

# **Pembrolizumab**

## **(head and neck squamous cell carcinoma, neoadjuvant and adjuvant)**

Benefit assessment according to §35a SGB V<sup>1</sup>

A decorative horizontal bar composed of 18 squares of varying shades of blue and grey. The word 'EXTRACT' is centered in a dark blue box that spans the width of the bar.

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**Patient and family involvement**

No feedback was received within the framework of this dossier assessment.

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## **Part I: Benefit assessment**

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# I List of abbreviations

| Abbreviation    | Meaning                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|
| ACT             | appropriate comparator therapy                                                                                            |
| AE              | adverse event                                                                                                             |
| BICR            | blinded independent central review                                                                                        |
| CPS             | Combined Positive Score                                                                                                   |
| CTCAE           | Common Terminology Criteria for Adverse Events                                                                            |
| ECOG PS         | Eastern Cooperative Oncology Group Performance Status                                                                     |
| EFS             | event-free survival                                                                                                       |
| EORTC QLQ-C30   | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30                          |
| EORTC QLQ-H&N35 | Quality of Life Questionnaire-Head and Neck Cancer 35                                                                     |
| G-BA            | Gemeinsamer Bundesausschuss (Federal Joint Committee)                                                                     |
| IQWiG           | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen<br>(Institute for Quality and Efficiency in Health Care) |
| PD-L1           | programmed death-ligand 1                                                                                                 |
| RCT             | randomized controlled trial                                                                                               |
| SAE             | serious adverse event                                                                                                     |
| SGB             | Sozialgesetzbuch (Social Code Book)                                                                                       |
| SmPC            | Summary of Product Characteristics                                                                                        |
| TPS             | Tumour Proportion Score                                                                                                   |

## **I 1 Executive summary of the benefit assessment**

### **Background**

In accordance with § 35a Social Code Book 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 pembrolizumab for neoadjuvant therapy followed by adjuvant therapy in combination with radiotherapy with or without cisplatin and then as monotherapy. 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 24 November 2025.

### **Research question**

The aim of this report is to assess the added benefit of pembrolizumab as monotherapy for neoadjuvant treatment and subsequently for adjuvant treatment in combination with radiotherapy, with or without concomitant cisplatin therapy, and subsequently as monotherapy, in comparison with the appropriate comparator therapy (ACT) in adult patients with resectable locally advanced head and neck squamous cell carcinoma whose tumours express programmed death-ligand 1 (PD-L1) (Combined Positive Score [CPS  $\geq$  1]).

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of pembrolizumab

| Research question                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Therapeutic indication                                                                                                                                                       | ACT <sup>a</sup>                                                                                                                                                                                                                                                                                                                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Adult patients with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS $\geq 1$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                            |
| 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | With a high postoperative risk profile for whom cisplatin-based therapy is suitable, or with a low postoperative risk profile; neoadjuvant and adjuvant therapy <sup>b</sup> | A therapy regimen consisting of <ul style="list-style-type: none"> <li>▪ surgery (tumour resection)</li> <li>▪ followed by individualized treatment, choosing from<sup>c, d</sup>: <ul style="list-style-type: none"> <li>▫ adjuvant chemoradiotherapy with cisplatin and</li> <li>▫ adjuvant radiotherapy</li> </ul> </li> </ul>                          |
| 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | With a high postoperative risk profile for whom cisplatin-based therapy is not suitable; neoadjuvant and adjuvant therapy <sup>b</sup>                                       | A therapy regimen consisting of <ul style="list-style-type: none"> <li>▪ surgery (tumour resection)</li> <li>▪ followed by adjuvant chemoradiotherapy with: <ul style="list-style-type: none"> <li>▫ mitomycin + 5-fluorouracil (5-FU)<sup>e</sup> or</li> <li>▫ carboplatin + 5-FU<sup>e</sup> or</li> <li>▫ docetaxel<sup>e</sup></li> </ul> </li> </ul> |
| <p>a. Presented is the respective ACT specified by the G-BA.</p> <p>b. For this therapeutic indication, it is assumed that the term 'locally advanced disease' covers stage III–IVA tumours.</p> <p>c. The treatment decision is made under particular consideration of the post-operative risk profile.</p> <p>d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study).</p> <p>e. In this therapeutic indication, the drugs carboplatin, cetuximab and bleomycin are approved for use as adjuvant treatment in patients with a high postoperative risk profile for whom cisplatin-based therapy is not suitable. According to the G-BA, these are either not recommended in the guideline or are recommended in a different combination. Instead, the guideline recommends mitomycin + 5-FU or carboplatin + 5-FU or docetaxel. The G-BA therefore assumes that, according to the generally accepted current state of medical knowledge, the off-label use of mitomycin + 5-FU or carboplatin + 5-FU or docetaxel is generally to be preferred to the drugs approved so far for this therapeutic indication for patients with a high postoperative risk profile for whom cisplatin-based therapy is not suitable (§6(2), sentence 3, number 3, AM-NutzenV).</p> <p>5-FU: 5-fluorouracil; ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; Pharmaceutical Directive; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death-ligand 1</p> |                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                            |

For research question 1 (adult patients with a high postoperative risk profile for whom cisplatin-based therapy is suitable, or with a low postoperative risk profile), the company followed the G-BA's definition of the ACT.

The company did not address research question 2 (adult patients with a high postoperative risk profile for whom cisplatin-based therapy is not suitable). The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit. This concurred with the company's inclusion criteria.

**Research question 1: adult patients with a high postoperative risk profile for whom cisplatin-based therapy is suitable, or with a low postoperative risk profile.*****Study pool and study design***

The KEYNOTE 689 study was included in the benefit assessment for research question 1. KEYNOTE 689 is an ongoing, open-label RCT comparing pembrolizumab as neoadjuvant therapy and as postoperative adjuvant therapy in combination with radiotherapy, with or without concomitant cisplatin therapy followed by pembrolizumab as monotherapy, against postoperative adjuvant radiotherapy with or without concomitant cisplatin therapy in adult patients with resectable, locally advanced head and neck squamous cell carcinoma.

The study included adult patients with histologically confirmed, newly diagnosed, resectable, locally advanced head and neck squamous cell carcinoma. In this case, either

- a p16-positive stage III oropharyngeal carcinoma, or
- a p16-negative stage III or IVA oropharyngeal carcinoma, or
- a stage III or IVA squamous cell carcinoma of the larynx, hypopharynx or oral cavity

had to be present.

The subpopulation of patients with PD-L1-expressing tumours with CPS  $\geq 1$  (N = 347 vs. N = 335) is relevant for the benefit assessment.

Patients in the intervention arm of the KEYNOTE 689 study initially received neoadjuvant treatment with two cycles of pembrolizumab following randomization. This was followed by the surgery. This was to take place 6 weeks ( $\pm 10$  days) after randomization. In the comparator arm, patients should undergo surgery within 4 weeks of randomization.

Following the surgery, the risk of postoperative recurrence was rated as high or low on the basis of pathological findings. This categorisation was based on an assessment of the surgically resected samples of the primary tumour and the cervical lymph nodes. A high risk of postoperative recurrence is defined as extranodal extension and/or positive resection margins ( $< 1$  mm); otherwise, a low risk of postoperative recurrence has been determined. Patients with a high risk of postoperative recurrence received adjuvant radiotherapy in combination with cisplatin and, in the intervention arm, these patients additionally received pembrolizumab for a maximum of 15 cycles. Patients with a low risk of postoperative recurrence received adjuvant radiotherapy and, in the intervention arm, these patients additionally received pembrolizumab for a maximum of 15 cycles. For patients in both study arms, adjuvant therapy was to be initiated within 6 weeks of surgery.

Primary outcome of the KEYNOTE 689 study was event-free survival (EFS). Patient-relevant secondary outcomes were overall survival as well as outcomes from the categories of morbidity, health-related quality of life, and side effects.

KEYNOTE 689 is an ongoing study. Relevant for this benefit assessment are the results of the data cut of 25 July 2024, based on the prespecified first interim analysis following approximately 207 events for the outcome EFS in patients whose tumours express PD-L1 with a CPS  $\geq 10$ .

***Implementation of the individualized therapy in the adjuvant treatment phase – definition of a high risk of postoperative recurrence in the KEYNOTE 689 study deviates from guideline recommendations***

In accordance with the specification of the ACT, the treatment decision between adjuvant chemoradiotherapy with cisplatin and adjuvant radiotherapy should be made on an individual basis. The decision regarding adjuvant therapy with cisplatin in addition to radiotherapy following tumour resection particularly depends on the risk of postoperative recurrence.

In the KEYNOTE 689 study, the decision to administer adjuvant therapy with cisplatin in addition to adjuvant radiotherapy was based on postoperative risk and thus in accordance with the requirements for the ACT. In this context, a high postoperative risk is defined as positive resection margins ( $< 1$  mm in the primary resection sample) or extranodal extension of the squamous cell carcinoma beyond the lymph node capsule. This definition deviates from the current guideline recommendations. The S3 guidelines on oral cavity cancer and oropharyngeal and hypopharyngeal cancer recommend adjuvant cisplatin therapy not only in cases of extranodal extension, but also where the resection margin in the primary resection sample is  $< 5$  mm.

This deviation affects the proportion of patients in the KEYNOTE 689 study who receive adjuvant treatment with cisplatin. It must be assumed that some of the patients in the KEYNOTE 689 study were not treated in accordance with the guideline recommendations and were therefore potentially undertreated. This applies in particular to the comparator arm, as these patients received no study medication other than radiotherapy. This aspect limits the transferability of the study results to the German health care context and is taken into account in the assessment of the certainty of conclusions.

***Risk of bias***

The risk of bias across outcomes for the KEYNOTE 689 study was rated as low.

There is a high risk of bias in the results for the outcome overall survival, as selective reporting for cannot be ruled out this outcome. The risk of bias for the results of the outcomes of the category of side effects was also rated as high. There is a large difference between the study

arms (> 5 percentage points) regarding the proportion of patients who were not considered in the analysis. Moreover, there are incomplete observations for potentially informative reasons with different observation periods. Furthermore, in some cases, selective reporting cannot be ruled out. As far as the results for the outcome discontinuation due to adverse events are concerned, the high risk of bias is also due to the lack of blinding in subjective recording of outcomes.

### ***Summary assessment of the certainty of conclusions***

It remains unclear whether the results of the KEYNOTE 689 study can be transferred to the German health care context without any restrictions. This is because the definition of a high risk of postoperative recurrence used in the study deviates from the valid guidelines in Germany. Based on the KEYNOTE 689 study, at most hints, e.g. of an added benefit, can therefore be derived for all presented outcomes, irrespective of the risk of bias.

## ***Results***

### ***Mortality***

A statistically significant difference in favour of pembrolizumab was shown between the study arms for the outcome overall survival. There is a hint of added benefit of pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy with or without ( $\pm$ ) cisplatin (adjuvant), followed by pembrolizumab as monotherapy over the ACT.

### ***Morbidity***

#### **Failure of curative treatment**

No suitable data were available for the outcome of failure of the curative treatment approach. There is no hint of added benefit of pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy  $\pm$  cisplatin (adjuvant), followed by pembrolizumab as monotherapy over the ACT; an added benefit is therefore not proven.

#### **Symptoms (EORTC QLQ-C30 and EORTC QLQ-H&N35)**

No suitable data were available for the outcomes on symptoms recorded with the scales 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 35-Item Quality of Life Questionnaire for head and neck cancer patients (EORTC QLQ-H&N35E). There is no hint of added benefit of pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy  $\pm$  cisplatin (adjuvant), followed by pembrolizumab as monotherapy over the ACT; an added benefit is therefore not proven.

#### **Health status (EQ-5D VAS)**

No suitable data were available for the outcome health status recorded using EQ-5D VAS. There is no hint of added benefit of pembrolizumab (neoadjuvant) + pembrolizumab and

radiotherapy ± cisplatin (adjuvant), followed by pembrolizumab as monotherapy over the ACT; an added benefit is therefore not proven.

#### *Health-related quality of life*

##### EORTC QLQ-C30 and EORTC QLQ-H&N35

No suitable data were available for the outcomes on health-related quality of life recorded with the scales of the EORTC QLQ-C30 and the EORTC QLQ-H&N35E. There is no hint of added benefit of pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy ± cisplatin (adjuvant), followed by pembrolizumab as monotherapy over the ACT; an added benefit is therefore not proven.

#### *Side effects*

##### Serious adverse events (SAEs)

The event time analyses showed no statistically significant difference between the study arms for the outcome SAEs. It is notable that the Kaplan-Meier curves cross each other. Consequently, the assumption of proportional hazards is not met and the hazard ratio cannot be interpreted. However, given the different follow-up durations between the treatment arms (longer follow-up in the intervention arm), there were significantly more events in the intervention arm than in the comparator arm (49.6% vs. 37.3%). Consequently, a possible disadvantage of pembrolizumab cannot be ruled out with sufficient certainty.

Overall, for this outcome, there is no hint for greater or lesser harm from pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy ± cisplatin (adjuvant), followed by pembrolizumab as monotherapy, compared with the ACT; an added benefit is therefore not proven. The uncertainties described above regarding a possible disadvantage are taken into account in the overall conclusion on the added benefit.

