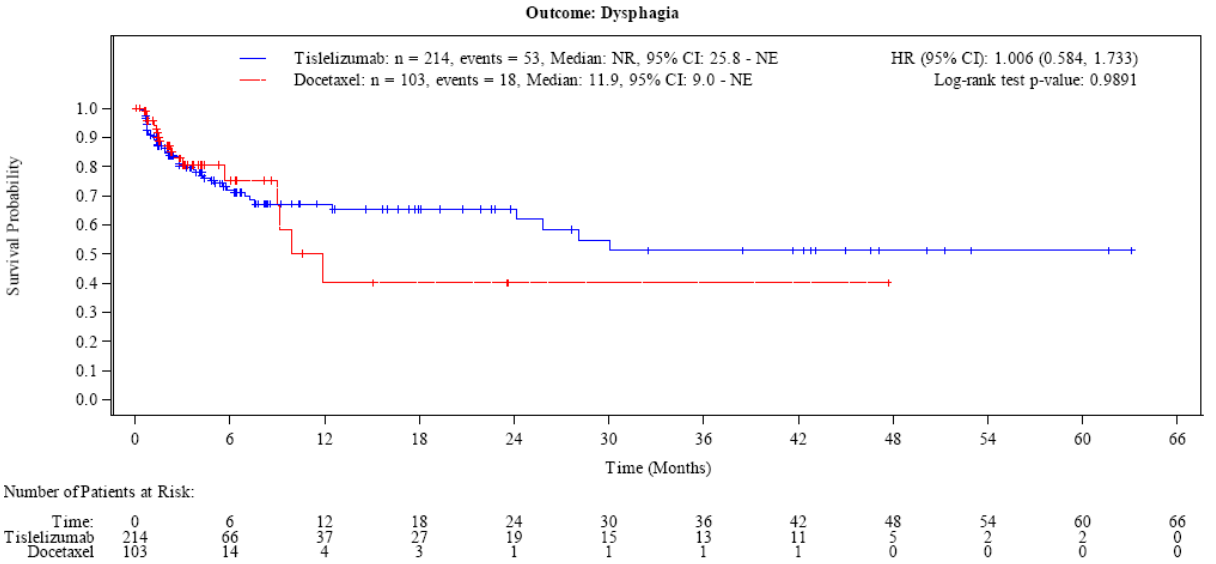

Figure 11: Kaplan-Meier curves for the outcome of dysphagia (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

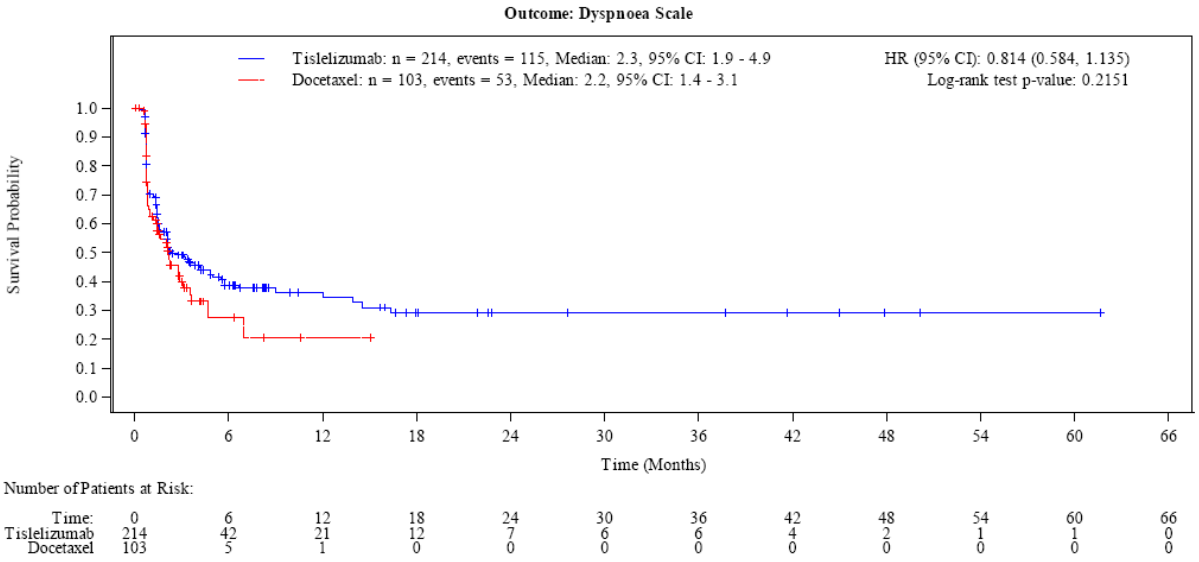

Figure 12: Kaplan-Meier curves for the outcome of dyspnoea (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

