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Nivolumab (oesophageal cancer) –

Benefit assessment according to §35a Social Code Book V[1] (new therapeutic indication)

Extract

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AWMF	Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (Association of the Scientific Medical Societies in Germany)
BSC	best supportive care
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) 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 nivolumab. 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 17 December 2020.

Research question

The aim of this report is to assess the added benefit of nivolumab in comparison with best supportive care (BSC) as the appropriate comparator therapy (ACT) in adult patients with unresectable, advanced, recurrent, or metastatic oesophageal squamous cell carcinoma. The treatment is performed in patients who have received prior fluoropyrimidine-based and platinum-based combination chemotherapy.

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of nivolumab

Indication	**ACT[a]**
Adults with unresectable, advanced, recurrent, or metastatic oesophageal squamous cell carcinoma following prior fluoropyrimidine-based and platinum-based combination chemotherapy[b,c]	BSC[d]

a. Presented is the ACT specified by the G-BA.
b. The planned therapeutic indication is assumed to also include patients with locally advanced or metastatic oesophageal carcinoma following first-line therapy.
c. Patients for whom radiotherapy with curative intent is indicated are the exception in the patient group covered by this therapeutic indication; therefore, they are not included in the present research question. The target population is assumed to comprise patients for whom radiotherapy with curative intent is typically not indicated.
d. BSC is defined as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

The company departs from the G-BA's specification. It has defined 2 subpopulations within the patient population with the therapeutic indication by postulating a subpopulation of patients for whom another antineoplastic therapy is indicated. As the ACT for this group, the company has specified a further antineoplastic therapy upon the physician's discretion. For the second subpopulation defined by the company within this therapeutic indication, further antineoplastic therapy is not indicated. For these patients, the company has specified BSC as the ACT.

The company's approach is not appropriate. The assessment was conducted for the total population in the therapeutic indication by means of patient-relevant outcomes on the basis of the data provided in the company's dossier and in comparison with the ACT specified by the G-BA.

Results

During its information retrieval, the company found the approval study ATTRACTION-3 and used it for assessing the added benefit of nivolumab for the subpopulation of patients who, in its opinion, are indicated for a further antineoplastic therapy. However, this randomized controlled trial (RCT) is unsuitable for the assessment of added benefit of nivolumab in the present therapeutic indication since BSC, the ACT specified by the G-BA, was inadequately implemented in the study's control arm. In the comparator arm of the ATTRACTION-3 study, patients were allocated to docetaxel or paclitaxel monochemotherapy. The study prohibited any further treatment, even when the guidelines included their use as BSC for the symptomatic treatment of advanced oesophageal carcinoma.

Hence, no suitable data are available for the assessment of added benefit of nivolumab in comparison with the ACT of BSC in adults with unresectable, advanced, recurrent, or metastatic oesophageal squamous cell carcinoma following prior fluoropyrimidine-based and platinum-based combination chemotherapy. Consequently, there is no hint of an added benefit of nivolumab in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

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

[3] 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].

Table 3: Nivolumab – probability and extent of added benefit

Indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with unresectable, advanced, recurrent, or metastatic oesophageal squamous cell carcinoma following prior fluoropyrimidine-based and platinum-based combination chemotherapy[b,c]	BSC[d]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The planned therapeutic indication is assumed to also include patients with locally advanced or metastatic oesophageal carcinoma following first-line therapy.
c. Patients for whom radiotherapy with curative intent is indicated are the exception in the patient group covered by this therapeutic indication; therefore, they are not included in the present research question. The target population is assumed to comprise patients for whom radiotherapy with curative intent is typically not indicated.
d. BSC is defined as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of nivolumab in comparison with BSC as the ACT in adult patients with unresectable, advanced, recurrent, or metastatic oesophageal squamous cell carcinoma. The treatment is performed in patients who received prior fluoropyrimidine-based and platinum-based combination chemotherapy.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of nivolumab