##### Severe adverse events (AEs)

Based on the time-to-event analysis, a statistically significant difference in favour of pembrolizumab was shown between the study arms for the outcome severe AEs. Given that the event rates were almost identical between the study arms (76.2% vs. 74.7%), this effect is attributable solely to the earlier occurrence of the events in the comparator arm. The consideration of the Kaplan-Meier curves reveals an almost parallel course, merely staggered in time. The effect observed in the hazard ratio is therefore solely attributable to the later onset of AEs and does not justify an added benefit in this data situation.

Overall, for this outcome, there is no hint for greater or lesser harm from pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy ± cisplatin (adjuvant), followed by pembrolizumab as monotherapy, compared with the ACT; an added benefit is therefore not proven.

### Discontinuation due to AEs

The time-to-event analysis showed no statistically significant difference between the study arms for the outcome discontinuation due to AEs. It is notable that the Kaplan-Meier curves cross each other. Consequently, the assumption of proportional hazards is not met and the hazard ratio cannot be interpreted. However, given the different follow-up durations between the treatment arms (longer follow-up in the intervention arm), there were significantly more events in the intervention arm than in the comparator arm (24.6% vs. 15.0%). Consequently, a possible disadvantage of pembrolizumab cannot be ruled out with sufficient certainty.

Overall, for this outcome, there is no hint for greater or lesser harm from pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy ± cisplatin (adjuvant), followed by pembrolizumab as monotherapy, compared with the ACT; an added benefit is therefore not proven. The uncertainties described above regarding a possible disadvantage are taken into account in the overall conclusion on the added benefit.

### Immune-mediated SAEs and severe AEs

For the relative risk, a statistically significant difference to the disadvantage of pembrolizumab between the study arms was shown for each of the outcomes immune-mediated SAEs and immune-mediated severe AEs. Given the very pronounced effect, the relative risk is considered interpretable in this data situation, despite the unequal observation periods between the study arms, and is therefore used to determine the extent of the effect.

There is a hint of greater harm from pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy ± cisplatin (adjuvant), followed by pembrolizumab as monotherapy in comparison with the ACT.

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

In the overall consideration, there were both positive and negative effects of pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy ± cisplatin (adjuvant), followed by pembrolizumab as monotherapy in comparison with the ACT.

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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].

A hint of an added benefit with the extent “considerable” was shown for the outcome overall survival.

In contrast, there were hints of greater harm of major extent in the category serious/severe side effects for the immune-mediated AEs. Furthermore, disadvantages in other outcomes on SAEs and discontinuation due to AEs cannot be ruled out with sufficient certainty. No suitable data are available for the patient-reported outcomes on morbidity and health-related quality of life. Overall, however, these aspects do not entirely call into question the positive effect in the outcome overall survival.

In summary, there is a hint of minor added benefit from pembrolizumab (neoadjuvant) followed by pembrolizumab in combination with radiotherapy, with or without concomitant cisplatin therapy, and subsequently as monotherapy over the ACT for adult patients with resectable, locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS  $\geq 1$  and who exhibit a high post-operative risk profile and for whom cisplatin-based therapy is suitable, or for those with a low postoperative risk profile.

**Research question 2: adult patients with a high postoperative risk profile for whom cisplatin-based therapy is not suitable**

The company did not present any data for adult patients with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS  $\geq 1$ , with a high postoperative risk profile for whom cisplatin-based therapy is not suitable. There is no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

**Summary**

Table 3 summarizes the probability and extent of added benefit of pembrolizumab.

Table 3: Pembrolizumab – probability and extent of added benefit

| Research question                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Therapeutic indication                                                                                                                                                       | ACT <sup>a</sup>                                                                                                                                                                                                                                                                                                                          | Probability and extent of added benefit  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| Adult patients with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS $\geq 1$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                           |                                          |
| 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | With a high postoperative risk profile for whom cisplatin-based therapy is suitable, or with a low postoperative risk profile; neoadjuvant and adjuvant therapy <sup>b</sup> | A therapy regimen consisting of <ul style="list-style-type: none"> <li>▪ surgery (tumour resection)</li> <li>▪ followed by individualized treatment, choosing from<sup>c, d</sup>: <ul style="list-style-type: none"> <li>▫ adjuvant chemoradiotherapy with cisplatin and</li> <li>▫ adjuvant radiotherapy</li> </ul> </li> </ul>         | Hint of minor added benefit <sup>e</sup> |
| 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | With a high postoperative risk profile for whom cisplatin-based therapy is not suitable; neoadjuvant and adjuvant therapy <sup>b</sup>                                       | A therapy regimen consisting of <ul style="list-style-type: none"> <li>▪ surgery (tumour resection)</li> <li>▪ followed by adjuvant chemoradiotherapy with: <ul style="list-style-type: none"> <li>▫ mitomycin + 5-FU<sup>f</sup> or</li> <li>▫ carboplatin + 5-FU<sup>f</sup> or</li> <li>▫ docetaxel<sup>f</sup></li> </ul> </li> </ul> | Added benefit not proven <sup>g</sup>    |
| <p>a. Presented is the respective ACT specified by the G-BA.</p> <p>b. For this therapeutic indication, it is assumed that the term 'locally advanced disease' covers stage III–IVA tumours.</p> <p>c. The treatment decision is made under particular consideration of the post-operative risk profile.</p> <p>d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study).</p> <p>e. The KEYNOTE 689 study only included patients with an ECOG PS of 0 or 1. Therefore, it remains unclear whether the observed effects can be transferred to patients with an ECOG PS of <math>&gt; 2</math>.</p> <p>f. In this therapeutic indication, the drugs carboplatin, cetuximab and bleomycin are approved for use as adjuvant treatment in patients with a high postoperative risk profile for whom cisplatin-based therapy is not suitable. According to the G-BA, these are either not recommended in the guideline or are recommended in a different combination. Instead, the guideline recommends mitomycin + 5-FU or carboplatin + 5-FU or docetaxel. The G-BA therefore assumes that, according to the generally accepted current state of medical knowledge, the off-label use of mitomycin + 5-FU or carboplatin + 5-FU or docetaxel is generally to be preferred to the drugs approved so far for this therapeutic indication for patients with a high postoperative risk profile for whom cisplatin-based therapy is not suitable (§6(2), sentence 3, number 3, AM-NutzenV).</p> <p>g. There are no data from randomized trials available for patients who have a high post-operative risk profile but for whom cisplatin-based therapy is not suitable.</p> <p>5-FU: 5-fluorouracil; ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; Pharmaceutical Directive; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death-ligand 1</p> |                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                           |                                          |

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

## I 2 Research question

The aim of this report is to assess the added benefit of pembrolizumab as monotherapy for neoadjuvant treatment and subsequently for adjuvant treatment in combination with radiotherapy, with or without concomitant cisplatin therapy, and subsequently as monotherapy, in comparison with the ACT in adult patients with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 (CPS  $\geq$  1).

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of pembrolizumab

| Research question                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Therapeutic indication                                                                                                                                                       | ACT <sup>a</sup>                                                                                                                                                                                                                                                                                                                          |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Adult patients with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS $\geq 1$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                           |
| 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | With a high postoperative risk profile for whom cisplatin-based therapy is suitable, or with a low postoperative risk profile; neoadjuvant and adjuvant therapy <sup>b</sup> | A therapy regimen consisting of <ul style="list-style-type: none"> <li>▪ surgery (tumour resection)</li> <li>▪ followed by individualized treatment, choosing from<sup>c, d</sup>: <ul style="list-style-type: none"> <li>▫ adjuvant chemoradiotherapy with cisplatin and</li> <li>▫ adjuvant radiotherapy</li> </ul> </li> </ul>         |
| 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | With a high postoperative risk profile for whom cisplatin-based therapy is not suitable; neoadjuvant and adjuvant therapy <sup>b</sup>                                       | A therapy regimen consisting of <ul style="list-style-type: none"> <li>▪ surgery (tumour resection)</li> <li>▪ followed by adjuvant chemoradiotherapy with: <ul style="list-style-type: none"> <li>▫ mitomycin + 5-FU<sup>e</sup> or</li> <li>▫ carboplatin + 5-FU<sup>e</sup> or</li> <li>▫ docetaxel<sup>e</sup></li> </ul> </li> </ul> |
| <p>a. Presented is the respective ACT specified by the G-BA.</p> <p>b. For this therapeutic indication, it is assumed that the term 'locally advanced disease' covers stage III–IVA tumours.</p> <p>c. The treatment decision is made under particular consideration of the post-operative risk profile.</p> <p>d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study).</p> <p>e. In this therapeutic indication, the drugs carboplatin, cetuximab and bleomycin are approved for use as adjuvant treatment in patients with a high postoperative risk profile for whom cisplatin-based therapy is not suitable. According to the G-BA, these are either not recommended in the guideline or are recommended in a different combination. Instead, the guideline recommends mitomycin + 5-FU or carboplatin + 5-FU or docetaxel. The G-BA therefore assumes that, according to the generally accepted current state of medical knowledge, the off-label use of mitomycin + 5-FU or carboplatin + 5-FU or docetaxel is generally to be preferred to the drugs approved so far for this therapeutic indication for patients with a high postoperative risk profile for whom cisplatin-based therapy is not suitable (§6(2), sentence 3, number 3, AM-NutzenV).</p> <p>5-FU: 5-fluorouracil; ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; Pharmaceutical Directive; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death-ligand 1</p> |                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                           |

For easier presentation and better readability, the running text uses the following terms for the research questions in this benefit assessment:

- Research question 1: adult patients with a high postoperative risk profile for whom cisplatin-based therapy is suitable, or with a low postoperative risk profile.
- Research question 2: adult patients with a high postoperative risk profile for whom cisplatin-based therapy is not suitable.

For research question 1 (adult patients with a high postoperative risk profile for whom cisplatin-based therapy is suitable, or with a low postoperative risk profile), the company followed the G-BA's definition of the ACT.

The company did not address research question 2 (adult patients with a high postoperative risk profile for whom cisplatin-based therapy is not suitable) as it did not consider these patients to be covered by the given therapeutic indication. It justifies this on the grounds that the approved therapeutic indication explicitly required cisplatin to constitute a suitable treatment for the patients. The company's reasoning is not appropriate. According to the SmPC [3], pembrolizumab is approved for use in adjuvant treatment in combination with radiotherapy, with or without concomitant cisplatin therapy. The benefit assessment was conducted in comparison with the comparator therapy specified by the G-BA, as shown in Table 4.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used to derive the added benefit. This concurred with the company's inclusion criteria.

### I 3 Research question 1: adult patients with a high postoperative risk profile for whom cisplatin-based therapy is suitable, or with a low postoperative risk profile

#### I 3.1 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on pembrolizumab (status: 25 September 2025)
- Bibliographical literature search on pembrolizumab (last search on 09 September 2025)
- Search of trial registries/trial results databases for studies on pembrolizumab (last search on 01 October 2025)
- Search on the G-BA website for pembrolizumab (last search on 01 October 2025)

To check the completeness of the study pool:

- Search in trial registries for studies on pembrolizumab (last search on 03 December 2025); for search strategies, see I Appendix A of the full dossier assessment

The search did not identify any additional relevant studies.

##### I 3.1.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin

| Study                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Study category                                                            |                                       |                            | Available sources       |                                                   |                                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------|----------------------------|-------------------------|---------------------------------------------------|----------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Study for the marketing authorization of the drug to be assessed (yes/no) | Sponsored study <sup>a</sup> (yes/no) | Third-party study (yes/no) | CSR (yes/no [citation]) | Registry entries <sup>b</sup> (yes/no [citation]) | Publication and other sources <sup>c</sup> (yes/no [citation]) |
| MK-3475-689 (KEYNOTE-689 <sup>d</sup> )                                                                                                                                                                                                                                                                                                                                                                                                                      | Yes                                                                       | Yes                                   | No                         | Yes [4]                 | Yes [5-7]                                         | Yes [8,9]                                                      |
| <p>a. Study sponsored by the company.</p> <p>b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.</p> <p>c. Other sources: documents from the search on the G-BA website and other publicly available sources.</p> <p>d. In the following tables, the study is referred to by this acronym.</p> <p>G-BA: Federal Joint Committee; RCT: randomized controlled trial</p> |                                                                           |                                       |                            |                         |                                                   |                                                                |

The study KEYNOTE 689 was used for the benefit assessment. The study pool was consistent with that selected by the company.