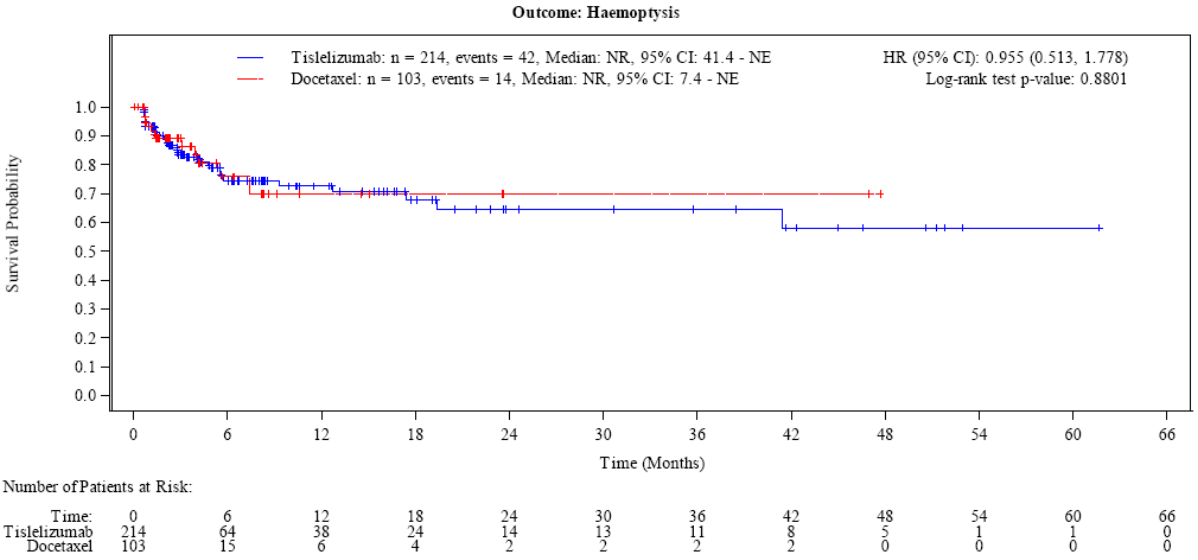

Figure 13: Kaplan-Meier curves for the outcome of haemoptysis (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

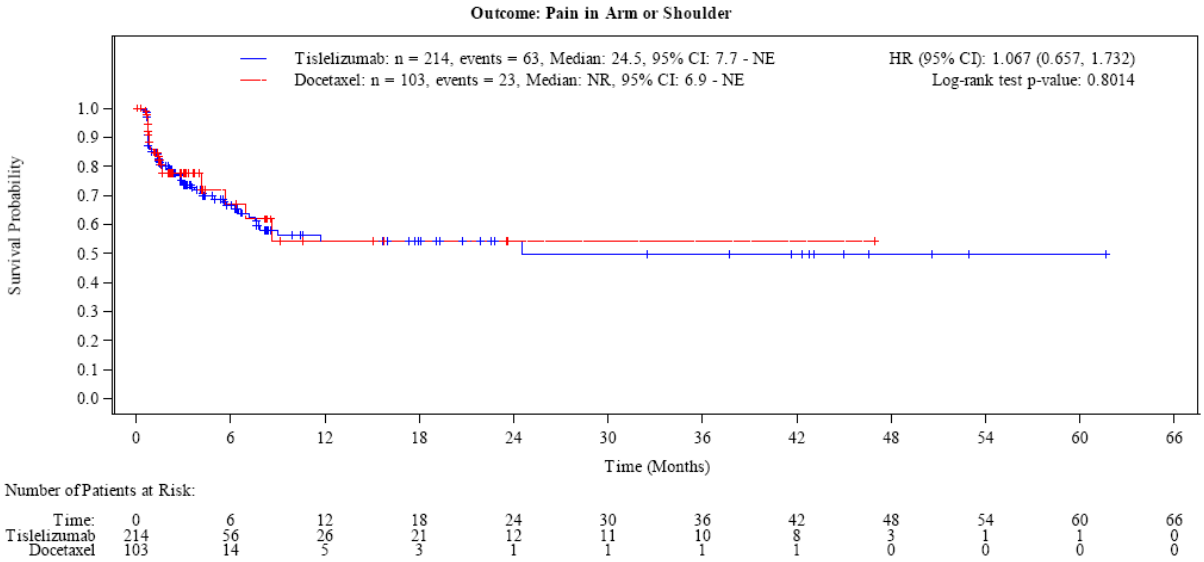

Figure 14: Kaplan-Meier curves for the outcome of pain (arm/shoulder) (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

