Recommendation No. 106/2019

of 04 December 2019

issued by the President of the Agency for Health Technology Assessment and Tariff System

on the evaluation of Bavencio (avelumab) under the following pharmaceutical programme: "Treatment of Merkel cell carcinoma with avelumab (ICD-10 C44"

The President of AOTMiT recommends reimbursing Bavencio (avelumab) under the following pharmaceutical programme: "Treatment of Merkel cell carcinoma with avelumab (ICD-10 C44)" **on condition that** the risk-sharing scheme in question is enhanced and an additional performance-based mechanism is introduced.

Statement of reasons for the recommendation

Taking into account the position of the Transparency Council, the available scientific evidence, clinical guidelines and reimbursement recommendations, the President of AOTMiT believes that public funding of the health technology in question is justified.

No clinical trials directly comparing avelumab with chemotherapy, which was considered as the comparator in first-line treatment (1L), and with best supportive care (BSC), which was selected as the comparator in second-line treatment and subsequent lines of treatment (+2L), have been identified as part of the clinical analysis. The efficacy of the intervention in question has been demonstrated only on the basis of a comparison of single-arm studies of the pharmaceutical technology in question and its comparators.

The comparison indicates that in JAVELIN Merkel 200 B (the use of avelumab), the median overall survival (OS) in the 1L patient population was not achieved, while in Cowey 2017 and Iyer 2016 (the use of chemotherapy), the median OS was 10.2 and 9.5 months, respectively. In the same population, the median duration of response (DOR) in JAVELIN Merkel 200B was 15.2 months, while in studies where chemotherapy constituted the intervention, median DOR ranged from 3.0 to 5.7 months. For the progression free survival (PFS) outcome, the median achieved values may be considered as similar in the studies on both interventions.

In the case of the +2L population, the compared results for both the median OS and DOR were significantly more in favour of avelumab than in the studies on the comparators; in the case of BSC — results of chemotherapy treatment in the second-line and subsequent lines of treatment. The median OS in JAVELIN Merkel 200 A (where avelumab was used) was 12.9

months, while in studies where chemotherapy was used, the median OS ranged from 4.4 to 5.7 months.

However, it should be borne in mind that a comparison of results, not suggesting significant differences between the results for the 1L population or the +2L population as well the comparison suggesting higher efficacy of avelumab in comparison to its comparators, cannot be considered as conclusive evidence on the similarity/ superiority of avelumab over its comparators. The reason for this is that it has not been possible to carry out either a direct or indirect comparison, and this is merely a collation of the results, subject to considerable limitations.

The results of the economic analysis demonstrate that the use of Bavencio therapy in place of its comparators in both of the above-mentioned populations is associated with greater health effects and higher therapy costs. The results of the analysis demonstrate the lack of cost-effectiveness of the medicine in question, *[information protected as a trade secret]*.

The results of the budget impact analysis demonstrate an increase in the payer's annual expenditure by several million zlotys, however, the possibility of drawing conclusions on the basis of these estimates is limited due to the lack of data allowing for verification of the target population size.

In view of the above, the RSS should be enhanced and, since it is not possible to clearly confirm the efficacy of the technology in question, inclusion of a performance-based mechanism should be considered.

The identified guidelines demonstrate that it is currently not possible to determine a standard procedure recommended for metastatic MCC treatment. The PTOK 2018, NCCN 2019 and NICE 2018 guidelines recommend the use of immunotherapy in the form of PDL1/PD-1 inhibitors, avelumab and pembrolizumab included; additionally, US guidelines also mention nivolumab therapy. PTOK 2018 recommends introducing avelumab after the failure of systemic chemotherapy, while pembrolizumab is recommended without prior systemic therapy. However, it is worth bearing in mind that the medicines listed in the guidelines except for avelumab are not currently registered in the indication in question. The EDF/EADO/EORTC 2015 guidelines do not refer to the use of avelumab in metastatic Merkel cell carcinoma, probably due to the fact that they were developed at a time when no MCC treatment was registered by either the EMA or the FDA.

6 reimbursement recommendations have been identified, 4 of which were positive, one conditionally positive and one negative.