### **I 3.1.2 Study characteristics**

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the included study – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin (multipage table)

| Study       | Study design              | Population                                                                                           | Interventions (number of randomized/included patients)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Study duration                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Location and period of study                                                                                                                                                                                                                                                                                            | Primary outcome; secondary outcomes <sup>a</sup>                                                       |
|-------------|---------------------------|------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| KEYNOTE 689 | RCT, open-label, parallel | Adult patients with resectable locally advanced HNSCC (stages III–IVA) <sup>b</sup><br>▪ ECOG PS ≤ 1 | <p>Intervention arm (N = 363)</p> <ul style="list-style-type: none"> <li>▪ neoadjuvant: pembrolizumab</li> <li>▪ surgery</li> <li>▪ adjuvant: pembrolizumab and radiotherapy ± cisplatin<sup>c</sup>, followed by monotherapy with pembrolizumab</li> </ul> <p>comparator arm (N = 351)</p> <ul style="list-style-type: none"> <li>▪ surgery</li> <li>▪ adjuvant: radiotherapy ± cisplatin</li> </ul> <p>relevant subpopulation thereof<sup>d</sup>:</p> <ul style="list-style-type: none"> <li>▪ Intervention arm (N = 347)</li> <li>▪ comparator arm (N = 335)</li> </ul> | <p>Screening: up to 28 days</p> <p>treatment:</p> <ul style="list-style-type: none"> <li>▪ neoadjuvant: 6 weeks (2 cycles)</li> <li>▪ surgery: within 6 weeks (± 10 days) of randomization<sup>e</sup></li> <li>▪ adjuvant: <ul style="list-style-type: none"> <li>▫ Intervention arm: up to 45 weeks</li> <li>▫ Comparator arm: up to 7 weeks</li> <li>▫ or until disease progression, unacceptable toxicity, or treatment discontinuation as decided by the investigator or the patient, or withdrawal of consent</li> </ul> </li> </ul> <p>observation: outcome-specific, at most until death, withdrawal of consent or end of study<sup>f</sup>:</p> | <p>192 study centres in Argentina, Australia, Austria, Belgium, Brazil, Canada, Chile, Colombia, France, Germany, Hungary, Ireland, Israel, Japan, Poland, Portugal, Russia, South Korea, Spain, Switzerland, Taiwan, Ukraine, United Kingdom, USA</p> <p>12/2018–ongoing</p> <p>data cut: 25 July 2024<sup>g</sup></p> | <p>Primary: EFS</p> <p>secondary: overall survival, morbidity, health-related quality of life, AEs</p> |

Table 6: Characteristics of the included study – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin (multipage table)

| Study                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Study design | Population | Interventions (number of randomized/included patients) | Study duration | Location and period of study | Primary outcome; secondary outcomes <sup>a</sup> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|------------|--------------------------------------------------------|----------------|------------------------------|--------------------------------------------------|
| <p>a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.</p> <p>b. Staging took place according to UICC/AJCC, 8th Edition [10].</p> <p>c. Cisplatin was administered only to patients with a high postoperative risk and for whom cisplatin therapy was suitable. In the KEYNOTE 689 study, a high risk of postoperative recurrence is defined as positive resection margins (&lt; 1 mm) or extranodal extension of the squamous cell carcinoma beyond the lymph node capsule.</p> <p>d. Patients with tumour PD-L1 expression with CPS ≥ 1, in accordance with the approved therapeutic indication.</p> <p>e. Patients in the intervention arm could undergo surgery outside this time frame, provided that the delay was attributable to an AE. Patients in the comparator arm were to undergo surgery within 4 weeks of randomization.</p> <p>f. Outcome-specific information is provided in Table 8.</p> <p>g. Prespecified interim analysis after 207 events in the primary outcome EFS in patients with tumour PD-L1 expression with CPS ≥ 10.</p> <p>AE: adverse event; AJCC: American Joint Committee on Cancer; CPS: combined positive score; EFS: event-free survival; HNSCC: head and neck squamous cell carcinoma; ND: no data; n: relevant subpopulation/subpopulation analysed by the company; N: number of randomized (enrolled) patients; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial; UICC: Union for International Cancer Control</p> |              |            |                                                        |                |                              |                                                  |

Table 7: Characteristics of the interventions – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin (multipage table)

| Study       | Intervention                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Comparison                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| KEYNOTE 689 | <p><u>Neoadjuvant therapy:</u></p> <ul style="list-style-type: none"> <li>pembrolizumab 200 mg IV on Day 1 for 2 cycles (21 days each)</li> </ul> <p><u>surgery</u></p> <p><u>adjuvant therapy:</u><br/>patients with a low risk of postoperative recurrence<sup>a</sup></p> <ul style="list-style-type: none"> <li>Pembrolizumab 200 mg IV on Day 1 for 15 cycles (21 days each)</li> </ul> <p>+</p> <ul style="list-style-type: none"> <li>radiotherapy with a total dose of 60 Gy (30 single doses of 2 Gy per day on 5 days per week)<sup>b</sup></li> </ul> <p><b>or</b></p> <p>patients with a high risk of postoperative recurrence<sup>a</sup></p> <ul style="list-style-type: none"> <li>pembrolizumab 200 mg IV on Day 1 for 15 cycles (21 days each)</li> </ul> <p>+</p> <ul style="list-style-type: none"> <li>radiotherapy with a total dose of 66 Gy (33 single doses of 2 Gy per day on 5 days per week)</li> </ul> <p>+</p> <ul style="list-style-type: none"> <li>cisplatin 100 mg/m<sup>2</sup> BSA, IV, on day 1 for 3 cycles (21 days each)</li> </ul> <p>Dose modification:</p> <ul style="list-style-type: none"> <li>pembrolizumab: no dose adjustment permitted; treatment could be interrupted or discontinued due to toxicity or in the event of immune-mediated or infusion-mediated AEs</li> <li>cisplatin: ≤ 2 dose adjustments permitted; further dose escalation was not permitted thereafter</li> <li>radiotherapy: Treatment could be interrupted in the event of acute toxicity</li> </ul> | <p><u>Surgery</u></p> <p><u>adjuvant therapy:</u><br/>patients with a low risk of postoperative recurrence<sup>a</sup></p> <ul style="list-style-type: none"> <li>radiotherapy with a total dose of 60 Gy (30 single doses of 2 Gy per day on 5 days per week)<sup>b</sup></li> </ul> <p><b>or</b></p> <p>patients with a high risk of postoperative recurrence<sup>a</sup></p> <ul style="list-style-type: none"> <li>radiotherapy with a total dose of 66 Gy (33 single doses of 2 Gy per day on 5 days per week)</li> </ul> <p>+</p> <ul style="list-style-type: none"> <li>cisplatin 100 mg/m<sup>2</sup> BSA, IV, on Day 1 for 3 cycles (21 days each)</li> </ul> |

Table 7: Characteristics of the interventions – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin (multipage table)

| Study                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Intervention                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Comparison |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <p><b>Disallowed prior treatment</b></p> <ul style="list-style-type: none"><li>▪ any systemic anti-cancer treatment</li><li>▪ anti-PD-1, anti-PD-L1 or anti-PD-L2 drugs, or any other drug targeting co-inhibitory T-cell receptors</li><li>▪ radiotherapy targeted against head and neck squamous cell carcinoma</li><li>▪ live vaccines within 30 days prior to randomization</li></ul> <p><b>allowed concomitant treatment</b></p> <ul style="list-style-type: none"><li>▪ supportive standard treatments at the investigator’s discretion</li><li>▪ inhaled steroids and prophylactic corticosteroids</li></ul> <p><b>disallowed concomitant treatment</b></p> <ul style="list-style-type: none"><li>▪ other antineoplastic systemic chemotherapy or biologic treatments</li><li>▪ other chemotherapies, radiotherapies or immunotherapies</li><li>▪ systemic glucocorticoids, except for the treatment of immune-mediated AEs or as pre- or post-medication for a chemotherapy administered as part of the study, or in the event of infusion-related reactions</li><li>▪ prophylactic granulocyte colony-stimulating factors (exception: therapeutic use in cases of clinically indicated neutropenia)</li></ul> |            |
| <p>a. In the KEYNOTE 689 study, a high risk of postoperative recurrence is defined as positive resection margins (&lt; 1 mm) or extranodal extension of the squamous cell carcinoma beyond the lymph node capsule.</p> <p>b. Patients who had not undergone surgery, or who had undergone incomplete surgery with measurable minimal residual disease (MRD), could be treated with a total radiation of 70 Gy (in 35 individual doses).</p> <p>BSA: body surface area; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; Gy: Gray; IV: intravenous; MRD: minimal residual disease; PD-1: programmed cell death 1; PD-L1/2: programmed cell death-ligand 1/2; RCT: randomized controlled trial</p> |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |            |

### Study design

KEYNOTE 689 is an ongoing, open-label RCT comparing pembrolizumab as neoadjuvant therapy and as postoperative adjuvant therapy in combination with radiotherapy, with or without concomitant cisplatin therapy followed by pembrolizumab as monotherapy, against postoperative adjuvant radiotherapy ± cisplatin therapy in adult patients with resectable, locally advanced head and neck squamous cell carcinoma.

The study included adult patients with histologically confirmed, newly diagnosed, resectable, locally advanced head and neck squamous cell carcinoma, irrespective of the PD-L1 status. In this case, either

- a p16-positive stage III oropharyngeal carcinoma, or
- a p16-negative stage III or IVA oropharyngeal carcinoma, or
- a stage III or IVA squamous cell carcinoma of the larynx, hypopharynx or oral cavity

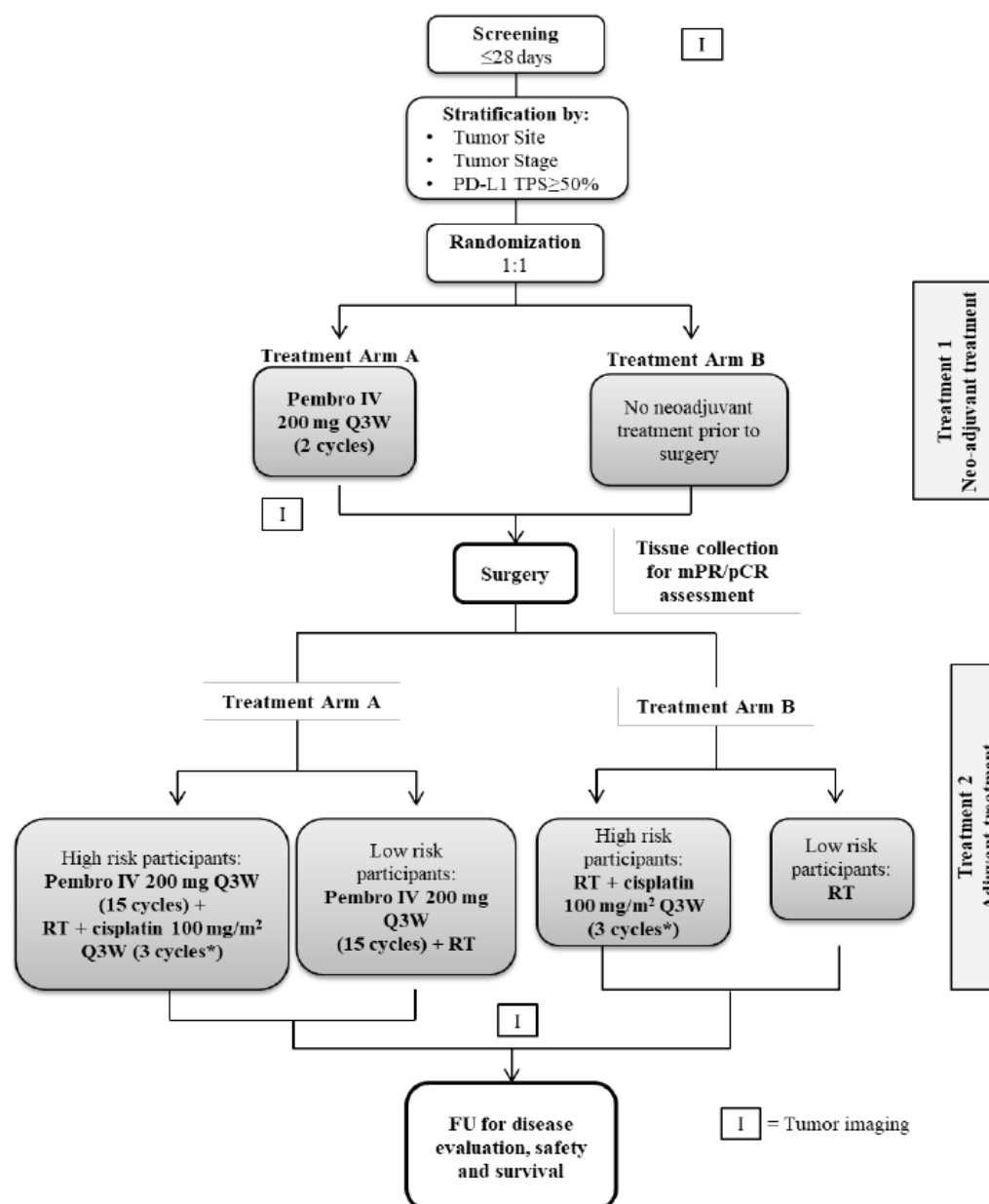
had to be present.

Patients had to have an ECOG PS of 0 or 1 on study entry.

The PD-L1 expression in the tumour tissue had to be determined for study inclusion. The company's dossier does not provide any information on which test was used to determine PD-L1 expression.

In the KEYNOTE 689 study, a total of 714 patients were randomized in a 1:1 to the study arms (N = 363 vs. N = 351). Randomization was stratified by location of the primary tumour (oropharynx/oral cavity vs. larynx vs. hypopharynx), tumour stage (III vs. IVA) and PD-L1 Tumour Proportion Score (TPS) status (TPS  $\geq$  50% vs. TPS < 50%). The company presented a subpopulation of patients with PD-L1-expressing tumours with CPS  $\geq$  1 (N = 347 vs. N = 335) corresponding to the approved therapeutic indication. This subpopulation was used for the benefit assessment.

Figure 1 shows the design of the KEYNOTE 689 study:



\*If there are delays in cisplatin treatment, cisplatin therapy may be continued for up to 1 week after the completion of radiotherapy.

