



IQWiG Reports – Commission No. A18-69

**Durvalumab  
(locally advanced,  
unresectable NSCLC) –**

**Benefit assessment according to §35a  
Social Code Book V<sup>1</sup>**

**Extract**

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<sup>1</sup> Translation of the executive summary of the dossier assessment *Durvalumab (lokal fortgeschrittenes, inoperables NSCLC) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 10 January 2019). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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## Executive summary of the benefit assessment

### Background

In accordance with §35a Social Code Book (SBG) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug durvalumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the “company”). The dossier was sent to IQWiG on 16 October 2018.

### Research question

This report aims to assess the added benefit of durvalumab in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in patients with locally advanced, inoperable, non-small cell lung cancer (NSCLC) whose tumours express programmed cell death ligand-1 (PD-L1) on  $\geq 1\%$  of tumour cells and whose disease did not progress following platinum-based chemoradiotherapy.

Table 2 presents the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2<sup>2</sup>: Research question of the benefit assessment of durvalumab

Indication	ACT <sup>a</sup>
Adults with locally advanced, inoperable NSCLC whose tumours express PD-L1 on $\geq 1\%$ of tumour cells and whose disease has not progressed following platinum-based chemoradiotherapy.	Best supportive care (BSC) <sup>b</sup>
a: Presentation of the ACT specified by the G-BA. b: BSC is defined as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; NSCLC: non-small-cell lung cancer; PD-L1: programmed cell death ligand 1	

The company followed the G-BA’s specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

## Results

### Study pool

The PACIFIC multicentre, double-blind, randomized trial, which compared durvalumab with placebo, was included in the benefit assessment. In both arms of the study, patients received concomitant BSC.

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<sup>2</sup> Table numbers start with “2” as numbering follows that of the full dossier assessment.

Included were adult patients with locally advanced, inoperable NSCLC (stage III according to the International Association for the Study of Lung Cancer [IASLC] Version 7) with no disease progression following definitive, combined, platinum-based chemoradiotherapy. In the study, 713 patients were randomized, 476 to the intervention arm and 237 to the comparator arm.

In both arms, treatment was initially administered until the maximum treatment duration (12 months) was reached. For patients who had disease progression during the follow-up period (only after completion of the 12-month treatment phase), it was possible to add a 2<sup>nd</sup> treatment phase for a maximum of 12 more months. Treatment was discontinued in case of disease progression, commencement of alternative antineoplastic therapy, occurrence of unacceptable toxicities, or withdrawal of consent.

The approval of durvalumab covers patients with locally advanced, inoperable NSCLC whose tumours express PD-L1 on  $\geq 1\%$  of tumour cells. In the PACIFIC study, information on PD-L1 status was available for only 451 (63%) of 713 patients. Among the 451 patients, 67.2% (n = 303) of patients had PD-L1 expression on  $\geq 1\%$  of tumour cells. The PACIFIC study's subpopulation which was relevant for this assessment (PD-L1 population: PD-L1 status  $\geq 1\%$ ) therefore comprises a total of 303 patients, 212 randomized to the durvalumab arm and 91 to the placebo arm.

The two primary outcomes of the PACIFIC study were progression-free survival (PFS) and overall survival. Patient-relevant secondary outcomes were symptoms, health-related quality of life, and adverse events (AEs).

### ***Limitations of the PACIFIC study***

The benefit assessment was based on the analyses of results for the PD-L1 population of the PACIFIC study. However, there were the following limitations:

- In the PACIFIC study, the G-BA's specified ACT of BSC was adequately implemented. In case of disease progression, however, various approved treatment options are available. The outcomes of morbidity, health-related quality of life, and adverse events were surveyed only for the period of treatment with the study drug (plus 30 or 90 days) or (for the questionnaires) until confirmed progression in case of treatment discontinuation before progression. Therefore, the data are incomplete regarding whether – and if so, which – patient-relevant events occurred under the respective follow-up treatments. This is considered problematic particularly because the type of follow-up therapies differs between treatment arms. It is unclear to what extent this systematic difference between treatment arms would also be reflected in continued care with follow-up therapies in the results on adverse events, morbidity, and health-related quality of life. To be able to draw a reliable conclusion over the entire study period or the time until patient death, these outcomes, like survival, would have to be surveyed and analysed over the entire period. Furthermore, given the different standards of care in the various countries of the international PACIFIC study, it is unclear whether all patients in the comparator arm had

access to PD-L1 therapies (as follow-up therapy). Furthermore, no information is available on the sequence or potential combination of follow-up treatment used in the two treatment arms.