Subject of the application

The commission of the Minister for Health concerns assessing whether the following medicinal product should be financed from public funds:

Bavencio (avelumab), concentrate for solution for infusion 20 mg/mL, 10 mL per 1 vial, EAN: 04054839462153, for which the proposed ex-factory price amounts to PLN *[information protected as a trade secret]*

The proposed payment and reimbursement availability category: a free-of-charge medicine available under a pharmaceutical programme, as part of a new joint-limit group. The applicant has proposed a risk-sharing scheme.

Health problem

The ICD-10 code: C44 – other malignant neoplasm of skin is used in the MoH's commission to describe Metastatic Merkel cell carcinoma. Neither the 2008 edition of the ICD-10 classification, nor the latest 2016 edition included a separate code for Merkel cell carcinoma (MCC). As a result, this code covers patients from a wider population than the population specified in the application.

Merkel cell carcinoma, otherwise known as neuroendocrine skin carcinoma, is a rare, highly malignant skin cancer. This cancer most likely originates from neuroendocrine cells (Merkel cells), which are located in the skin, where they form touch receptors. It usually occurs in the form of a fleshy, bluish or purple-red nodule located most often on the skin of the face, head, neck, and rarely on the arms or legs; however, these lesions can occur anywhere on the body.

According to the RARECARE database, the incidence of MCC in Europe between 1995 and 2002 was 0.13 per 100 000 individuals. The available literature indicates an MCC incidence rate of 0.1 individuals– 0.4/100,000 in EU Member States and 0.2 – 0.4/100,000 individuals in Europe. The MCC incidence is low; in Poland, this rate it is estimated at 0.25-0.32/100,000 inhabitants per year. This type of skin malignant cancer is almost forty times less frequent than malignant melanoma. 5-12% of newly diagnosed patients have metastases upon diagnosis

The risk of developing this cancer by patients under 50 years of age is very low, and increases significantly between 50 and 65 years of age. MCC lesions are most commonly located on the scalp and neck (44-48% of cases), upper limb skin (about 19% of cases) and lower limb skin (16-20% of cases). It rarely occurs in other locations, e.g., mucous membranes or MCC metastases from an unknown primary focus.

According to available literature, in approx. 20% of cases long-term sun exposure is the main factor in the development of this cancer. The remaining 80% of patients are diagnosed with a Merkel-cell polyomavirus (MCPyV), which, combined with exposure to the sun, is likely to contribute to the development of this cancer. However, this virus also frequently occurs in a non-aggressive, malignant form.

In approx. 50% of cases, Merkel cell carcinoma causes expression of programmed death-1 receptor (PD-1) on tumour-infiltrating lymphocytes and demonstrates expression of programmed death-ligand 1 receptor (PD-L1) on neoplasm cells or macrophage infiltration (focused on the leading edges of tumours).

The most important prognostic factors are the size of the primary tumour, the presence of metastases at the time of diagnosis and the extent of metastases to lymph nodes. Ten-year survival of MCC patients is estimated at an average of approx. 57% (65% in women, 50.5% in men). Depending on the primary tumour, the 10-year survival rate is 61% for tumours with a diameter of 2 cm or less, while for tumours larger than 2 cm, the survival rate is 39%. Based on data collected by the American Joint Committee on Cancer (AJCC), the 2-year survival of patients with stage IV of the disease does not exceed 26%.

Alternative health technologies

Taking into account clinical guidelines, expert opinion and technologies currently financed from public funds, chemotherapy regimens (for first-line treatment) and best supportive care (BSC) (for second-line and subsequent lines of treatment) should be considered as comparators for the intervention in question.

However, it should be borne in mind that the chemotherapy regimens indicated by the applicant include both medicines currently financed from public funds in Poland and non-reimbursed medicines.

Description of the proposed intervention

Avelumab is a human immunoglobulin G1 (IgG1) monoclonal antibody directed against programmed death ligand 1 (PD-L1). Avelumab binds PD-L1 and blocks the interaction between PD-L1 and the programmed death 1 (PD-1) and B7.1 receptors. This removes the suppressive effects of PD-L1 on cytotoxic CD8+ T-cells, resulting in the restoration of anti-tumour T-cell responses.

Avelumab has also shown to induce natural killer (NK) cell-mediated direct tumour cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC).

In line with the summary of product characteristics (SPC), Bavencio is indicated as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC) which is consistent with the indication in question under the commission of the Minister of Health.