FU: follow-up; IV: intravenous; mPR: major Pathological Response; pCR: pathological Complete Response; PD-L1: programmed cell death ligand 1; pembro = pembrolizumab; Q3W: every 3 weeks; RT: radiotherapy; TPS = Tumour Proportion Score

Figure 1: Design of the KEYNOTE 689 study

Patients in the intervention arm of the KEYNOTE 689 study initially received neoadjuvant treatment with two cycles of pembrolizumab following randomization. This was followed by the surgery. This was to take place 6 weeks ( $\pm 10$  days) after randomization. In the comparator arm, patients should undergo surgery within 4 weeks of randomization. In the intervention group, a repeat computed tomography (CT) or magnetic resonance imaging (MRI) scan of the

head and neck region was carried out prior to surgery; in the comparator arm, this was only done if the previous scan was more than 14 days old.

Following the surgery, the risk of postoperative recurrence was rated as high or low on the basis of pathological findings. This categorisation was based on an assessment of the surgically resected samples of the primary tumour and the cervical lymph nodes. A high risk of postoperative recurrence is defined as extranodal extension and/or positive resection margins ( $< 1$  mm); otherwise, a low risk of postoperative recurrence has been determined (see also below). Patients with a high risk of postoperative recurrence received adjuvant radiotherapy in combination with cisplatin and, in the intervention arm, these patients additionally received pembrolizumab for a maximum of 15 cycles. Patients with a low risk of postoperative recurrence received adjuvant radiotherapy and, in the intervention arm, these patients additionally received pembrolizumab for a maximum of 15 cycles. For patients in both study arms, adjuvant therapy was to be initiated within 6 weeks of surgery.

In both study arms, patients who did not undergo surgery or whose tumour was incompletely resected were nevertheless able to continue with treatment analogous to the adjuvant therapy.

Treatment with pembrolizumab in the intervention arm was in compliance with the specifications of the Summary of Product Characteristics (SmPC) [3]. Dose adjustments were not allowed. Treatment interruptions due to toxicity were possible and were in line with the specifications set out in the SmPC [3]. If treatment with pembrolizumab was discontinued, patients could continue to be treated with cisplatin and radiotherapy.

The SmPC for cisplatin provides no details regarding this therapeutic indication. However, the radiotherapy administered in both study arms, as well as the concomitant treatment with cisplatin, are in line with the recommendations of current guidelines [11-13].

Treatment with the study medication was continued until the onset of disease progression, unacceptable toxicity, discontinuation of treatment at the investigator's discretion, withdrawal of consent, or until the scheduled completion of study treatment after 45 weeks in the intervention arm or 7 weeks in the control arm.

Primary outcome of the KEYNOTE 689 study was EFS. Patient-relevant secondary outcomes were overall survival as well as outcomes from the categories of morbidity, health-related quality of life, and side effects.

### **Data cuts**

KEYNOTE 689 is an ongoing study. So far, one data cut is available:

- first data cut (25 July 2024): prespecified interim analysis after 207 events for the outcome EFS in patients with tumour PD-L1 expression CPS  $\geq 10$ .

Two further data cuts are planned:

- second data cut: prespecified interim analysis after 232 events for the outcome EFS in patients with tumour PD-L1 expression CPS  $\geq 10$  and approximately 22 months after the completion of recruitment
- third data cut: final analysis prespecified after 201 events in the outcome overall survival in patients with tumour PD-L1 expression CPS  $\geq 10$  and approximately 34 months after the end of recruitment

The first data cut of 25 July 2024 is relevant for this benefit assessment.

**Implementation of the individualized therapy in the adjuvant treatment phase – definition of a high risk of postoperative recurrence in the KEYNOTE 689 study deviates from guideline recommendations**

In accordance with the specification of the ACT, the treatment decision between adjuvant chemoradiotherapy with cisplatin and adjuvant radiotherapy should be made on an individual basis. The decision regarding adjuvant therapy with cisplatin in addition to radiotherapy following tumour resection particularly depends on the risk of postoperative recurrence.

In the KEYNOTE 689 study, the decision to administer adjuvant therapy with cisplatin in addition to adjuvant radiotherapy was based on postoperative risk and thus in accordance with the requirements for the ACT. In this context, a high postoperative risk is defined as positive resection margins ( $< 1$  mm in the primary resection sample) or extranodal extension of the squamous cell carcinoma beyond the lymph node capsule. However, this definition deviates from the current guideline recommendations. The S3 guidelines on oral cavity cancer and oropharyngeal and hypopharyngeal cancer recommend adjuvant cisplatin therapy not only in cases of extranodal extension, but also where the resection margin in the primary resection sample is  $< 5$  mm [12,13].

This deviation affects the proportion of patients in the KEYNOTE 689 study who receive adjuvant treatment with cisplatin. As no data were available for the relevant subpopulation regarding the proportion of patients who received cisplatin, data from the total population taken from the clinical study report were used below, as these show sufficient similarity to the relevant subpopulation (see Table 6). In the intervention arm, 107 (39%) of 275 patients, and in the comparator arm 139 (51%) of 275 patients receiving adjuvant therapy, underwent chemoradiotherapy with cisplatin.

This means that in both study arms, a relevant proportion (61% vs. 49%) of patients did not receive cisplatin treatment. The company's dossier does not provide any information on how many of these patients had a resection margin of < 5 mm in the primary resection sample and for whom adjuvant cisplatin treatment would have been indicated in accordance with current guideline recommendations. It must therefore be assumed that some of the patients in the KEYNOTE 689 study were not treated in accordance with the guideline recommendations and were therefore potentially undertreated. This applies in particular to the comparator arm, as these patients received no study medication other than radiotherapy. It is unclear how this affects the results of the KEYNOTE 689 study. This aspect limits the transferability of the study results to the German health care context and is taken into account in the assessment of the certainty of conclusions (see Sections I 3.2.2).

### **Special characteristics of the study design**

Due to the study design of the KEYNOTE 689 study, different treatment regimens are used in the study arms. As described above, patients in the intervention arm received neoadjuvant treatment with pembrolizumab, whilst those in the comparator arm did not receive any neoadjuvant treatment. Patients in the comparator arm underwent surgery earlier and also received adjuvant therapy earlier. This time lag between surgery and adjuvant therapy in the intervention arm, which is due to the study design, was the reason for the earlier occurrence of specific AEs in the comparator arm, and is taken into account when interpreting the results on side effects (see Section I 3.2.3).

### **Planned duration of follow-up**

Table 8 shows the planned duration of patient follow-up for the individual outcomes.

Table 8: Planned duration of follow-up – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin

| Study outcome category<br>outcome                                                                                                                                                                                                                                    | Planned follow-up                                                                                                                                         |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>KEYNOTE 689</b>                                                                                                                                                                                                                                                   |                                                                                                                                                           |
| Mortality                                                                                                                                                                                                                                                            |                                                                                                                                                           |
| Overall survival                                                                                                                                                                                                                                                     | Up to death, withdrawal of consent or end of study, whichever is first                                                                                    |
| Morbidity                                                                                                                                                                                                                                                            |                                                                                                                                                           |
| Symptoms (EORTC QLQ-C30; EORTC QLQ-H&N35)                                                                                                                                                                                                                            | up to 5 years after the last dose of the study medication, until withdrawal of consent or disease progression <sup>a</sup>                                |
| Health status (EQ-5D VAS)                                                                                                                                                                                                                                            | up to 5 years after the last dose of the study medication, until withdrawal of consent or disease progression                                             |
| Health-related quality of life                                                                                                                                                                                                                                       |                                                                                                                                                           |
| EORTC QLQ-C30                                                                                                                                                                                                                                                        | up to 5 years after the last dose of the study medication, until withdrawal of consent or disease progression                                             |
| Side effects                                                                                                                                                                                                                                                         |                                                                                                                                                           |
| AEs                                                                                                                                                                                                                                                                  | until 30 days after the last dose of the study medication or up to the initiation of a new antineoplastic treatment, whichever occurs first               |
| SAEs                                                                                                                                                                                                                                                                 | until 90 days after the last dose of the study medication or up to 30 days after the initiation of a new antineoplastic treatment, whichever occurs first |
| a. Regular imaging to capture disease progression was carried out for up to 5 years after the end of radiotherapy ± cisplatin.                                                                                                                                       |                                                                                                                                                           |
| AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RCT: randomized controlled trial; SAE: serious adverse event |                                                                                                                                                           |

The observation periods for the outcomes symptoms, health status and health-related quality of life were systematically shortened because they were only recorded until disease progression. The outcomes in the side effects category were only recorded for the period of treatment with the study medication (plus 30 or 90 days), so that the observation times for these outcomes were also systematically shortened. However, to draw a reliable conclusion on the total study period or the time to patient death, it would also be necessary to record these outcomes for the total period, as was done for survival.

### Patient characteristics

Table 9 shows the characteristics of the relevant subpopulation in the study included.

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin (multipage table)

| Study characteristic category     | Pembrolizumab neoadjuvant + adjuvant and radiotherapy ± cisplatin<br>N = 347 | Radiotherapy ± cisplatin<br>N = 335 |
|-----------------------------------|------------------------------------------------------------------------------|-------------------------------------|
| <b>KEYNOTE 689</b>                |                                                                              |                                     |
| Age [years], mean (SD)            | 60 (10)                                                                      | 60 (10)                             |
| Sex [F/M], %                      | 22/78                                                                        | 21/79                               |
| Family origin, n (%)              |                                                                              |                                     |
| White                             | 273 (79)                                                                     | 260 (78)                            |
| Black                             | 8 (2)                                                                        | 9 (3)                               |
| Asian                             | 47 (14)                                                                      | 42 (13)                             |
| Other <sup>a</sup>                | 10 (3) <sup>b</sup>                                                          | 18 (5) <sup>b</sup>                 |
| Missing                           | 9 (3)                                                                        | 6 (2)                               |
| Location of primary tumour, n (%) |                                                                              |                                     |
| Oropharynx                        | 34 (10)                                                                      | 37 (11)                             |
| Oral cavity                       | 210 (61)                                                                     | 205 (61)                            |
| Larynx                            | 77 (22)                                                                      | 67 (20)                             |
| Hypopharynx                       | 26 (7)                                                                       | 25 (7)                              |
| ECOG PS, n (%)                    |                                                                              |                                     |
| 0                                 | 187 (54)                                                                     | 201 (60)                            |
| 1                                 | 160 (46)                                                                     | 134 (40)                            |
| HPV status, n (%)                 |                                                                              |                                     |
| Positive                          | 11 (3)                                                                       | 14 (4)                              |
| Negative                          | 336 (97)                                                                     | 320 (96)                            |
| Unknown                           | 0 (0)                                                                        | 1 (< 1)                             |
| Tumour stage at baseline, n (%)   |                                                                              |                                     |
| III                               | 86 (25)                                                                      | 88 (26)                             |
| IVA                               | 259 (75)                                                                     | 246 (73)                            |
| IVB                               | 2 (< 1)                                                                      | 0 (0)                               |
| Missing                           | 0 (0)                                                                        | 1 (< 1)                             |
| Smoking status, n (%)             |                                                                              |                                     |
| Never                             | 61 (18)                                                                      | 76 (23)                             |
| Former                            | 170 (49)                                                                     | 135 (40)                            |
| Active                            | 110 (32)                                                                     | 121 (36)                            |
| Unknown                           | 6 (2)                                                                        | 3 (< 1)                             |
| Alcohol consumption, n (%)        |                                                                              |                                     |
| Yes                               | 238 (69)                                                                     | 228 (68)                            |
| No                                | 103 (30)                                                                     | 104 (31)                            |
| Unknown                           | 6 (2)                                                                        | 3 (< 1)                             |

Table 9: Characteristics of the relevant subpopulation as well as study/treatment discontinuation – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin (multipage table)

| Study characteristic category                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Pembrolizumab neoadjuvant + adjuvant and radiotherapy ± cisplatin<br>N = 347 | Radiotherapy ± cisplatin<br>N = 335 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|-------------------------------------|
| Treatment discontinuation, n (%) <sup>c</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 185 (54)                                                                     | 52 (17)                             |
| Study discontinuation, n (%) <sup>d</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 115 (33)                                                                     | 142 (42)                            |
| <p>a. Includes Native North Americans, Native Alaskans, Native Hawaiians or other Pacific Islanders, and several.</p> <p>b. Institute's calculation.</p> <p>c. Common reasons for treatment discontinuation in the intervention arm versus the control arm were (percentages refer to the randomized patients who started treatment [N = 344 vs. N = 301]; 3 vs. 34 patients did not commence treatment): disease progression (21% vs. 3%), adverse event (18% vs. 5%), withdrawal of consent (8% vs. 4%). Furthermore, 43 % vs. 83 % of the patients completed treatment as planned.</p> <p>d. Frequent reasons for study discontinuation in the intervention arm vs. the control arm were (percentages refer to randomized patients): withdrawal of consent (3% vs. 4%), lost to follow-up (&lt; 1% vs. &lt; 1%). The data additionally include patients who died during the course of the study (29% vs. 37%).</p> <p>ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; HPV: human papillomavirus; M: male; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation</p> |                                                                              |                                     |

The patient characteristics in the KEYNOTE 689 study are largely balanced between the 2 treatment arms. The mean age of the patients was 60 years and the majority were male in both treatment arms (approximately 80 %). In both treatment arms, the patients were largely of white family origin (approximately 80%). The majority of patients in both study arms had tumour stage IVA (75% versus 73%).