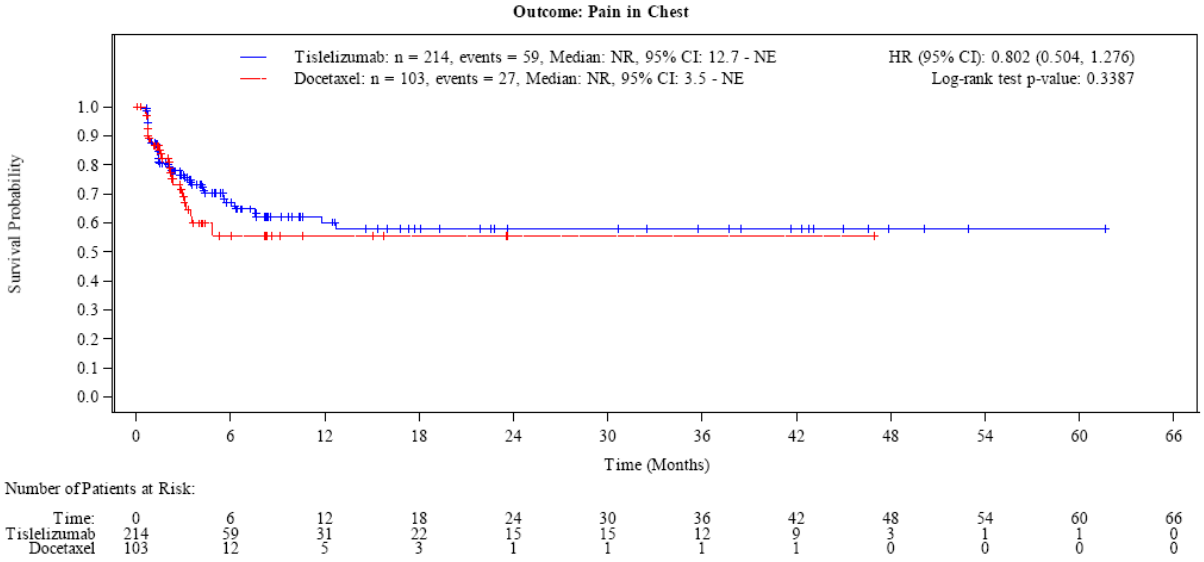

Figure 15: Kaplan-Meier curves for the outcome of pain (chest) (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

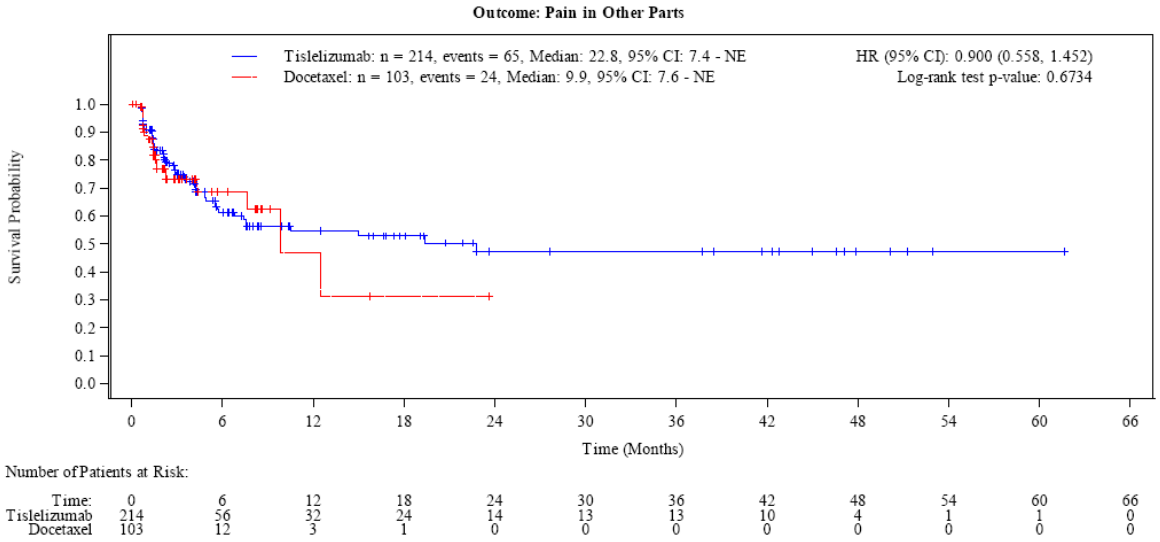

Figure 16: Kaplan-Meier curves for the outcome of pain (other) (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