Indication	**ACT**[a]
Adults with unresectable, advanced, recurrent, or metastatic oesophageal squamous cell carcinoma following prior fluoropyrimidine-based and platinum-based combination chemotherapy[b,c]	BSC[d]
a. Presented is the ACT specified by the G-BA. b. The planned therapeutic indication is assumed to also include patients with locally advanced or metastatic oesophageal carcinoma following first-line therapy. c. Patients for whom radiotherapy with curative intent is indicated are the exception in the patient group covered by this therapeutic indication; therefore, they are not included in the present research question. The target population is assumed to comprise patients for whom radiotherapy with curative intent is typically not indicated. d. BSC is defined as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee	

The company departs from the G-BA's specification. It has defined 2 subpopulations within the patient population of the therapeutic indication by postulating a subpopulation of patients who are indicated for a further antineoplastic therapy. As the ACT for this group, the company specified a further antineoplastic therapy upon the physician's discretion. For the second subpopulation defined by the company within this therapeutic indication, further antineoplastic therapy is not indicated. For these patients, the company has specified BSC as the ACT. The company justified this specification by citing information from disease-specific guidelines [3-6] as well as the healthcare context in Germany, for which it relied on a retrospective analysis of patient records commissioned by the company (Module 3 L). Here, the company equated its specified antineoplastic therapy with systemic chemotherapy, which the guidelines list among the therapy options for the present therapeutic indication. According to the company, the analysis of the patient records shows that only a small percentage of patients receives BSC, while the majority of patients is treated with one of the two taxanes: docetaxel or paclitaxel.

The company's approach is inappropriate because it evidently assumes the existence of 2 distinct patient populations with different treatment needs within the present therapeutic indication: reportedly, one requiring a further antineoplastic therapy, while the other is receiving appropriate treatment with BSC. However, the company fails to define the criteria by which the two populations can be differentiated. In particular, the intended treatment goal of a further antineoplastic therapy remains unclear.

The company's approach cannot be inferred from the information provided by the guidelines (particularly: S3 guideline of the Association of the Scientific Medical Societies in Germany (AWMF) [4], European Society for Medical Oncology guideline [3], National Comprehensive Cancer Networks guideline [5]). For the disease stage of oesophageal cancer after completion of first-line therapy, which is the subject matter of this benefit assessment, the guidelines explicitly do not define different treatment goals based on specific patient characteristics. The overarching treatment goal is palliation rather than targeted antitumour therapy for extending survival. Patient treatment is to focus on an individualized approach for alleviating typical symptoms of advanced disease. Various interdisciplinary treatment options are available, which can also be combined in the form of multimodal therapy. Options include radiotherapy, endoscopic and surgical methods, and – for patients in good general condition – chemotherapy for symptom control. No robust evidence is available on the efficacy of second-line chemotherapy in the form of an extension of survival, maintenance of quality of life, or any superiority of isolated chemotherapy in comparison with other options of multimodal palliative treatment. Therefore, the AWMF guideline describes symptom control merely as a theoretical treatment goal for second-line chemotherapy. The decision as to whether to use any treatment option alone or in combination with others is not solely based on a patient characteristic such as general condition (see Section 2.3 on the suitability of the data presented by the company) but should be made in view of each individual patient's symptoms.

In summary, this therapeutic indication presents neither separate patient populations with different treatment goals nor any evidence of second-line chemotherapy being superior to the other options as part of BSC. The assessment was therefore conducted for the total population in the therapeutic indication by means of patient-relevant outcomes on the basis of the data provided in the company's dossier and in comparison with the ACT specified by the G-BA.

2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on nivolumab (as of 30 September 2020)
- Bibliographic literature search on nivolumab (most recent search on 30 September 2020)
- Search in trial registries / study results databases on nivolumab (most recent search on 30 September 2020)
- Search on the G-BA website on nivolumab (most recent search on 24 September 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on nivolumab (most recent search on 19 January 2021)

The check did not reveal any relevant RCT for assessing the added benefit of nivolumab in comparison with the ACT.

The data presented by the company are unsuitable for the benefit assessment of nivolumab in comparison with the ACT. The reasons are explained below. For this purpose, the data considered by the company are described first.

Evidence provided by the company

During its information retrieval, the company identified the approval study ATTRACTION-3 [7] and used it for assessing the added benefit of nivolumab for the subpopulation of patients who, in its opinion, are indicated for further antineoplastic therapy.