A relevant proportion of patients in the comparator arm (n = 34, 10% of the randomized patients) did not commence treatment with the study medication after randomization (in the intervention arm: n = 3, or 1%). The reasons for this are unclear. These patients were not included in the analysis for the outcomes in the side effects category, and this is taken into account when assessing the risk of bias (see Section I 3.2.3).

In the intervention arm, patients discontinued treatment more frequently (54% vs. 17%). The most common reasons for treatment discontinuation were disease progression (21% vs. 3%), followed by AEs (18% vs. 5%) and withdrawal of consent (8% vs. 4%). 33% of the patients in the intervention arm and 42% of the patients in the comparator arm discontinued the study.

### Information on the course of the study

Table 10 shows patients' median treatment duration and the median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin

| Study<br>duration of the study phase<br>outcome category<br>outcome                                                                                                                                                                                                                                                                                              | Pembrolizumab neoadjuvant +<br>adjuvant and radiotherapy ± cisplatin<br>N = 347 | Radiotherapy ± cisplatin<br>N = 335 |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------|
| <b>KEYNOTE 689</b>                                                                                                                                                                                                                                                                                                                                               |                                                                                 |                                     |
| Treatment duration [months]                                                                                                                                                                                                                                                                                                                                      | N = 344                                                                         | N = 301                             |
| Median [Q1; Q3]                                                                                                                                                                                                                                                                                                                                                  | 9.1 [3.4; 12.6]                                                                 | 2.9 [2.6; 3.3]                      |
| Mean (SD)                                                                                                                                                                                                                                                                                                                                                        | 8.0 (5.1)                                                                       | 2.7 (1.2)                           |
| Observation period [months]                                                                                                                                                                                                                                                                                                                                      |                                                                                 |                                     |
| Overall survival <sup>a</sup>                                                                                                                                                                                                                                                                                                                                    | N = 347                                                                         | N = 335                             |
| Median [Q1; Q3]                                                                                                                                                                                                                                                                                                                                                  | 29.2 [14.7; 45.3]                                                               | 23.0 [11.8; 40.7]                   |
| Mean (SD)                                                                                                                                                                                                                                                                                                                                                        | 30.6 (18.0)                                                                     | 27.1 (18.3)                         |
| Symptoms, health-related quality of<br>life (EORTC QLQ-C30)                                                                                                                                                                                                                                                                                                      | N = 340                                                                         | N = 291                             |
| Median [Q1; Q3]                                                                                                                                                                                                                                                                                                                                                  | 13.3 [4.3; 31.2]                                                                | 12.1 [5.4; 29.5]                    |
| Mean (SD)                                                                                                                                                                                                                                                                                                                                                        | 18.4 (16.2)                                                                     | 17.4 (15.4)                         |
| Symptoms (EORTC QLQ-H&N35)                                                                                                                                                                                                                                                                                                                                       | N = 340                                                                         | N = 291                             |
| Median [Q1; Q3]                                                                                                                                                                                                                                                                                                                                                  | 13.6 [5.0; 31.3]                                                                | 13.2 [5.5; 29.5]                    |
| Mean (SD)                                                                                                                                                                                                                                                                                                                                                        | 19.2 (16.1)                                                                     | 18.0 (15.3)                         |
| Health status (EQ-5D VAS)                                                                                                                                                                                                                                                                                                                                        | N = 340                                                                         | N = 290                             |
| Median [Q1; Q3]                                                                                                                                                                                                                                                                                                                                                  | 13.4 [4.3; 31.2]                                                                | 12.2 [5.4; 29.5]                    |
| Mean (SD)                                                                                                                                                                                                                                                                                                                                                        | 18.4 (16.2)                                                                     | 17.5 (15.4)                         |
| Side effects                                                                                                                                                                                                                                                                                                                                                     | N = 344                                                                         | N = 301                             |
| AEs                                                                                                                                                                                                                                                                                                                                                              |                                                                                 |                                     |
| Median [Q1; Q3]                                                                                                                                                                                                                                                                                                                                                  | 9.9 [4.1; 13.6]                                                                 | 3.9 [3.6; 4.2]                      |
| Mean (SD)                                                                                                                                                                                                                                                                                                                                                        | 9.0 (5.1)                                                                       | 3.7 (1.2)                           |
| SAEs                                                                                                                                                                                                                                                                                                                                                             |                                                                                 |                                     |
| Median [Q1; Q3]                                                                                                                                                                                                                                                                                                                                                  | 10.9 [5.5; 15.5]                                                                | 5.8 [5.6; 6.2]                      |
| Mean (SD)                                                                                                                                                                                                                                                                                                                                                        | 10.7 (5.2)                                                                      | 5.5 (1.4)                           |
| a. Calculated as the time from randomization to death, last contact or database lock, if the patient was still alive.                                                                                                                                                                                                                                            |                                                                                 |                                     |
| AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; N: number of analysed patients; Q1: 1st quartile; Q3: 3rd quartile; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-H&N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RCT: randomized controlled trial; SAE: serious adverse event; SD: standard deviation |                                                                                 |                                     |

In the KEYNOTE 689 study, the median treatment duration was notably longer in the intervention arm, at 9.1 months, than in the comparator arm, at 2.9 months. This is due to the

different treatment strategies, in particular the adjuvant treatment with pembrolizumab in the intervention arm (see Table 7).

In the intervention arm (29.2 months) the median follow-up duration for the outcome overall survival was longer than in the comparator arm (23.0 months).

The median follow-up durations for the outcomes symptoms, health-related quality of life (EORTC QLQ-C30), symptoms (EORTC QLQ-H&N35) and health status (EQ-5D VAS) are shortened compared to the outcome overall survival. The median follow-up durations between the study arms are sufficiently comparable for these outcomes.

For the outcome category of side effects, the median follow-up durations are also significantly shorter than for the outcome overall survival and, furthermore, vary considerably between the treatment arms. For the outcomes on AEs, the median duration of follow-up was 9.9 months in the intervention arm versus 3.9 months in the comparator arm; for the outcome SAE, it was 10.9 months versus 5.8 months.

### **Subsequent therapies**

Table 11 shows the subsequent therapies patients received after discontinuing the study medication.

Table 11: Information on subsequent antineoplastic therapies ( $\geq 2$  patients in at least 1 treatment arm) – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy  $\pm$  cisplatin vs. surgery, adjuvant radiotherapy  $\pm$  cisplatin (multipage table)

| Study<br>type of therapy<br>drug class <sup>a</sup><br>drug              | Patients with subsequent therapy, n (%)                                  |                              |
|--------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------------------|
|                                                                          | pembrolizumab neoadjuvant +<br>adjuvant and radiotherapy $\pm$ cisplatin | radiotherapy $\pm$ cisplatin |
|                                                                          | N = 347                                                                  | N = 335                      |
| <b>KEYNOTE 689</b>                                                       |                                                                          |                              |
| EFS events without deaths <sup>b, c</sup>                                | 65 (18.7)                                                                | 94 (28.1)                    |
| Distant metastases <sup>b</sup>                                          | 24 (6.9)                                                                 | 51 (15.2)                    |
| Local progression and distant metastases <sup>b</sup>                    | 4 (1.2)                                                                  | 6 (1.8)                      |
| Local progression/recurrence <sup>b</sup>                                | 37 (10.7)                                                                | 37 (11.0)                    |
| Any subsequent systemic therapy                                          | 64 (18.4)                                                                | 76 (22.7)                    |
| First subsequent therapy: systemic therapy                               | 42 (12.1)                                                                | 59 (17.6)                    |
| First subsequent therapy: systemic therapy and radiotherapy <sup>d</sup> | 14 (4.0)                                                                 | 8 (2.4)                      |
| First subsequent therapy: radiotherapy                                   | 20 (5.8)                                                                 | 17 (5.1)                     |
| First subsequent systemic therapy                                        | 56 (16.1)                                                                | 67 (20.0)                    |
| EGFR inhibitors                                                          | 14 (4.0)                                                                 | 4 (1.2)                      |
| Cetuximab                                                                | 13 (3.7)                                                                 | 4 (1.2)                      |
| Multiple                                                                 | 12 (3.5)                                                                 | 9 (2.7)                      |
| Paclitaxel                                                               | 12 (3.5)                                                                 | 5 (1.5)                      |
| Evorpacept                                                               | 0 (0.0)                                                                  | 2 (0.6)                      |
| PD-1/PD-L1 inhibitors                                                    | 8 (2.3)                                                                  | 37 (11.0)                    |
| Pembrolizumab                                                            | 7 (2.0)                                                                  | 28 (8.4)                     |
| Nivolumab                                                                | 1 (0.3)                                                                  | 9 (2.7)                      |
| Platinum compounds                                                       | 42 (12.1)                                                                | 39 (11.6)                    |
| Cisplatin                                                                | 28 (8.1)                                                                 | 27 (8.1)                     |
| Carboplatin                                                              | 14 (4.0)                                                                 | 13 (3.9)                     |
| Pyrimidine analogues                                                     | 10 (2.9)                                                                 | 21 (6.3)                     |
| Fluorouracil                                                             | 10 (2.9)                                                                 | 20 (6.0)                     |
| Taxanes                                                                  | 8 (2.3)                                                                  | 3 (0.9)                      |
| Docetaxel                                                                | 8 (2.3)                                                                  | 3 (0.9)                      |

Table 11: Information on subsequent antineoplastic therapies ( $\geq 2$  patients in at least 1 treatment arm) – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy  $\pm$  cisplatin vs. surgery, adjuvant radiotherapy  $\pm$  cisplatin (multipage table)

| Study<br>type of therapy<br>drug class <sup>a</sup><br>drug                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Patients with subsequent therapy, n (%)                                  |                              |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | pembrolizumab neoadjuvant +<br>adjuvant and radiotherapy $\pm$ cisplatin | radiotherapy $\pm$ cisplatin |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | N = 347                                                                  | N = 335                      |
| Any subsequent systemic therapy                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 64 (18.4)                                                                | 76 (22.7)                    |
| EGFR inhibitors                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 19 (5.5)                                                                 | 19 (5.7)                     |
| Cetuximab                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 18 (5.2)                                                                 | 19 (5.7)                     |
| Multiple                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 22 (6.3)                                                                 | 22 (6.6)                     |
| Paclitaxel                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 17 (4.9)                                                                 | 19 (5.7)                     |
| Methotrexate                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 4 (1.2)                                                                  | 0 (0)                        |
| Evorpacept                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0 (0)                                                                    | 2 (0.6)                      |
| Other protein kinase inhibitors                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 0 (0)                                                                    | 2 (0.6)                      |
| Lenvatinib                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0 (0)                                                                    | 2 (0.6)                      |
| PD-1/PD-L1 inhibitors                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 12 (3.5)                                                                 | 46 (13.7)                    |
| Pembrolizumab                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 8 (2.3)                                                                  | 32 (9.6)                     |
| Nivolumab                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 4 (1.2)                                                                  | 15 (4.5)                     |
| Platinum compounds                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 52 (15.0)                                                                | 52 (15.5)                    |
| Cisplatin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 38 (11.0)                                                                | 36 (10.7)                    |
| Carboplatin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 18 (5.2)                                                                 | 19 (5.7)                     |
| Pyrimidine analogues                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 16 (4.6)                                                                 | 30 (9.0)                     |
| Fluorouracil                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 13 (3.7)                                                                 | 26 (7.8)                     |
| Gemcitabine                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 3 (0.9)                                                                  | 1 (0.3)                      |
| Gimeracil; oteracil potassium;<br>tegafur                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 1 (0.3)                                                                  | 2 (0.6)                      |
| Taxanes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 11 (3.2)                                                                 | 4 (1.2)                      |
| Docetaxel                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 11 (3.2)                                                                 | 4 (1.2)                      |
| Vinca alkaloids and analogues                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 2 (0.6)                                                                  | 0 (0)                        |
| <p>a. If several systemic therapies were administered in one drug class, patients were only counted once in the respective drug class.</p> <p>b. The information is based on data provided by the company in Module 4A on the outcome EFS according to the blinded independent central review (BICR).</p> <p>c. Institute's calculation.</p> <p>d. Patients who received both systemic therapy and radiotherapy were only counted once in the composite category.</p> <p>BICR: blinded independent central review; EGFR: epidermal growth factor receptor; n: number of patients with subsequent therapy; N: number of analysed patients; PD-1: programmed cell death 1; PD-L1: programmed cell death ligand 1; RCT: randomized controlled trial</p> |                                                                          |                              |

In the KEYNOTE 689 study, subsequent antineoplastic therapies were permitted without restrictions in both study arms. Overall, 64 (18.4%) patients in the intervention arm and 76 (22.7%) patients in the comparator arm received at least one subsequent systemic therapy. Of the patients with qualifying EFS events (excluding deaths), 64 out of 65 (98%) in the intervention arm and 76 out of 94 (81%) in the comparator arm received at least one subsequent therapy.

According to the S3 guidelines on oral cavity cancer and oropharyngeal/hypopharyngeal cancer, the choice of the subsequent therapy depends on whether the patient is in a curative or palliative setting following disease progression or recurrence [11-13]. However, the company does not provide any information on this, so it is not possible to make a clear assignment.