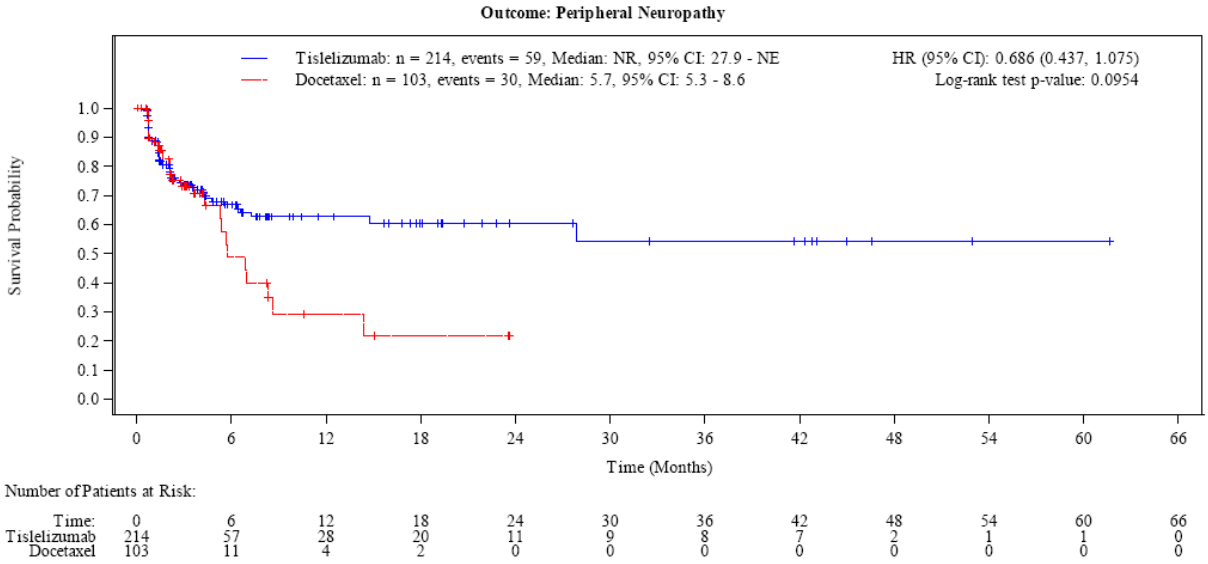

Figure 17: Kaplan-Meier curves for the outcome of peripheral neuropathy (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