Efficacy, effectiveness and safety assessment

The assessment consists in the collection of data on health consequences (efficacy and safety) resulting from the use of a new therapy in a given health problem and other publicly financed therapies which constitute an alternative treatment option available in a given health problem. Then, the assessment requires determining the reliability of the collected data and comparing the results regarding the efficacy and safety of the new therapy with those of therapies already available in a given health problem.

Based on the above, the efficacy and safety assessment allows for obtaining information about the extent of the health effect (with regard to both efficacy and safety) to be expected in relation to the new therapy compared to the other considered therapeutic options.

The conducted systematic review failed to identify any studies comparing the efficacy of avelumab and selected comparators for particular treatment lines. Therefore, separate systematic searches were carried out for the intervention in question and the alternative intervention. The following studies have been identified:

- For avelumab:
    - JAVELIN Merkel 200 – a prospective single-arm clinical study assessing the efficacy of avelumab as monotherapy used in adult patients with metastatic Merkel cell carcinoma. The study consisted of two parts:
        - JAVELIN Merkel 200 A (publication: Kaufman 2018) – the results of the study refer to the efficacy in patients receiving second-line treatment and subsequent lines of treatment (after progression following chemotherapy treatment). Median follow-up period: 29.2 months (range from 24.8 months to 38.1 months). Number of patients: 88. Study quality score on the NICE scale: 8/8.
        - JAVELIN Merkel 200 B – the results of the study refer to the efficacy in naive (previously untreated) patients (first-line treatment). Median follow-up period: 5.1 months (range from 0.3 months to 11.3 months). Number of patients: 39. Study quality score on the NICE scale: 8/8.
- For chemotherapy:
    - 4 retrospective single-arm observational studies:
        - Iyer 2016:
            - First-line treatment: 17 different chemotherapy regimens used as first-line treatment were reported. 69% (43/62) of patients received etoposide together with carboplatin (n = 31) or cisplatin (n = 12). The median follow-up for 62 patients who received the first-line treatment was 775 days (201-2056 days). Number of patients: 62

- Second-line treatment: 13 different chemotherapy regimens used as second-line treatment were reported. Topotecan (7 out of 30 patients, 23%) and paclitaxel (5 out of 30 patients, 17%) were the most commonly used substances. The median follow-up for 30 patients who received the second-line treatment was 634 days (201-2056 days). Number of patients: 30.

Study quality score on the NICE scale: 5/8. Three points were not awarded because the study was not prospective, the recruitment was not carried out consecutively and the results were not presented in layers.

- Becker 2017:
  - First-line treatment: paclitaxel (34.5%) and liposomal doxorubicin / doxorubicin as monotherapy (31.0%)
  - Second-line treatment: doxorubicin monotherapy (34.5%), carboplatin combined with etoposide (27.6%), paclitaxel monotherapy (13.8%).

  Follow-up period: Until 31.12.2015 (patients who met the inclusion criteria in the period 01.11.2004-15.09.2005 were enrolled) Number of patients: 29 (immunocompetent patients); 34 – (general population). Study quality score on the NICE scale: 6/8. Two points were not awarded because the study was not prospective and the recruitment was not carried out consecutively.
- Covey 2017:
  - First-line treatment: Carboplatin + etoposide (62.7%-65.7%), cisplatin + etoposide (16.4%-17.6%), topotecan (9%-9.8%). Number of patients: 51 (immunocompetent), 67 (in total);
  - Second-line and subsequent lines of treatment: Topotecan (35%-42.9%), vincristine + cyclophosphamide + doxorubicin (25%-28.6%), Irinotecan (7.1-10%). Number of patients: 14 (immunocompetent), 20 (in total).

  Follow-up period: Until 30.06.2015, unless contact with the patient was lost before that date or the patient died (patients from the 01.11.2004 to 30.09.2014 period range meeting the inclusion criteria were registered). Study quality score on the NICE scale: 5/8. Three points were not awarded because the study was not prospective, no clear definition of outcomes was given and the recruitment was not carried out consecutively.
- Fields 2011: the study covered the first-line of treatment. The chemotherapy consisted of platinum-based compounds (cisplatin or carboplatin) administered as monotherapy (13 patients, 15%) or in combination with etoposide (62 patients, 71%) or irinotecan (12 patients, 14%). Follow-up period: median: 3 years. Number of patients: 412. Study quality score on the NICE scale: 3/8. Five points were not awarded because the study was not multi-centre nor prospective, the inclusion and exclusion criteria were not clearly specified, no clear definition of outcomes was given and the recruitment was not carried out consecutively.
- Allen 2005: the study covered first-line treatment. Interventions: complete resection, radiotherapy, radiotherapy as adjuvant therapy, elnd, slnb, chemotherapy, chemotherapy as adjuvant therapy (carboplatin and etoposide were the most commonly used agents). Follow-up period: the

median follow-up period was 40 months. Number of patients: 251. Study quality score on the NICE scale: 3/8. Five points were not awarded because the study was not multi-centre nor prospective, the inclusion and exclusion criteria were not clearly specified, no clear definition of outcomes was given and the recruitment was not carried out consecutively.