- It is unclear whether patients in the PACIFIC study were classified as stage III in accordance with German or international guidelines. The omission of imaging methods in the PACIFIC study might result in patients being included in the study who already have metastases and therefore should be classified as stage IV. For stage IV patients, however, different approved treatment options are available, and therefore, a different ACT would apply.
- In the PACIFIC study, patients had to have received a total radiation dose of 54 Gy to 66 Gy as part of chemoradiotherapy before study inclusion. The German S3 guideline states, however, that patients (who are on combined chemoradiotherapy for stage III) should receive a total radiotherapy dose of 60 Gy to 66 Gy.

### ***Risk of bias***

The risk of bias on the study level was rated as low. The risk of bias on the outcome level was rated as high, except for the two outcomes of overall survival and discontinuation due to AEs.

### ***Certainty of conclusions***

The uncertainties arising in the PACIFIC study, particularly relating to the follow-up therapies (incomplete survey of outcomes, type and sequence of follow-up therapies, access to PD-L1 therapies, see Section 2.3.2 of the full report) led to a reduced certainty of conclusions. Therefore, on the basis of the effects shown in the PACIFIC study, at most hints, for example of added benefit, can be derived for all outcomes.

## **Results**

### ***Mortality***

#### ***Overall survival***

For the outcome of overall survival, a statistically significant effect in favour of durvalumab was found. This results in a hint of added benefit of durvalumab + BSC in comparison with BSC.

### ***Morbidity***

*Symptoms surveyed using the symptom scales and individual symptoms of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 (EORTC QLQ-LC13)*

For the symptom scales of the EORTC QLQ-C30, mean changes in dyspnoea and fatigue each exhibit a statistically significant difference to the disadvantage of durvalumab. A relevant effect cannot be derived for either dyspnoea or fatigue (using the standardized mean difference in the form of Hedges'  $g$ ). All things considered, for the symptom scales, there is consequently no

hint of an added benefit of durvalumab + BSC in comparison with BSC; an added benefit is therefore not proven for the symptoms overall.

*Health status surveyed with the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D) questionnaire*

For the outcome of health status as measured by the EQ-5D VAS, no statistically significant difference between treatment arms was found. For health status, there was therefore no hint of an added benefit of durvalumab + BSC in comparison with BSC; an added benefit is therefore not proven.

*Health-related quality of life as surveyed by global health status and the functional scales of EORTC QLQ-C30*

Health-related quality of life was surveyed through the functional scales of the EORTC QLQ-C30. No statistically significant difference between treatment arms was found. For health-related quality of life, this did not result in a hint of an added benefit of durvalumab + BSC in comparison with BSC; an added benefit is therefore not proven.

*Adverse events*

*Serious AEs (SAEs), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or 4)*

For each of the outcomes of SAEs and serious AEs (CTCAE grade 3 or 4), the event time analysis shows no statistically significant difference between treatment arms. For these outcomes, there was therefore no hint of greater or lesser harm from durvalumab + BSC in comparison with BSC; therefore, there is no proof of greater or lesser harm.

*Discontinuation due to AEs*

For the outcome of discontinuation due to AEs, the event time analysis shows a statistically significant difference to the disadvantage of durvalumab + BSC. It should be noted that 15 of the 36 treatment discontinuations in the durvalumab arm were due to pneumonitis (n = 10) or radiation pneumonitis (n = 5) (compared to only 1 and 2 respective treatment discontinuations in the control group). For the outcome of discontinuation due to AEs, this results in a hint of greater harm from durvalumab + BSC in comparison with BSC.

*Immune-mediated AEs*

For the outcome of immune-mediated AEs, the event time analysis showed a statistically significant effect to the disadvantage of durvalumab + BSC for severe AEs (CTCAE grade 3 or 4). For immune-mediated SAEs, the event time analysis did not reveal a statistically significant difference between treatment arms, but the effect estimate is comparable with the effect estimate for immune-mediated severe AEs, and it is likely that nearly the same results were included in the respective analyses. For immune-mediated AEs, this results overall in a hint of greater harm from durvalumab + BSC in comparison with BSC.