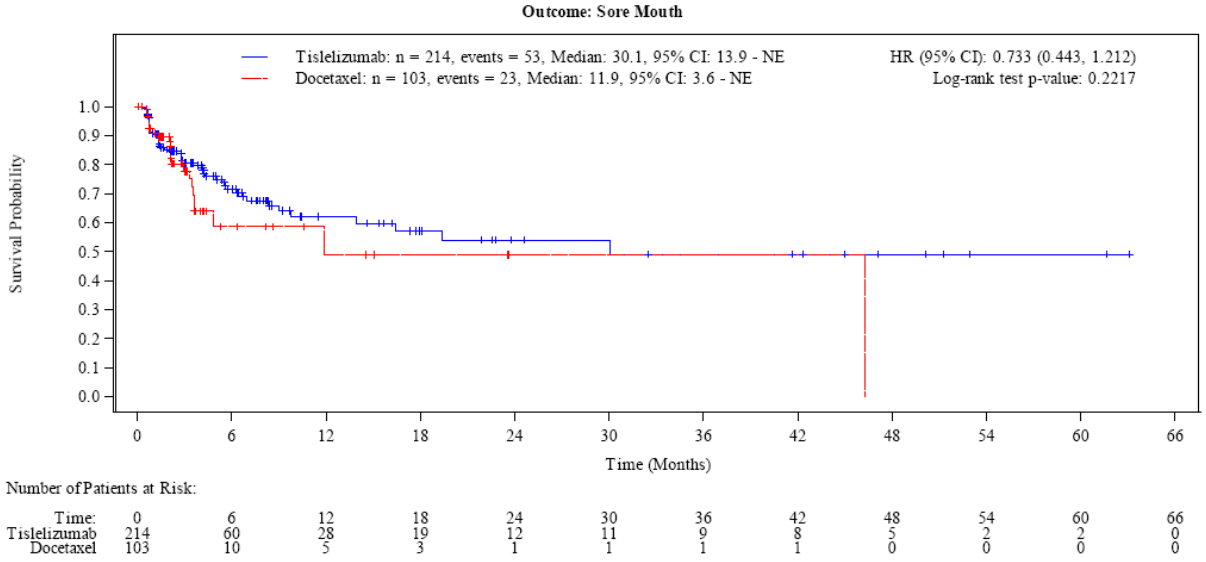

Figure 18: Kaplan-Meier curves for the outcome of oral pain (EORTC QLQ-LC13; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

B.1.3 Health status (EQ-5D VAS)

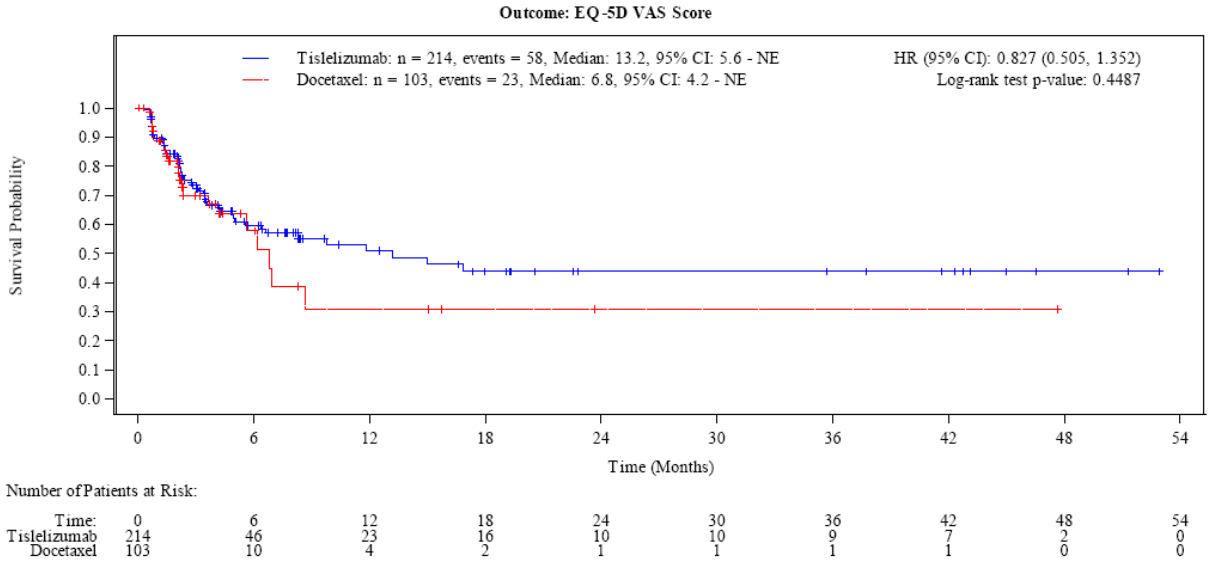

Figure 19: Kaplan-Meier curves for the outcome of health status (EQ-5D VAS; time to first deterioration by ≥ 15 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