- Santamaria-Barria 2013: the study covered first-line treatment. Interventions: surgical treatment, adjuvant radiotherapy, radiotherapy, chemotherapy, adjuvant chemotherapy, various combinations of the above. Study quality score on the NICE scale: 3/8. Five points were not awarded because the study was not multi-centre nor prospective, the inclusion and exclusion criteria were not clearly specified, no clear definition of outcomes was given and the recruitment was not carried out consecutively.
- Satpute 2014: scientific evidence in the form of conference reports on first-line treatment. Interventions: Most patients received 4-6 cycles of cisplatin or carboplatin plus etoposide. Follow-up period: The median follow-up period was 3 years. Number of patients: 41.
- Voog 1999: scientific evidence in the form of conference reports on first, second and subsequent lines of treatment. Interventions: 42 different chemotherapy regimens were applied. Cyclophosphamide- or ifosphosphamide-based chemotherapy was administered to 60 patients (56%), anthracycline-based regimens to 53 patients (49%), platinum-based regimens to 27 patients (25%), 5-fluorouracil to 4 patients (13%) and other regimens to 13 patients (12%). Number of patients: 107.

Characteristics of the outcomes examined in JAVELIN Merkel 200:

- CR (complete response) – disappearance of all measurable lesions and short axis of all involved lymph nodes <10 mm.
- PR (partial response) – reduction of the sum of the dimensions by at least 30% compared to the initial examination;
- SD (stable disease) – a change in the sum of dimensions not meeting the PR or PD criteria;
- PD (progressive disease) – increase in the sum of the dimensions by at least 20% and a minimum of 5 mm compared to the smallest sum obtained during treatment or the occurrence of a new lesion;
- non-PD, non-PR (no disease progression) – persistent elevated concentrations of cancer markers;
- ORR (objective overall response) – the sum of the overall and partial responses (CR+PR);
- DOR (duration of response) – time from the first response (overall or partial) to the observed disease progression or death.
- PFS (progression-free survival) – time from the administration of the first medicine dose to disease progression or death.
- OS (overall survival) – time from the administration of the first medicine dose to death.

Characteristics of the populations included in JAVELIN Merkel 200 A and B:

- 1L – part B: naive patients;
- +2L – part A: patients with disease progression following chemotherapy. In total, 52 (59%) patients have received 1 or more cancer therapy for MCC in the past, 26 (30%) have received

2 therapies and 10 (11%) have received 3 or more therapies. Metastases to internal organs were found in forty-seven (53%) patients.

The scale used in the analysis:

- FACT (*The Functional Assessment of Cancer Therapy*) – a 27-item questionnaire designed to measure physical, social, emotional, and functional well-being of patients. The intensity of the well-being is assessed by the patient on a 5-point (0-4) scale (from no problems at all to very significant problems).

Efficacy

Use of avelumab – JAVELIN Merkel 200

1) Overall survival

In the 1L population during follow-up

- During the follow-up period ≥ 3 months (with median 5.1 months), median OS was not achieved;
- During the follow-up ≥ 7 months, no data on the median OS is available.

In the +2L population during follow-up:

- During the follow-up ≥ 6 months, median OS=11.3 (95% CI: 7.5; 14.0);
- During the follow-up ≥ 24 months, median OS=12.6 (95% CI: 7.5; 17.5);
- During the follow-up ≥ 36 months, no data on the median OS is available.

The rates estimated for the +2L population based on the Kaplan-Meier curve of:

- 12-month OS=52%;
- 18-month OS=39%;
- 24-month OS=36%.

2) Progression-free survival (PFS)

In the 1L population in follow-up periods:

- During the follow-up period ≥ 7 months, median PFS=4.1 (95% CI: 1.4; 6.1).