For patients in the palliative setting with PD-L1-expressing tumours (CPS  $\geq 1$ ), the use of pembrolizumab or nivolumab is recommended as the preferred first-line treatment standard [11,14]. The combinations of pembrolizumab with chemotherapy or cetuximab with cisplatin and docetaxel are alternatives. There are no recommendations for patients whose disease has progressed or recurred following treatment with pembrolizumab. In the comparator arm, 51 patients developed distant metastases, whilst a further 6 experienced both local progression and distant metastases. It can be assumed that systemic therapy was indicated for these 57 patients and was administered accordingly. 37 patients received pembrolizumab or nivolumab as their first subsequent systemic therapy, and a further 4 received cetuximab; i.e., 41 (72%) of the patients for whom systemic therapy was indicated received a first subsequent therapy in accordance with the guidelines. The data on any subsequent therapies also show that pembrolizumab, nivolumab or cetuximab were used in later lines of treatment for other patients.

Curatively intended treatment options remain available for patients with local progression/recurrence (e.g. salvage surgery and/or radiotherapy or chemoradiotherapy [11-14]). In both study arms, local progression or recurrence occurred in 37 patients. The company's dossier provides no information as to whether these patients still had access to curative treatment options. Similarly, there is no information on how many of these patients received salvage surgery. In the intervention arm, 20 patients received radiotherapy and 14 patients received systemic therapy and radiotherapy. Based on patients with local progression or recurrence, this represents a proportion of 92%. 17 patients in the comparator arm received radiotherapy and 8 received systemic therapy and radiotherapy as their first subsequent therapy. Based on patients with local progression or recurrence, this represents a proportion of 68%.

Overall, it is assumed that the patients in the KEYNOTE 689 study received appropriate subsequent therapies.

### Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin

| Study                            | Adequate random sequence generation | Allocation concealment | Blinding |                | Reporting independent of the results | Absence of other aspects | Risk of bias at study level |
|----------------------------------|-------------------------------------|------------------------|----------|----------------|--------------------------------------|--------------------------|-----------------------------|
|                                  |                                     |                        | Patients | Treating staff |                                      |                          |                             |
| KEYNOTE 689                      | Yes                                 | Yes                    | No       | No             | Yes                                  | Yes                      | Low                         |
| RCT: randomized controlled trial |                                     |                        |          |                |                                      |                          |                             |

The risk of bias across outcomes is rated as low for the KEYNOTE 689 study. Limitations resulting from the open-label study design are described in Section I 3.2.2 under outcome-specific risk of bias.

### Transferability of the study results to the German health care context

The company argues that the results of the KEYNOTE 689 study can be transferred to the German health care context due to the characteristics of the investigated patient cohort, the study design and the on-label use of pembrolizumab as monotherapy for neoadjuvant treatment and subsequently for adjuvant treatment in combination with radiotherapy, with or without concomitant cisplatin therapy, and then as monotherapy. According to the company, 12 German study centres with a total of 73 included patients participate in the KEYNOTE 689 study.

The company did not provide any further information on the transferability of the study results to the German health care context. Further aspects regarding the transferability of the study results to the German health care context are described in the section on the implementation of individualized treatment in the adjuvant treatment phase (see Section I 3.1.2).

## I 3.2 Results on added benefit

### I 3.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - failure of curative treatment
  - symptoms, recorded using the EORTC QLQ-C30 and the EORTC QLQ-H&N35
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the EORTC QLQ-C30 and the EORTC QLQ-H&N35
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade  $\geq 3$ )
  - discontinuation due to AEs
  - immune-mediated SAEs
  - immune-mediated severe AEs (CTCAE grade  $\geq 3$ )
  - other specific AEs, if any

The selection of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A).

Table 13 shows for which outcomes data were available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin

| Study                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Outcomes         |                               |                                              |                           |                                                              |      |                         |                            |                                   |                                         |                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|-------------------------------|----------------------------------------------|---------------------------|--------------------------------------------------------------|------|-------------------------|----------------------------|-----------------------------------|-----------------------------------------|--------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Overall survival | Failure of curative treatment | Symptoms (EORTC QLQ-C30 and EORTC QLQ-H&N35) | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30 and QLQ-H&N35) | SAEs | Severe AEs <sup>b</sup> | Discontinuation due to AEs | Immune-mediated SAEs <sup>b</sup> | Immune-mediated severe AEs <sup>b</sup> | Other specific AEs |
| KEYNOTE 689                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Yes              | No <sup>a</sup>               | No <sup>a</sup>                              | No <sup>a</sup>           | No <sup>a</sup>                                              | Yes  | Yes                     | Yes                        | Yes                               | Yes                                     | No <sup>a</sup>    |
| <p>a. No suitable data available; for the reasoning, see the following text sections of this dossier assessment.</p> <p>b. Severe AEs are operationalized as CTCAE grade ≥ 3.</p> <p>AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; PT: Preferred Term; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-H&amp;N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale</p> |                  |                               |                                              |                           |                                                              |      |                         |                            |                                   |                                         |                    |

## Notes on outcomes

### *Failure of curative treatment*

In this therapeutic indication, surgery followed by radiotherapy or chemoradiotherapy constitutes a curative treatment approach. Failure of the curative treatment approach was therefore considered to be patient-relevant in this assessment. However, the analyses submitted by the company on the outcome EFS are not suitable for assessing the outcome failure of the curative treatment approach and are therefore not used for the benefit assessment. This is explained below.

According to the operationalization of the EFS as prespecified in the study documents, the following events should be included in the composite outcome:

- death from any cause
- radiological disease progression according to the blinded independent central review (BICR), according to RECIST 1.1
- radiological disease progression during the neoadjuvant phase, which prevents surgery (this subcomponent was only included with Protocol Amendment 8 of 7 September 2023)

- local progression, distant metastases or recurrence (assessed by biopsy, where indicated)

In the study documents and in Module 4A of its dossier, the company presents analyses of the outcome EFS according to BICR as the primary analysis. For these analyses, it presented details of the following qualifying events:

- death
- distant metastases
- local progression and distant metastases
- local progression/recurrence

Moreover, the company presented an analysis which it describes as a post-hoc adapted EFS according to BICR. In addition to the qualifying events mentioned above, this also includes the following two components:

- no R0 resection
- no surgery

Therefore, the qualifying events set out here differ from the prespecified events for the EFS. It remains unclear how the qualifying events recorded in the study in accordance with the study protocol were assigned to the qualifying events presented.

Moreover, in this operationalization, the subcomponent local progression does not necessarily reflect the failure of the curative treatment approach. Thus, based on the analyses submitted by the company, it remains unclear whether local progression prevented the curatively intended surgery or the subsequent radiotherapy, and therefore indicates that the treatment strategy has failed. The component 'radiological disease progression during the neoadjuvant phase that prevents surgery' was included in the outcome EFS as late as with the protocol amendment of 7 September 2023 (Amendment 8; approximately 5 years after the start of the study). In accordance with the original operationalization of the EFS (prior to Amendment 8), radiological disease progression was classified as an event, regardless of whether curatively intended surgery was subsequently performed (exception:  $\leq 10\%$  residual disease with invasive squamous cell carcinoma in the resected sample and/or all regional lymph nodes examined following surgery). It therefore remains unclear from the analyses presented whether patients who showed local progression prior to Amendment 8 but who nevertheless underwent surgery (and were potentially still receiving curative treatment) were included in the analyses. In the EPAR, the EMA also criticises the late change to the operationalization of the outcome EFS and further points out that the study design resulted

in a temporal imbalance in the recording of events, which does not comply with the FDA's recommendations [15].

Furthermore, it remains unclear how the 34 patients in the comparator arm who did not commence treatment following randomization were taken into account in the analyses (see Section I 3.1.2).

Notwithstanding these criticisms, the results presented on the EFS are not suitable for reflecting the outcome failure of the curative treatment approach due to the observation period being too short. In order to assess whether the curative treatment approach has failed, a sufficiently long follow-up period is generally required. Ideally, it should cover the high-risk period for the occurrence of relapses following the end of treatment for all patients. This ensures that the treatment actually prevents the failure of the curative treatment approach, rather than merely delaying it. For this therapeutic indication, the German Society for Haematology and Medical Oncology recommends follow-up every 6 months for the first 2 years and then annually for a further 3 years [11]. This is justified by the fact that the majority of relapses occur within the first two years following initial therapy. However, there were only 9 months between the enrolment of the last patient in October 2023 and the data cut of the KEYNOTE 689 study from July 2024. This is also shown by the frequent occurrence of administrative censorings from Month 9 onwards in the Kaplan-Meier curves. The high-risk period for the occurrence of relapses is therefore not covered by the follow-up period for a significant proportion of patients in both treatment arms, meaning that the occurrence of events after the end of treatment cannot be assessed with sufficient certainty.

#### ***Patient-reported outcomes on symptoms, health status and health-related quality of life***

For the outcomes of the categories morbidity and health-related quality of life (assessed with the EORTC QLQ-C30, EORTC QLQ-H&N35 and EQ-5D VAS), the company presents analyses with the help of constrained longitudinal data analysis (cLDA) in Module 4A.

According to the study protocol, baseline recordings of patient-reported outcomes in the intervention arm were to take place on Day 1 (+ 3 days) after randomization, prior to the first neoadjuvant treatment with pembrolizumab. In the comparator arm, the first survey was also scheduled for Day 1 after randomization, but it could also be carried out within four weeks prior to surgery. Thus, the time point of the baseline survey could already vary by up to 4 weeks between the study arms. It is unclear to what extent the baseline surveys actually differed between the study arms.

According to the study protocol, patient-reported outcomes in the intervention arm were to be recorded at baseline, during the neoadjuvant phase at Week 4, and prior to surgery at Week 6. As described above, the baseline survey of the questionnaires in the comparator arm was performed following randomization but no later than before the surgery. For both study

arms, no recordings are available for the approximately 6-week period between surgery and the start of adjuvant therapy. In both study arms, further recordings were carried out during the adjuvant phase, commencing with radiotherapy in Week 1 and Week 4. Further recordings followed 12 weeks after the end of radiotherapy, then every 3 months until the end of the third year of the study, and annually until the end of the fifth year of the study.

As the recordings were linked to the treatment phases and the treatment regimens differed between the study arms, the patient-reported outcomes were not collected in parallel, but at different points in time. In order to enable an analysis of the recorded data despite the different survey schemes, the company defined analysis time points based on the survey time points in the intervention arm. The survey time points of the comparator arm were assigned to these survey time points in the intervention arm. As a result of this assignment, some of the information relating to individual survey time points is lost, as it cannot be assigned appropriately or the dates are too far apart.

In the overall consideration, the results of the patient-reported outcomes are not used for the benefit assessment due to differences in data recordings between the study arms, particularly at baseline. In order to enable meaningful analyses of patient-reported outcomes in studies comparing different treatment strategies, the survey time points should not be linked to individual treatment phases, but should be determined on the basis of the time point of randomization.

### ***Analyses on side effects***

In the KEYNOTE 689 study, outcomes on side effects were recorded up to the last dose of the study medication plus 30 days (AEs) or 90 days (SAEs), or until the start of subsequent antineoplastic therapy (see Table 8). Due to the additional neoadjuvant and adjuvant administration of pembrolizumab in the intervention arm, for which there is no equivalent in the comparator arm, this results in significantly different observation periods between the treatment arms (see Table 10). Therefore, the company presented time-to-event analyses for the evaluations of the outcome category side effects. This is generally appropriate, as analyses based on relative risk cannot be meaningfully interpreted when the durations of observation differ significantly.

However, due to the study design, patients in the comparator arm undergo surgery earlier and begin adjuvant therapy earlier than those in the intervention arm. This time lag between surgery and adjuvant therapy in the intervention arm, which is due to the study design, means that, although adverse events associated with surgery and adjuvant radio(chemo)therapy occur at an earlier point in time in the comparator arm, they do not, as a rule, occur at a different frequency compared to that in the intervention arm. Due to the time lag of the events, effect estimates may arise in the event-time analyses which, in the context of this add-

on therapy with pembrolizumab, may not be plausible and therefore cannot be interpreted directly as an advantage or a disadvantage. Given the current data situation, the analyses submitted by the company for the outcomes SAEs, serious AEs and discontinuation due to AEs are each assessed to determine whether, taking the study design into account, it is possible to interpret the effects from the time-to-event analyses. If this is not possible, a qualitative interpretation of the results will follow, drawing on the Institute's calculations where necessary. No choice of specific AEs has been made in the current data situation.

Given the anticipated significant differences in the observation periods between the study arms due to the study design, and the shift of the treatment phases, a fixed observation period of approximately one year would have been appropriate for the outcomes on side effects in the KEYNOTE 689 study. This would have enabled analyses based on relative risk.

### ***Immune-mediated AEs***

The outcomes immune-mediated AEs, severe AEs and SAEs are of particular importance for the assessment of an immune checkpoint inhibitor such as pembrolizumab. The significance of these AEs specific to immune checkpoint inhibitors is generally acknowledged and is also reflected, for example, in the fact that the Association of the Scientific Medical Societies (AWMF) has included a separate chapter on the prevention, diagnosis and treatment of immune-mediated AEs in the current version of its guideline 'Supportive therapy for oncological patients' [16]. Accordingly, immune-mediated AEs represent relevant outcomes for the benefit assessment and are essential for weighing up the benefits and harms of the drug under assessment.

In Module 4A of its dossier, the company has not provided any analyses of immune-mediated AEs, severe AEs and SAEs for the relevant subpopulation, nor has it provided any justification for this.