B.2 Health-related quality of life

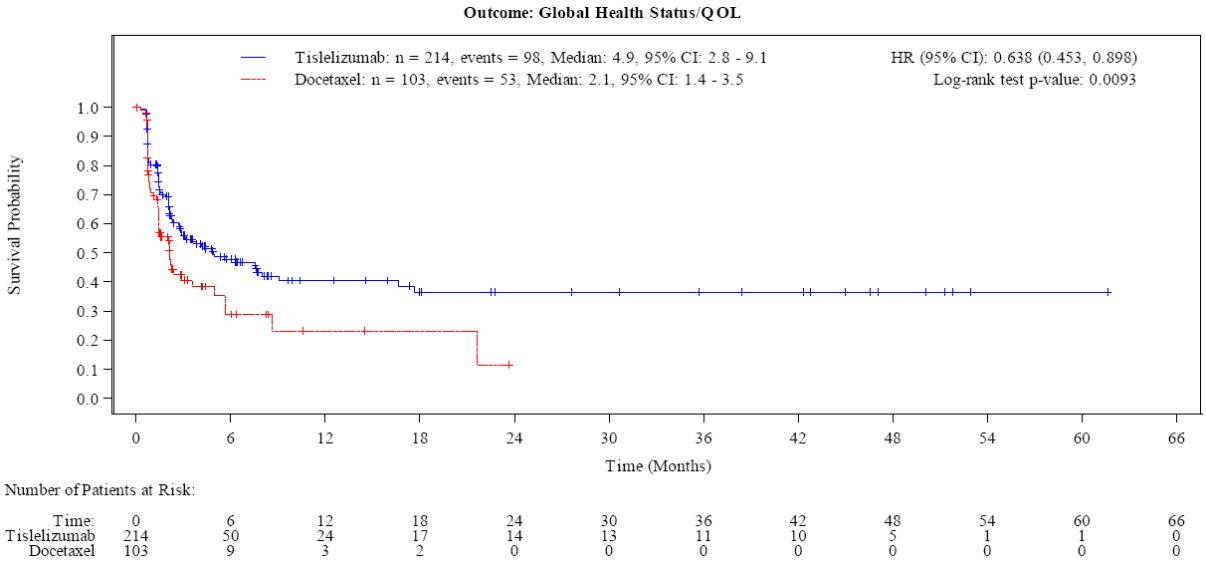

Figure 20: Kaplan-Meier curves for the outcome of global health status (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

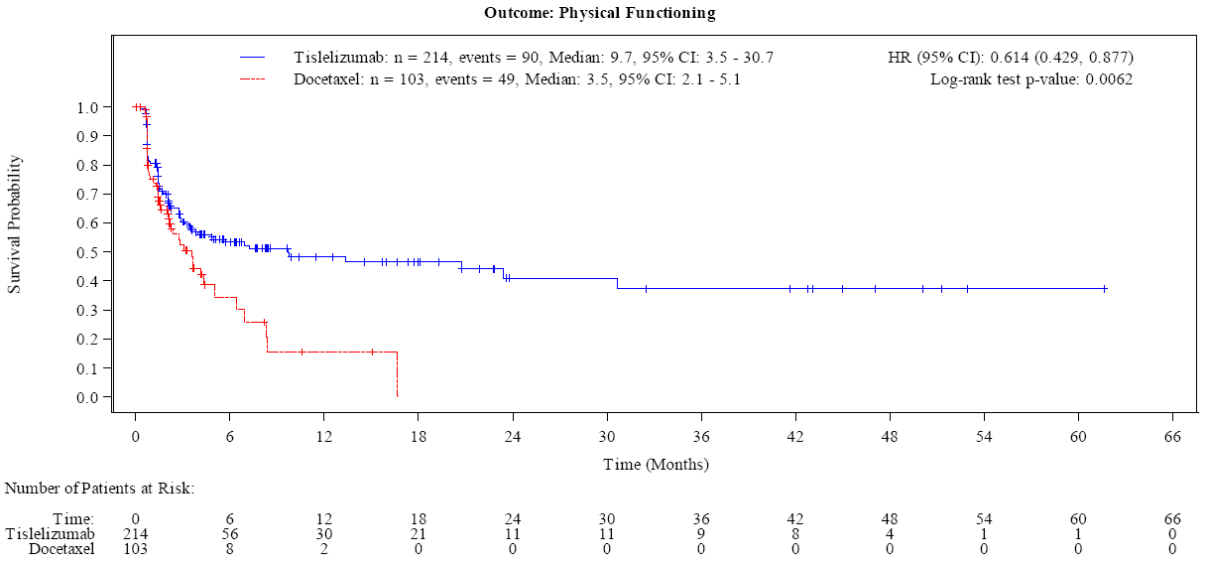

Figure 21: Kaplan-Meier curves for the outcome of physical functioning (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