The rate estimated based on the Kaplan-Meier curve of:

- 3-month PFS=51% (95% CI: 42; 60);
- 6-month PFS=41% (95% CI: 32; 50);
- 12-month PFS=29% (95% CI: 21; 38).

In the +2L population during follow-up:

- During follow-up ≥ 36 months, median PFS= 2.7 (95% CI: 1.4; 6.9).

The rate estimated from the Kaplan-Meier curve of:

- 6-month PFS=40% (95% CI: 29; 50);
- 12-month PFS=29% (95% CI: 19; 39);
- 24-month PFS=26% (95% CI: 17; 36);
- 36-month PFS=21% (95% CI: 12; 32).

3) Response to treatment

The analysis conducted in the subarms demonstrated that a total of 20 patients had an objective response to the treatment before the end of week t of the study and, in addition, 7 patients achieved the response in question between weeks 7 and 13 of treatment.

The 18-month OS rate in the 1L population with ORR up to 7 weeks (20 patients) from treatment initiation was 90% (95% CI: 65.6; 97.4), while in the arm of patients who did not have the same response, the rate amounted to only 26.2% (95% CI: 15.7; 37.8). The median OS was not achieved in ORR patients, while in the arm where no ORR occurred, median OS was 8.8 (95% CI: 6.4; 12.9) month.

4) Quality of life

In the +2L population, results specific for MCC (0 to 48) for health-related quality of life (HRQoL) assessment on the FACT scale were as follows:

- Baseline (n=70), amounted to 32.6 (SD=9.53)
- During the 25-week follow-up (n=27), the result amounted to 36.3 points (SD=6.91).

Comparison of the efficacy of avelumab and chemotherapy (first-line treatment)

JAVELIN Merkel 200 B (in the ≥ 7 months follow-up, n=116) for avelumab and Cowey 2017 (n=67) and Lyer 2016 (n=62) for chemotherapy were included to compare the results for the 1L population. The comparison of results indicates:

- Median OS:
  - For avelumab: not achieved;
  - For chemotherapy: in the range from 9.5 to 10.2 months;
- 6-month OS:
  - For avelumab: 83.0% (95% Cl: 64.0; 93.0);
  - For chemotherapy: 70.1% (95% Cl: 57.5; 79.5) – Cowey 2017.
- Median PFS:
  - for avelumab: 4.1 (95% CI: 1.4; 6.1);
  - for chemotherapy: from 3.1 to 4.6 months;
- 6-month PFS:
  - For avelumab:41% (95% Cl: 32; 50);
  - For chemotherapy: 44.8% (95% Cl: 32.7; 56.2)
- Median DOR:
  - For avelumab: 15.2% (95% Cl: 10.2; NR (not reached));
  - For chemotherapy: from 3% to 5.7%.
- ORR amounting to:
  - For avelumab: 39.7 % (95% Cl: 30.7; 49.2);
  - For chemotherapy: from 31.3% to 55%.
- CR amounting to:
  - For avelumab: 13.8%;
  - For chemotherapy: from 8 to 10%.

Comparison of the efficacy of avelumab and BSC (second-line and subsequent lines of treatment)

In order to compare the results for the +2L population, JAVELIN Merkel 200 A (during the 24-month follow-up, n=88) for avelumab and Cowey 2017 (n=67), Becker 2017 (n=34) Lyer 2016 (n=62) for chemotherapy were included. The comparison of results indicates:

- Median OS:
    - For avelumab: 12.9;
    - For chemotherapy: in the range from 4.4 to 5.7 months.
- 12-month OS:
    - For avelumab: 50.0%;
    - For chemotherapy: 0%.
- Median PFS:
    - for avelumab: 2.7 (95% CI: 1.4; 6.9);
    - for chemotherapy: from 2.1 to 3.0 months.
- 12-month PFS:
    - For avelumab:29% (95% CI: 19; 39);
    - For chemotherapy: 0%.
- Median DOR:
    - For avelumab: 40.5% (95% CI: 18; NR)
    - For chemotherapy: from 1.7% to 3.3%.
- ORR amounting to:
    - For avelumab: 39.7 % (95% CI: 30.7; 49.2);
    - For chemotherapy: from 31.3% to 55%.
- CR amounting to:
    - For avelumab: 10%;
    - For chemotherapy: from 0 to 1%.