The study documents of KEYNOTE 689 include data on the incidence of immune-mediated AEs in the total population. These were recorded as AEs of special interest (AESI). Given the sufficient similarity between the total population and the relevant subpopulation, with an overlap of approximately 95% (see Table 6), the AESIs on the immune-mediated AEs were used for the assessment.

### **I 3.2.2 Risk of bias**

Table 14 describes the risk of bias for the results of the relevant outcomes.

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin

| Study                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Study level | Outcomes         |                               |                                              |                           |                                                              |                      |                         |                            |                      |                                            |                    |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------------------|-------------------------------|----------------------------------------------|---------------------------|--------------------------------------------------------------|----------------------|-------------------------|----------------------------|----------------------|--------------------------------------------|--------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |             | Overall survival | Failure of curative treatment | Symptoms (EORTC QLQ-C30 and EORTC QLQ-H&N35) | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30 and QLQ-H&N35) | SAEs                 | Severe AEs <sup>a</sup> | Discontinuation due to AEs | Immune-mediated SAEs | Immune-mediated severe AEs <sup>a, b</sup> | Other specific AEs |
| KEYNOTE 689                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | N           | H <sup>b</sup>   | — <sup>c</sup>                | — <sup>c</sup>                               | — <sup>c</sup>            | — <sup>c</sup>                                               | H <sup>b, d, e</sup> | H <sup>b, d, e</sup>    | H <sup>b, d, e, f</sup>    | H <sup>d, e</sup>    | H <sup>d, e</sup>                          | — <sup>c</sup>     |
| <p>a. Severe AEs are operationalized as CTCAE grade ≥ 3.</p> <p>b. Possibly selective reporting; incomprehensible discrepancies in the information provided regarding the consideration of stratification factors within the dossier and between Module 4A and the statistical analysis plan.</p> <p>c. No suitable data available; see Section I 3.2.1 for reasoning.</p> <p>d. Large difference (&gt; 5 percentage points) between the study arms regarding the proportion of patients who were not considered in the analysis.</p> <p>e. Incomplete observations for potentially informative reasons with different observation periods.</p> <p>f. Lack of blinding in subjective recording of outcomes.</p> <p>AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; L: low; QLQ-C30: Quality of Life Questionnaire-Core 30; QLQ-H&amp;N35: Quality of Life Questionnaire-Head and Neck Cancer 35; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale</p> |             |                  |                               |                                              |                           |                                                              |                      |                         |                            |                      |                                            |                    |

The risk of bias across outcomes for the KEYNOTE 689 study was rated as low.

There was a high risk of bias for the results of the outcome overall survival. The reason for this is that there are discrepancies between the study documents and Module 4A regarding the handling of stratification factors in the analyses. Stratification factors in the KEYNOTE 689 study were the location of the primary tumour (oropharynx/oral cavity vs. larynx vs. hypopharynx), tumour stage (III vs. IVA) and PD-L1 status (TPS ≥ 50% vs. TPS < 50%). Deviating from this, the analyses on overall survival presented in Module 4A were not adjusted for PD-L1 status (TPS ≥ 50% vs. TPS < 50%). The company did not justify this approach. For this reason, selective reporting for the outcome overall survival cannot be ruled out.

The risk of bias for the results in the outcomes of the side effects category was rated as high. This is due to the large difference (> 5 percentage points) between the study arms regarding the proportion of patients who were not considered in the analysis. Moreover, there are

incomplete observations for potentially informative reasons with different follow-up periods. Furthermore, there are incomprehensible discrepancies in the information provided regarding the consideration of stratification factors within the dossier and between Module 4A and the statistical analysis plan for the outcomes SAEs, severe AEs (CTCAE grade  $\geq 3$ ), and discontinuation due to AEs. Therefore, selective reporting cannot be ruled out for these outcomes. As far as the results for the outcome discontinuation due to AEs are concerned, the high risk of bias is also due to the lack of blinding in subjective recording of outcomes.

### **Summary assessment of the certainty of conclusions**

It remains unclear whether the results of the KEYNOTE 689 study can be transferred to the German health care context without any restrictions. This is because the definition of a high risk of postoperative recurrence used in the study deviates from the valid guidelines in Germany (see Section I 3.1.2). Based on the KEYNOTE 689 study, at most hints, e.g. of an added benefit, can therefore be derived for all presented outcomes, irrespective of the risk of bias.

### **I 3.2.3 Results**

Table 15 summarizes the results on the comparison of pembrolizumab (neoadjuvant) followed by pembrolizumab in combination with radiotherapy, with or without concomitant cisplatin therapy, and subsequently as monotherapy with radiotherapy with or without concomitant cisplatin therapy in adult patients with resectable, locally advanced head and neck squamous cell carcinoma. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves on the included outcomes are presented in I Appendix B of the full dossier assessment, and the results on common AEs, SAEs, severe AEs, and discontinuations due to AEs in I Appendix C of the full dossier assessment.

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin (multipage table)

| Study outcome category<br>outcome            | Pembrolizumab neoadjuvant + adjuvant and radiotherapy ± cisplatin |                                                                      | Radiotherapy ± cisplatin |                                                                      | Pembrolizumab neoadjuvant + adjuvant and radiotherapy ± cisplatin vs. radiotherapy ± cisplatin |
|----------------------------------------------|-------------------------------------------------------------------|----------------------------------------------------------------------|--------------------------|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
|                                              | N                                                                 | median time to event in months [95% CI]<br>patients with event n (%) | N                        | median time to event in months [95% CI]<br>patients with event n (%) | HR [95% CI]; p-value                                                                           |
| KEYNOTE 689                                  |                                                                   |                                                                      |                          |                                                                      |                                                                                                |
| Mortality                                    |                                                                   |                                                                      |                          |                                                                      |                                                                                                |
| Overall survival                             | 347                                                               | NA<br>106 (30.5)                                                     | 335                      | 61.8 [49.2; NC]<br>128 (38.2)                                        | 0.72 [0.56; 0.94]; 0.014 <sup>a</sup>                                                          |
| Morbidity                                    |                                                                   |                                                                      |                          |                                                                      |                                                                                                |
| Failure of curative treatment                | No suitable data <sup>b</sup>                                     |                                                                      |                          |                                                                      |                                                                                                |
| Symptoms (EORTC QLQ-C30)                     | No suitable data <sup>b</sup>                                     |                                                                      |                          |                                                                      |                                                                                                |
| Symptoms (EORTC QLQ-H&N35)                   | No suitable data <sup>b</sup>                                     |                                                                      |                          |                                                                      |                                                                                                |
| Health status (EQ-5D VAS)                    | No suitable data <sup>d</sup>                                     |                                                                      |                          |                                                                      |                                                                                                |
| Health-related quality of life               | No suitable data <sup>d</sup>                                     |                                                                      |                          |                                                                      |                                                                                                |
| EORTC QLQ-C30                                | No suitable data <sup>b</sup>                                     |                                                                      |                          |                                                                      |                                                                                                |
| EORTC QLQ-H&N35                              | No suitable data <sup>b</sup>                                     |                                                                      |                          |                                                                      |                                                                                                |
| Side effects                                 |                                                                   |                                                                      |                          |                                                                      |                                                                                                |
| AEs (supplementary information) <sup>c</sup> | 345                                                               | 3.1 [3.0; 3.4]<br>333 (96.5)                                         | 300                      | 0.7 [0.4; 0.9]<br>291 (97.0)                                         | –                                                                                              |
| SAEs <sup>c</sup>                            | 345                                                               | 37.0 [24.9; NC]<br>171 (49.6)                                        | 300                      | NA [30.9; NC]<br>112 (37.3)                                          | 1.14 [0.89; 1.45]; 0.307 <sup>d</sup>                                                          |
| Severe AEs <sup>e, c</sup>                   | 345                                                               | 11.9 [9.3; 14.0]<br>263 (76.2)                                       | 300                      | 9.0 [6.4; 10.0]<br>224 (74.7)                                        | 0.64 [0.54; 0.78]; 0.001 <sup>d</sup>                                                          |
| Discontinuation due to AEs <sup>c</sup>      | 345                                                               | NA<br>85 (24.6)                                                      | 300                      | NA [28.0; NC]<br>45 (15.0)                                           | 1.01 [0.68; 1.49]; 0.970 <sup>d</sup>                                                          |

Table 15: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin (multipage table)

| Study outcome category outcome                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Pembrolizumab neoadjuvant + adjuvant and radiotherapy ± cisplatin |                                                                   | Radiotherapy ± cisplatin |                                                                   | Pembrolizumab neoadjuvant + adjuvant and radiotherapy ± cisplatin vs. radiotherapy ± cisplatin |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------|--------------------------|-------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | N                                                                 | median time to event in months [95% CI] patients with event n (%) | N                        | median time to event in months [95% CI] patients with event n (%) | HR [95% CI]; p-value                                                                           |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Events n (%)                                                      |                                                                   | Events n (%)             |                                                                   | RR [95% CI]; p-value <sup>g</sup>                                                              |
| Immune-mediated AEs <sup>f</sup> (supplementary information)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 361                                                               | 158 (43.8)                                                        | 315                      | 34 (10.8)                                                         | –                                                                                              |
| Immune-mediated SAEs <sup>f</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 361                                                               | 29 (8.0)                                                          | 315                      | 1 (0.3)                                                           | 25.30 [3.47; 184.70]; < 0.001                                                                  |
| Immune-mediated severe AEs, <sup>e, f</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 361                                                               | 36 (10.0)                                                         | 315                      | 2 (0.6)                                                           | 15.71 [3.81; 64.71]; < 0.001                                                                   |
| <p>a. Cox proportional hazards model with Efron's method for the handling of ties; stratified by location of the primary tumour (oropharynx/oral cavity vs. larynx vs. hypopharynx) and tumour stage (III vs. IVA).</p> <p>b. See Section I 3.2.10 of this dossier assessment for the reasoning.</p> <p>c. without the PTs neoplasm progression, malignant neoplasm progression and disease progression.</p> <p>d. Cox proportional hazards model with Efron's method for the handling of ties.</p> <p>e. Operationalized as CTCAE grade ≥ 3.</p> <p>f. The data relate to the total population as set out in the clinical study report.</p> <p>g. Institute's calculation of RR, 95% CI (asymptotic), and p-value (unconditional exact test, CSZ method according to [17]).</p> <p>AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event</p> |                                                                   |                                                                   |                          |                                                                   |                                                                                                |

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

## Mortality

A statistically significant difference in favour of pembrolizumab was shown between the study arms for the outcome overall survival. There is a hint of added benefit of pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy ± cisplatin (adjuvant), followed by pembrolizumab as monotherapy in comparison with the ACT.

## **Morbidity**

### ***Failure of curative treatment***

No suitable data were available for the outcome of failure of the curative treatment approach. There is no hint of added benefit of pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy ± cisplatin (adjuvant), followed by pembrolizumab as monotherapy over the ACT; an added benefit is therefore not proven.

### ***Symptoms (EORTC QLQ-C30 and EORTC QLQ-H&N35)***

No suitable data were available for the outcomes on symptoms recorded with the scales of the EORTC QLQ-C30 and the EORTC QLQ-H&N35E. There is no hint of added benefit of pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy ± cisplatin (adjuvant), followed by pembrolizumab as monotherapy over the ACT; an added benefit is therefore not proven.

### ***Health status (EQ-5D VAS)***

No suitable data were available for the outcome health status recorded using EQ-5D VAS. There is no hint of added benefit of pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy ± cisplatin (adjuvant), followed by pembrolizumab as monotherapy over the ACT; an added benefit is therefore not proven.

## **Health-related quality of life**

### ***EORTC QLQ-C30 and EORTC QLQ-H&N35***

No suitable data were available for the outcomes on health-related quality of life recorded with the scales of the EORTC QLQ-C30 and the EORTC QLQ-H&N35E. There is no hint of added benefit of pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy ± cisplatin (adjuvant), followed by pembrolizumab as monotherapy over the ACT; an added benefit is therefore not proven.

## **Side effects**

### ***SAEs***

The event time analyses showed no statistically significant difference between the study arms for the outcome SAEs. It is notable that the Kaplan-Meier curves cross each other. Consequently, the assumption of proportional hazards is not met and the hazard ratio cannot be interpreted. However, given the different follow-up durations between the treatment arms (longer follow-up in the intervention arm), there were significantly more events in the intervention arm than in the comparator arm (49.6% vs. 37.3%). Consequently, a possible disadvantage of pembrolizumab cannot be ruled out with sufficient certainty.

Overall, for this outcome, there is no hint for greater or lesser harm from pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy ± cisplatin (adjuvant), followed by

pembrolizumab as monotherapy, compared with the ACT; an added benefit is therefore not proven. The uncertainties described above regarding a possible disadvantage are taken into account in the overall conclusion on the added benefit.

### ***Severe AEs***

Based on the time-to-event analysis, a statistically significant difference in favour of pembrolizumab was shown between the study arms for the outcome severe AEs. Given that the event rates were almost identical between the study arms (76.2% vs. 74.7%), this effect is attributable solely to the earlier occurrence of the events in the comparator arm. The consideration of the Kaplan-Meier curves reveals an almost parallel course, merely staggered in time. The effect observed in the hazard ratio is therefore solely attributable to the later onset of AEs and does not justify an added benefit in this data situation.

Overall, for this outcome, there is no hint for greater or lesser harm from pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy  $\pm$  cisplatin (adjuvant), followed by pembrolizumab as monotherapy, compared with the ACT; an added benefit is therefore not proven.