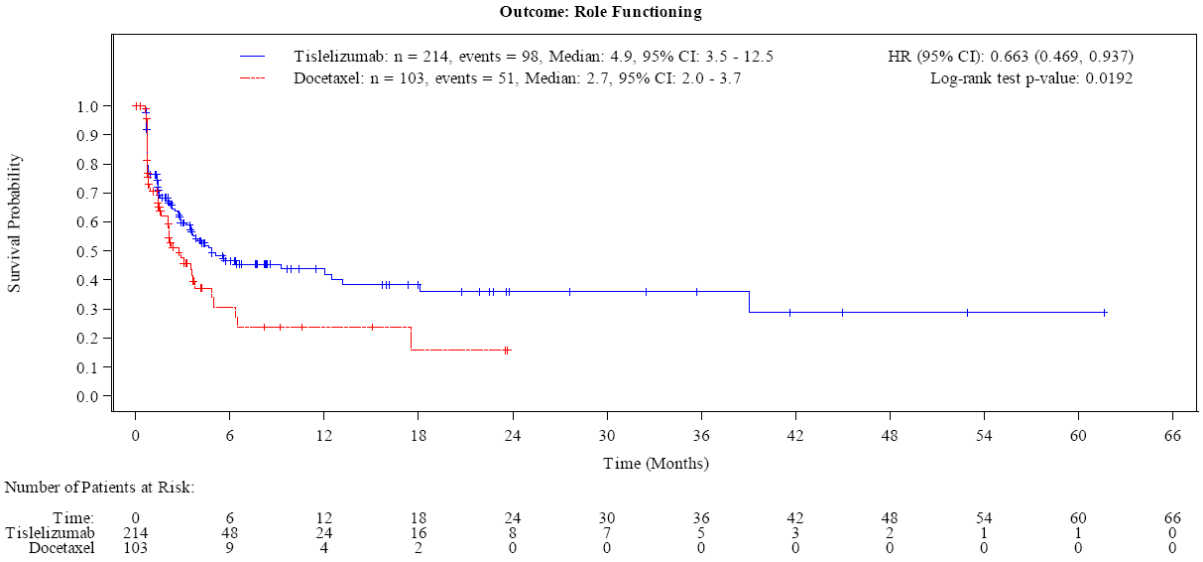

Figure 22: Kaplan-Meier curves for the outcome of role functioning (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

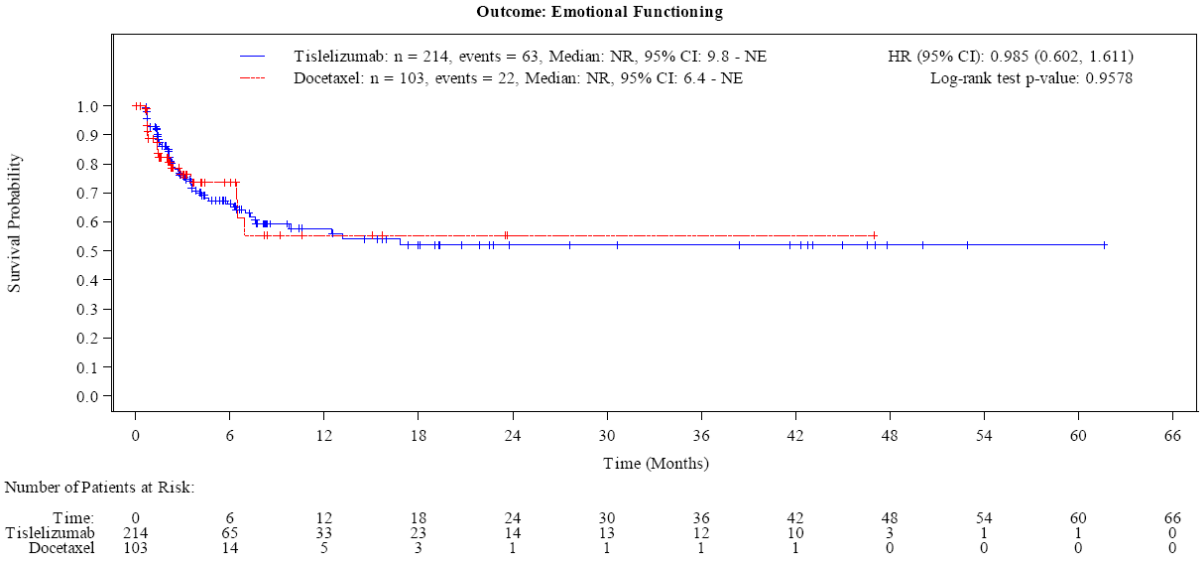

Figure 23: Kaplan-Meier curves for the outcome of emotional functioning (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