Safety

Use of avelumab – JAVELIN Merkel 200

In JAVELIN Merkel 200, a safety assessment was carried out for patients who received at least one infusion of avelumab (mITT [modified intention to treat] population). The median treatment period for the 1L population was 12 weeks (range: 2-49.9), whereas for the +2L population – 17 weeks (quartile range IQR:7-37).

Deaths

Death due to an adverse event identified as treatment-related by the investigator has not been reported in any of the patient populations covered by the study.

Treatment discontinuation

In the 1L population, a total of 15 (38.5%) patients discontinued treatment, mainly due to disease progression (7), adverse events (6) and death (2). Avelumab treatment was terminated in 6 (15.4%) patients.

In the +2L population, 62 (70.5%) patients discontinued avelumab treatment. Disease progression was the most common cause of treatment discontinuation in this patient arm (44). Treatment was discontinued as a consequence of an adverse event in only 3 (4.4%) patients.

TEAE (*treatment-emergent adverse events*) – adverse events exacerbating or occurring during treatment

The prevalence of TEAEs during avelumab treatment was assessed only for the +2L population. Almost all patients (97.7%) have experienced TEAEs, 61.3% of which were grade III or more severe events.

Among patients taking avelumab in second-line or subsequent lines of treatment, the most frequently observed TEAEs included: fatigue (37.5%), asthenia (25%, of which 12.5% was of grade III of severity), diarrhoea (22.7%) and nausea (20.5%). The vast majority of observed cases were of low severity (grades I-II). Single cases of grades IV and V of TEAEs were reported (8 cases in each category).

TRAE – *treatment-related adverse events*

TRAEs have occurred in 28 (71.8%) patients in the 1L population who received avelumab treatment. Eight (20.5%) patients experienced grade III TRAEs (infusion-related reactions). No grade IV or V TRAEs have been reported.

In the +2L population, in the longest follow-up period (≥ 24 months), avelumab treatment led to the occurrence of a treatment-related adverse event in 67 (76.1%) patients. 10 (11.4%) patients experienced at least grade III TRAEs.

Authors of JAVELIN Merkel 200 reported that a total of 36 (40.9 %) patients in the population of patients treated under the second-line and subsequent lines of treatment had experienced a serious adverse event (SAE).

Use of chemotherapy (first-line treatment)

The applicant has conducted a safety assessment of chemotherapy in the population in question on the basis of Iyer 2016 and Voog 1999.

Iyer 2016

The most frequent adverse events accompanying the administration of chemotherapy included: fatigue, nausea, vomiting, mucositis, neutropaenia, pancytopaenia, alopecia and nephrotoxicity.

Serious adverse events included neutropaenia, which occurred in 6.5% of patients undergoing treatment, and sepsis, which affected 4.8% of patients.

Use of BSC (second-line treatment)

The applicant did not provide safety data for chemotherapy, considering it inadequate in this case due to the fact that BSC consists mainly of patient monitoring and dedicated treatment (e.g., use of pain relievers). The applicant's preliminary analysis of the similarity of the evaluated outcomes in JAVELIN Merkel 200 B and Iyer 2016 and Voog 1999 publications demonstrated that there are few similar outcomes and they are mainly limited to the occurrence of the following similar adverse events: fatigue and gastrointestinal events such as nausea, vomiting, diarrhoea; however, the authors of Iyer 2016 did not provide data demonstrating the e.g., prevalence of these AEs and instead only stated that they were among the most frequently observed ones.

Use of treatment in 1L and +2L populations

Voog 1999

In total, 9 (9%) cases of deaths identified as treatment-related were reported, 7 (7%) of them occurred after the administration of second-line systemic treatment. When analysing the causes of death in five

cases, the death was preceded by septic shock in the course of neutropenic fever; one patient died of nephrotoxicity, while the causes of the other three deaths were not determined.

It was reported in the study that myelosuppression and granulocytopaenia were the most common adverse events.

Additional safety and efficacy data

Additional safety information has been included based on the Summary of Product Characteristics for Bavencio.

Adverse events occurring:

- very common (≥1/10): anaemia, decreased appetite, cough, dyspnoea, nausea, diarrhoea, constipation, vomiting, abdominal pain, back pain, arthralgia, fatigue, pyrexia, oedema peripheral, weight decreased, infusion related reaction;
- often (≥1/100 to <1/10): lymphopenia, hypothyroidism, headache, dizziness, neuropathy peripheral, hypertension, hypotension, pneumonitis, dry mouth, rash, pruritus, rash maculo-papular, dry skin, asthenia, chills, influenza like illness, Gamma-glutamyltransferase increased, blood alkaline phosphatase increased, amylase increased, lipase increased, blood creatinine increased.