ATTRACTION-3 is an open-label RCT comparing nivolumab with docetaxel or paclitaxel monochemotherapy upon the physician's discretion. It included adults with oesophageal carcinoma who were refractory or intolerant to fluoropyrimidine-based and platinum-based combination chemotherapy, had already received a treatment regimen, and were ineligible for radical resection. A total of 419 patients were randomly allocated to the two study arms in a 1:1 ratio. The patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of 0 or 1. Prior to randomization, the investigator determined for each patient individually whether, in case of allocation to the study's control arm, monochemotherapy was to be administered using either docetaxel or paclitaxel. The study protocol allowed no further interventions, such as surgical measures or radiotherapy/chemotherapy, to be administered alongside the drug treatment options of nivolumab or docetaxel/paclitaxel. The primary outcome of the study was overall survival; patient-relevant secondary outcomes were health status and adverse events.

Unsuitability of the data presented by the company for the benefit assessment

The ATTRACTION-3 study is unsuitable for the assessment of added benefit of nivolumab in the present therapeutic indication since BSC, the ACT specified by the G-BA, was inadequately implemented in the study's control arm. BSC is defined as the therapy ensuring the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.

The study participants were in good general condition (ECOG-PS 0 or 1) and therefore generally eligible for systemic therapy for symptom control as part of palliative therapy according to guidelines [3-5]. However, the guidelines explicitly state that the decision to administer a treatment option either alone or in combination with other options should always be based on the patient's individual symptoms rather than on general patient characteristics. The ATTRACTION-3 study disallowed additional treatment options beyond monochemotherapy, which are used for the symptomatic treatment of advanced oesophageal carcinoma in the sense of BSC. Therefore, it was impossible to adjust patients' palliative therapy based on their individual symptoms. The company has not provided any reasons as to why both the use of monochemotherapy and the preselection of the two substances docetaxel

and paclitaxel would represent the only or best patient-specific selection for all patients of the control group. Moreover, the company fails to describe why it was not necessary to adjust therapy to the individual symptoms of control group patients by adding further treatment options beyond monochemotherapy.

Overall, monochemotherapy as the sole treatment option is therefore believed to insufficiently cover multimodal, individualized, symptom-oriented therapy as in BSC for the patients of the ATTRACTION-3 study's control group.

Furthermore, in the approval letter [8], the European Medicines Agency (EMA) states that due to the selection of taxane monochemotherapy (docetaxel or paclitaxel) instead of BSC as the comparator therapy, the efficacy and tolerability of nivolumab might generally be overestimated in the ATTRACTION-3 study. The EMA supports this assertion by the (expected) low efficacy of taxanes in combination with elevated toxicity, a reduction in health-related quality of life, and possibly even poorer overall survival.

2.4 Results on added benefit

No suitable data are available for assessing any added benefit of nivolumab in comparison with the ACT of BSC in adults with unresectable, advanced, recurrent or metastatic oesophageal squamous cell carcinoma following prior fluoropyrimidine-based and platinum-based combination chemotherapy. Consequently, there is no hint of an added benefit of nivolumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 presents a summary of the results regarding the benefit assessment of nivolumab in comparison with the ACT.

Table 5: Nivolumab – probability and extent of added benefit

Indication	ACT[a]	Probability and extent of added benefit
Adults with unresectable, advanced, recurrent, or metastatic oesophageal squamous cell carcinoma following prior fluoropyrimidine-based and platinum-based combination chemotherapy[b,c]	BSC[d]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The planned therapeutic indication is assumed to also include patients with locally advanced or metastatic oesophageal carcinoma following first-line therapy.
c. Patients for whom radiotherapy with curative intent is indicated are the exception in the patient group covered by this therapeutic indication; therefore, they are not included in the present research question. The target population is assumed to comprise patients for whom radiotherapy with curative intent is typically not indicated.
d. BSC is defined as the therapy that ensures the best possible, individually optimized supportive care to alleviate symptoms and improve the quality of life.

ACT: appropriate comparator therapy; BSC: best supportive care; G-BA: Federal Joint Committee

The assessment described above departs from that of the company in that, on the basis of the results of the ATTRACTION-3 study, the company has derived a hint of considerable added benefit for patients who, in its view, are indicated for further antineoplastic therapy.

The G-BA decides on the added benefit.

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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