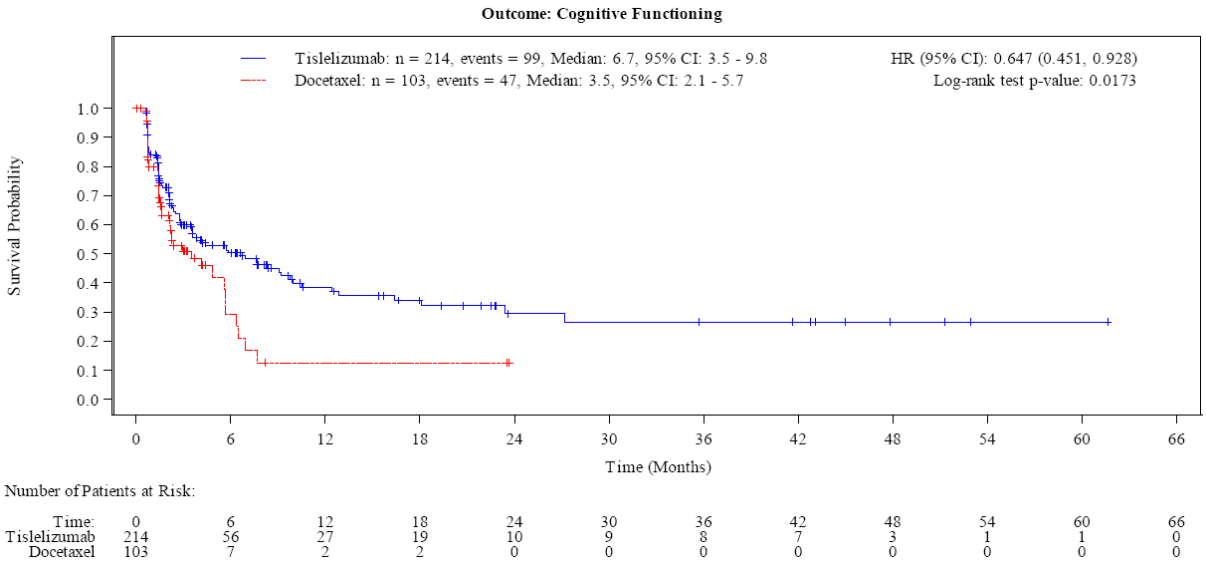

Figure 24: Kaplan-Meier curves for the outcome of cognitive functioning (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)

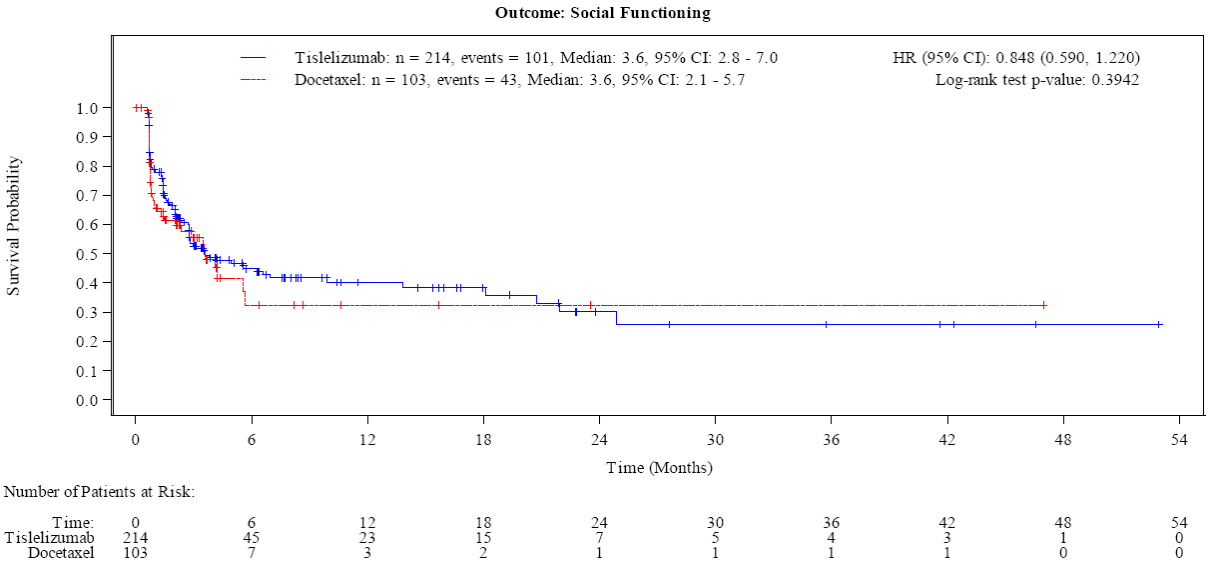

Figure 25: Kaplan-Meier curves for the outcome of social functioning (EORTC QLQ-C30; time to first deterioration by ≥ 10 points), RATIONALE 303, relevant subpopulation (PD-L1 expression < 1%), 3rd data cut-off (18 January 2024)