No documents have been identified on the URPL and FDA websites regarding the safety of avelumab. However, an assessment report for Bavencio (EPAR EMA) was identified on the EMA website; in this report, the relation of health benefit to the risk of use of the medicine in the indication in question was assessed as positive.

Limitations

The main limitation of the clinical analysis is the lack of studies directly or indirectly comparing the medicine in question with its comparators. The results of the studies included in the analysis were presented in the form of a tabulated (qualitative) summary of the results. Due to the high heterogeneity of the compared studies (e.g. in terms of observation periods or type of studies: e.g. prospective phase II study vs. real-word data study (Cowey 2017, Becker 2017) as well as result reporting (discrepancies in the defining of the outcomes in terms of treatment response for avelumab treatment with and selected studies on the comparator (RECIST criteria (in Merkel 200, Cowey 2017, Iver 2016) vs. the investogator's assessment (Becker 2017, Voog 1999)), performing a quantitative comparison was not possible. Therefore, it is impossible to draw conclusions on the possible superiority or similarity in terms of the efficacy of the technology in question and the optional technologies, and any conclusion is subject to considerable uncertainty.

In addition, the following factors impact the uncertainty of the presented results:

- The population in question is not accurately reflected in the population of patients included in the studies:
    - No studies have been identified for the population of patients with unresectable cancer, who are in stage III of the disease;
    - the inclusion criteria for a pharmaceutical programme include only immunocompetent patients, whereas in this analysis, the applicant has considered the results for both populations (immunocompetent patients and the total population). In the subarms, however, the immune status of patients did not influence their overall survival.
- The applicant has not identified any scientific reports demonstrating the efficacy of the best supportive treatment (BSC) for previously treated patients with metastatic Merkel cell

carcinoma. Therefore, the applicant assumed that the efficacy of the best supportive treatment (BSC) is not superior to that of chemotherapy.

- The applicant has failed to take into account the most recent data published in JAVELIN Merkel 200 B:
    - for patients treated with avelumab as part of the first-line treatment: data for 39 patients with a minimum follow-up period of 6 months (cut-off date 24 March 2017) have been included, while data for 116 patients with a minimum follow-up period of 7 months are available in SPC for Bavencio (cut-off date 14 September 2018);
    - in case of second-line treatment: the most recent data for the 36-month follow-up period (cut-off date 14 September 2018) which are presented in the SPC for Bavencio have not been included.
- Number of patients:
    - the number of patients in studies on the comparator was small and information on the criteria for the assessment of treatment results and the follow-up period was limited;
    - JAVELIN Merkel 200 B included a small number of patients, especially after the ≥ 6-month follow-up in the study. The low number of patients is due to the ultra-rare nature of the assessed indication and the partial (*interim*) analysis;
- Furthermore, there is no safety assessment performed for specific treatment lines in the identified studies on chemotherapy;
- Limited data on survival – the median follow-up period in JAVELIN Merkel 200 B was 5.1 months, therefore the data on patient survival in this study are immature; there are no data on overall survival (OS) of untreated patients (first-line treatment) from a longer follow-up period which would include the target size of the study arm;
- There are no data on the quality of life of patients treated with avelumab under the first-line treatment.

Proposals of risk-sharing schemes

As part of the proposed risk-sharing scheme (RSS), *[information protected as a trade secret]*

Economic analysis, including a cost-effectiveness estimation

An economic analysis consists in estimating and comparing the costs and health effects which may be associated with the use of a new therapy in an individual patient instead of therapies which are currently reimbursed.

The costs of the therapy are estimated in the Polish currency and the health effects are usually expressed using the life years gained (LYG) or the quality-adjusted life year (QALY) as a result of the therapy.

The comparison of values concerning the costs and effects related to the implementation of a new therapy and comparing them to the costs and effects of already reimbursed therapies allow to answer the question whether the health effect achieved as a result of a new therapy is associated with higher costs in comparison to already reimbursed therapies.