### *Pneumonitis*

For pneumonitis, analyses are available for the PT of pneumonitis and the PT of radiation pneumonitis. For the outcome of radiation pneumonitis (PT, AE), a statistically significant effect to the disadvantage of durvalumab was found (HR: 1.97 [1.04; 4.14];  $p = 0.036$ ). For pneumonitis (PT, AE), no statistically significant differences were found between the two treatment groups (HR: 1.80 [0.79; 4.84];  $p = 0.168$ ).

For the PTs of pneumonitis and radiation pneumonitis, no data were available for either of the categories of severe AEs and SAEs since they occurred at a frequency below the 5% limit specified by the company.

In general, a proper analysis of the outcome of pneumonitis requires a combined analysis of radiation pneumonitis (PT) and pneumonitis (PT) (each for AE, SAE, and severe SAE) since both of these PTs (as also stated by the company) are difficult (or impossible) to distinguish. Such a summary analysis of these two operationalizations was not found in the dossier.

### *Specific AEs*

For each of the outcomes of skin and subcutaneous tissue disorders (SOC, AE), cardiac disorders (SOC, SAE), as well as injury, poisoning, and procedural complications (SOC, AE), the event time analysis showed a statistically significant difference to the disadvantage of durvalumab + BSC in comparison with BSC. For each of these outcomes, this results in a hint of greater harm from durvalumab + BSC in comparison with BSC.

For the outcome of dizziness, the event time analysis shows a statistically significant difference in favour of durvalumab + BSC in comparison with BSC. For this outcome, this results in a hint of lesser harm from durvalumab + BSC in comparison with BSC. An effect modification by the attribute of sex was found. For the outcome of dizziness, for men, there is a hint of lesser harm from durvalumab + BSC in comparison with BSC, while for women, there is no hint of greater or lesser harm from durvalumab + BSC in comparison with BSC.

## **Probability and extent of added benefit, patient groups with therapeutically important added benefit<sup>3</sup>**

On the basis of the results presented, the probability and extent of added benefit of the drug durvalumab in comparison with the ACT is assessed as follows:

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<sup>3</sup> On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

All things considered, regarding positive effects, there is a hint of considerable added benefit for the outcome of overall survival and, for men only, a hint of considerable added benefit for the outcome of dizziness (category of non-serious/non-severe adverse events).

Regarding negative effects, on the other hand, there are 2 hints (of minor and non-quantifiable extent) of greater harm in the category of serious/severe adverse events. In addition, there are 3 hints of greater harm in the category of non-serious/non-severe adverse events, each of considerable extent.

Overall, the negative effects reduce the extent of added benefit. In summary, for patients with locally advanced, inoperable NSCLC whose tumours express PD-L1 on  $\geq 1\%$  of tumour cells and who had no disease progression after platinum-based chemoradiotherapy, there is a hint of considerable added benefit of durvalumab in comparison with the ACT of BSC.

Table 3 presents a summary of the probability and extent of added benefit of durvalumab.

Table 3: Durvalumab – probability and extent of added benefit

Indication	ACT <sup>a</sup>	Probability and extent of added benefit <sup>b</sup>
Adults with locally advanced, inoperable NSCLC whose tumours express PD-L1 on $\geq 1\%$ of tumour cells and whose disease has not progressed after platinum-based chemotherapy.	Best supportive care (BSC) <sup>c</sup>	Hint of considerable added benefit
<p>a: Presentation of the respective ACT specified by the G-BA.  b: Patients with a WHO-PS of 0 or 1 were included in the relevant study. It remains unclear whether the observed effects translate to patients with WHO-PS &gt; 1.  c: BSC is defined as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.  ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee; NSCLC: non-small-cell lung cancer; PD-L1: programmed cell death ligand 1; WHO-PS: World Health Organization Performance Status</p>		

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

**Note:**

An addendum (A19-21) to dossier assessment A18-69 has been published.

### References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 4 June 2018]. URL: [https://www.iqwig.de/download/General-Methods\\_Version-5-0.pdf](https://www.iqwig.de/download/General-Methods_Version-5-0.pdf).
2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. *Biom J* 2015; 58(1): 43-58

*The full report (German version) is published under <https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-69-durvalumab-non-small-cell-lung-cancer-benefit-assessment-according-to-35a-social-code-book-v.10758.html>.*