### ***Discontinuation due to AEs***

The time-to-event analysis showed no statistically significant difference between the study arms for the outcome discontinuation due to AEs. It is notable that the Kaplan-Meier curves cross each other. Consequently, the assumption of proportional hazards is not met and the hazard ratio cannot be interpreted. However, given the different follow-up durations between the treatment arms, there were significantly more events in the intervention arm than in the comparator arm (24.6% vs. 15.0%). Consequently, a possible disadvantage of pembrolizumab cannot be ruled out with sufficient certainty.

Overall, for this outcome, there is no hint for greater or lesser harm from pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy  $\pm$  cisplatin (adjuvant), followed by pembrolizumab as monotherapy, compared with the ACT; an added benefit is therefore not proven. The uncertainties described above regarding a possible disadvantage are taken into account in the overall conclusion on the added benefit.

### ***Immune-mediated SAEs and severe AEs***

For the relative risk, a statistically significant difference to the disadvantage of pembrolizumab between the study arms was shown for each of the outcomes immune-mediated SAEs and immune-mediated severe AEs. Given the very pronounced effect, the relative risk is considered interpretable in this data situation, despite the unequal observation periods between the study arms, and is therefore used to determine the extent of the effect.

There is a hint of greater harm from pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy ± cisplatin (adjuvant), followed by pembrolizumab as monotherapy in comparison with the ACT.

### **I 3.2.4 Subgroups and other effect modifiers**

The following subgroup characteristics were taken into account for this benefit assessment:

- Age (< 65 years versus ≥ 65 years)
- Sex (male versus female)
- PD-L1 TPS status (TPS < 50% vs. TPS ≥ 50%)
- Tumour stage (III versus IVA)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also 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 only presented if there is a statistically significant and relevant effect in at least one subgroup.

Using the methods described above, the available subgroup analyses did not reveal any effect modifications.

### **I 3.3 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 [18].

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.

#### **I 3.3.1 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 I 3.2 (see Table 16).

Table 16: Extent of the added benefit at outcome level: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin (multipage table)

| Outcome category outcome                                        | Intervention vs. comparator median time to event (months) or proportion of events (%) effect estimation [95% CI]; p-value probability <sup>a</sup> | Derivation of extent <sup>b</sup>                                                                               |
|-----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| <b>Outcomes with observation over the entire study duration</b> |                                                                                                                                                    |                                                                                                                 |
| <b>Mortality</b>                                                |                                                                                                                                                    |                                                                                                                 |
| Overall survival                                                | NA vs. 61.8<br>HR: 0.72 [0.56; 0.94];<br>p = 0.014<br>probability: hint                                                                            | Outcome category: mortality<br>$0.85 \leq Cl_u < 0.95$<br>added benefit, extent: considerable                   |
| <b>Outcomes with shortened observation period</b>               |                                                                                                                                                    |                                                                                                                 |
| <b>Morbidity</b>                                                |                                                                                                                                                    |                                                                                                                 |
| Failure of curative treatment                                   | No suitable data <sup>c</sup>                                                                                                                      | Lesser benefit not proven / added benefit not proven                                                            |
| Symptoms (EORTC QLQ-C30)                                        | No suitable data <sup>c</sup>                                                                                                                      | Lesser benefit not proven / added benefit not proven                                                            |
| Symptoms (EORTC QLQ-H&N35)                                      | No suitable data <sup>c</sup>                                                                                                                      | Lesser benefit not proven / added benefit not proven                                                            |
| Health status (EQ-5D VAS)                                       | No suitable data <sup>c</sup>                                                                                                                      | Lesser benefit not proven / added benefit not proven                                                            |
| <b>Health-related quality of life</b>                           |                                                                                                                                                    |                                                                                                                 |
| EORTC QLQ-C30                                                   | No suitable data <sup>c</sup>                                                                                                                      | Lesser benefit not proven / added benefit not proven                                                            |
| EORTC QLQ-H&N35                                                 | No suitable data <sup>c</sup>                                                                                                                      | Lesser benefit not proven / added benefit not proven                                                            |
| <b>Side effects</b>                                             |                                                                                                                                                    |                                                                                                                 |
| SAEs                                                            | Qualitative interpretation of results <sup>c</sup>                                                                                                 | Greater/lesser harm not proven                                                                                  |
| Severe AEs                                                      | Qualitative interpretation of results <sup>c</sup>                                                                                                 | Greater/lesser harm not proven                                                                                  |
| Discontinuation due to AEs                                      | Qualitative interpretation of results <sup>c</sup>                                                                                                 | Greater/lesser harm not proven                                                                                  |
| Immune-mediated SAEs                                            | 8.0% vs. 0.3%<br>RR: 25.30 [3.47; 184.70];<br>RR: 0.04 [0.005; 0.29] <sup>d</sup> ;<br>p < 0.001<br>probability: hint                              | Outcome category: serious/severe side effects<br>$Cl_u < 0.75$ ; risk $\geq 5\%$<br>greater harm, extent: major |

Table 16: Extent of the added benefit at outcome level: neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin vs. surgery, adjuvant radiotherapy ± cisplatin (multipage table)

| Outcome category<br>outcome                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Intervention vs. comparator<br>median time to event (months) or<br>proportion of events (%)<br>effect estimation [95% CI];<br>p-value<br>probability <sup>a</sup> | Derivation of extent <sup>b</sup>                                                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|
| Immune-mediated<br>severe AEs                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 10.0% vs. 0.6%<br>RR: 15.71 [3.81; 64.71];<br>RR: 0.06 [0.02; 0.26] <sup>d</sup> ;<br>p < 0.001<br>probability: hint                                              | Outcome category: serious/severe side effects<br>CI <sub>u</sub> < 0.75; risk ≥ 5%<br>greater harm, extent: major |
| <p>a. Probability provided if there is a statistically significant and relevant effect.<br/> b. Depending on the outcome category and the scale of the outcome, the effect size is estimated with different limits based on the upper limit of the confidence interval (CI<sub>u</sub>).<br/> c. See Sections I 3.2.1 and I 3.2.3 of this dossier assessment for the reasoning.<br/> d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.</p> <p>AE: adverse event; CI: confidence interval; CI<sub>u</sub>: upper limit of confidence interval; HR: hazard ratio; MD: mean difference; RR: relative risk; SAE: serious adverse event; SMD: standardized mean difference</p> |                                                                                                                                                                   |                                                                                                                   |

### I 3.3.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account for the overall conclusion on the extent of the added benefit.

Table 17: Positive and negative effects from the assessment of neoadjuvant pembrolizumab, surgery, adjuvant pembrolizumab + radiotherapy ± cisplatin in comparison with surgery, adjuvant radiotherapy ± cisplatin

| Positive effects                                                                                                                                                                                                                   | Negative effects                                                                                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Outcomes with observation over the entire study duration</b>                                                                                                                                                                    |                                                                                                                                                                       |
| Mortality<br>▪ overall survival: hint of an added benefit – extent: “considerable”                                                                                                                                                 | –                                                                                                                                                                     |
| <b>Outcomes with shortened observation period</b>                                                                                                                                                                                  |                                                                                                                                                                       |
| –                                                                                                                                                                                                                                  | Serious/severe side effects<br>▪ immune-mediated SAEs: hint of greater harm – extent: “major”<br>▪ immune-mediated severe AEs: hint of greater harm – extent: “major” |
| disadvantages in the outcomes SAEs and discontinuation due to AEs cannot be ruled out with sufficient certainty. No suitable data are available for the patient-reported outcomes on morbidity and health-related quality of life. |                                                                                                                                                                       |
| AE: adverse event; SAE: serious adverse event                                                                                                                                                                                      |                                                                                                                                                                       |

In the overall consideration, there were both positive and negative effects of pembrolizumab (neoadjuvant) + pembrolizumab and radiotherapy ± cisplatin (adjuvant), followed by pembrolizumab as monotherapy in comparison with the ACT.

A hint of an added benefit with the extent “considerable” was shown for the outcome overall survival.

In contrast, there were hints of greater harm of major extent in the category serious/severe side effects for the immune-mediated AEs. Furthermore, disadvantages in other outcomes on SAEs and discontinuation due to AEs cannot be ruled out with sufficient certainty. No suitable data are available for the patient-reported outcomes on morbidity and health-related quality of life. Overall, however, these aspects do not entirely call into question the positive effect in the outcome overall survival.

In summary, there is a hint of minor added benefit from pembrolizumab (neoadjuvant) followed by pembrolizumab in combination with radiotherapy, with or without concomitant cisplatin therapy, and subsequently as monotherapy over the ACT for adult patients with resectable, locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS  $\geq 1$  and who exhibit a high post-operative risk profile and for whom cisplatin-based therapy is suitable, or for those with a low postoperative risk profile.

This deviates from the company’s assessment, which derived an indication of considerable added benefit.

#### **I 4 Research question 2: adult patients with a high postoperative risk profile for whom cisplatin-based therapy is not suitable.**

##### **I 4.1 Information retrieval and study pool**

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on pembrolizumab (status: 25 September 2025)
- Bibliographical literature search on pembrolizumab (last search on 09 September 2025)
- Search of trial registries/trial results databases for studies on pembrolizumab (last search on 01 October 2025)
- Search on the G-BA website for pembrolizumab (last search on 01 October 2025)

To check the completeness of the study pool:

- Search in trial registries for studies on pembrolizumab (last search on 03 December 2025); for search strategies, see I Appendix A of the full dossier assessment

A review of the completeness of the study pool did not identify any relevant studies.

##### **I 4.2 Results**

The company did not present any data for adult patients with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS  $\geq 1$ , with a high postoperative risk profile for whom cisplatin-based therapy is not suitable. There is no hint of an added benefit of pembrolizumab in comparison with the ACT; an added benefit is therefore not proven.

##### **I 4.3 Probability and extent of added benefit**

An added benefit is not proven since the company did not present any data for the assessment of the added benefit in adult patients with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS  $\geq 1$ , with a high postoperative risk profile for whom cisplatin-based therapy is not suitable.

## I 5 Probability and extent of added benefit – summary

Table 18 summarizes the result of the assessment of the added benefit of the drug in comparison with the ACT.

Table 18: Pembrolizumab – probability and extent of added benefit

| Research question                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Therapeutic indication                                                                                                                                                       | ACT <sup>a</sup>                                                                                                                                                                                                                                                                                                                          | Probability and extent of added benefit  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| Adult patients with resectable locally advanced head and neck squamous cell carcinoma whose tumours express PD-L1 with a CPS $\geq 1$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                           |                                          |
| 1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | With a high postoperative risk profile for whom cisplatin-based therapy is suitable, or with a low postoperative risk profile; neoadjuvant and adjuvant therapy <sup>b</sup> | A therapy regimen consisting of <ul style="list-style-type: none"> <li>▪ surgery (tumour resection)</li> <li>▪ followed by individualized treatment, choosing from<sup>c, d</sup>: <ul style="list-style-type: none"> <li>▫ adjuvant chemoradiotherapy with cisplatin and</li> <li>▫ adjuvant radiotherapy</li> </ul> </li> </ul>         | Hint of minor added benefit <sup>e</sup> |
| 2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | With a high postoperative risk profile for whom cisplatin-based therapy is not suitable; neoadjuvant and adjuvant therapy <sup>b</sup>                                       | A therapy regimen consisting of <ul style="list-style-type: none"> <li>▪ surgery (tumour resection)</li> <li>▪ followed by adjuvant chemoradiotherapy with: <ul style="list-style-type: none"> <li>▫ mitomycin + 5-FU<sup>f</sup> or</li> <li>▫ carboplatin + 5-FU<sup>f</sup> or</li> <li>▫ docetaxel<sup>f</sup></li> </ul> </li> </ul> | Added benefit not proven <sup>g</sup>    |
| <p>a. Presented is the respective ACT specified by the G-BA.</p> <p>b. For this therapeutic indication, it is assumed that the term 'locally advanced disease' covers stage III–IVA tumours.</p> <p>c. The treatment decision is made under particular consideration of the post-operative risk profile.</p> <p>d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study).</p> <p>e. The KEYNOTE 689 study only included patients with an ECOG PS of 0 or 1. Therefore, it remains unclear whether the observed effects can be transferred to patients with an ECOG PS of <math>&gt; 2</math>.</p> <p>f. In this therapeutic indication, the drugs carboplatin, cetuximab and bleomycin are approved for use as adjuvant treatment in patients with a high postoperative risk profile for whom cisplatin-based therapy is not suitable. According to the G-BA, these are either not recommended in the guideline or are recommended in a different combination. Instead, the guideline recommends mitomycin + 5-FU or carboplatin + 5-FU or docetaxel. The G-BA therefore assumes that, according to the generally accepted current state of medical knowledge, the off-label use of mitomycin + 5-FU or carboplatin + 5-FU or docetaxel is generally to be preferred to the drugs approved so far for this therapeutic indication for patients with a high postoperative risk profile for whom cisplatin-based therapy is not suitable (§6(2), sentence 3, number 3, AM-NutzenV).</p> <p>g. There are no data available for patients who have a high postoperative risk profile but for whom cisplatin-based therapy is not suitable.</p> <p>5-FU: 5-fluorouracil; ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; Pharmaceutical Directive; CPS: combined positive score; G-BA: Federal Joint Committee; PD-L1: programmed cell death-ligand 1</p> |                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                           |                                          |

The approach for the derivation of an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

## I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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