The achieved cost-effectiveness ratios are compared with the so-called cost-effectiveness threshold, i.e., which indicates that taking into account the means at the disposal of Poland (expressed in its GDP), the maximum cost of a new therapy necessary to obtain a unit of health effect (1 LYG or 1 QALY),

compared to the currently available treatments, should not exceed three times the amount of per capita GDP.

Currently the cost-effectiveness threshold in Poland amounts to PLN 147,024 (3 x PLN 49,008).

The cost-effectiveness ratio does not estimate or determine the value of life, it only allows to assess and, among other things, select a therapy associated with the potentially best use of the currently available resources.

A cost utility analysis (CUA) was conducted as part of the cost-effectiveness analysis. The analysis was conducted from the public payer's (NHF) perspective in a lifetime (assumed maximum life expectancy of 40 years) time horizon. As no costs are to be incurred by patients, the decision was made not to present the results of the analysis from the common perspective. Discounting in the amount of 5% for costs and 3.5% was adopted for health effects.

The following direct medical costs were included in the analysis:

- the costs of active substances (avelumab, substances used in chemotherapy);
- the costs of hospitalisation associated with administration of medicines;
- the costs of BSC;
- the costs of treatment monitoring;
- the costs of treating adverse events;
- the costs of palliative radiotherapy, the cost of palliative care.

As part of the main analysis, it was assumed that the cost of BSC is equal to the cost of outpatient oncology consultation performed once every two months and that the cost of chemotherapy monitoring will consist of one follow-up visit per three-week treatment cycle and CT or MRI imaging every 12 weeks.

The use of Bavencio instead of chemotherapy in the first-line treatment of patients with metastatic Merkel cell carcinoma is associated with higher health effects and higher therapy costs, however, the technology in question is not cost-effective (regardless of the analysis perspective *[information protected as a trade secret]*). The incremental cost utility ratio (ICUR) from the NHF's perspective was estimated at:

[information protected as a trade secret]

- PLN 179,590.63/QALY without RSS.

The use of Bavencio instead of BSC in the second-line and subsequent lines of treatment is associated with greater health effects and higher therapy costs, however, the technology in question is not cost-effective (regardless of the analysis perspective *[information protected as a trade secret]*). The ICUR from the NHF's perspective was estimated at:

- *[information protected as a trade secret]*
- PLN 160,472.30/QALY without RSS.

The threshold net ex-factory price for one package of the medicine in question, taking into account the assumptions included in the applicant's basic analysis, amounts to:

- *[information protected as a trade secret]* for the comparison with chemotherapy;
- *[information protected as a trade secret]* for the comparison with BSC.

The results of a probabilistic sensitivity analysis indicate that the likelihood of cost-utility of the technology of:

- approx. *[information protected as a trade secret]* for the comparison with chemotherapy in the first-line treatment:
- approx. *[information protected as a trade secret]* for the comparison with BSC in the second-line and subsequent lines of treatment.

The greatest impact on the results of the analysis is associated with the assumptions *[information protected as a trade secret]*

The greatest impact on the decline *[information protected as a trade secret]*

Limitations

The basic limitation of the economic analysis, as well as of clinical analysis, is the failure to identify studies comparing the intervention in question with the comparators directly or indirectly. What is more, the remaining limitations of the clinical analysis apply also to the economic analysis.

Furthermore, the uncertainty of the presented results was impacted by the following aspects:

- Data on the survival of patients who received chemotherapy in the first-line treatment were obtained from seven clinical trials: Cowey 2017, Iyer 2016, Voog 1999, Satpute 2014, Santamaria-Barria 2013, Fields 2011, Allen 2005. The assumption to be met when combining data from different clinical trials is that the source studies are not heterogeneous. The included studies had different patient characteristics, but nevertheless the PFS curves remain similar. The results of Santamaria-Barria 2013 for OS demonstrate a lower survival in comparison to other studies; however, according to the applicant, this curve does not differ significantly from the others;
- Due to the fact that the clinical data on the first-line treatment with avelumab is immature (currently available data with an observation period of at least 6 months include 39 patients, with 112 patients planned to be included), they were considered inappropriate for use in the model. In the current economic analysis, as in the global economic model, OS and PFS for the first-line treatment of mMCC were estimated on the basis of clinical experts' opinions. Therefore, the economic analysis is not based on the clinical analysis submitted by the applicant to that extent, and its reliability is limited;
- *[information protected as a trade secret]*
- Given the lack of reliable clinical data assessing the efficacy of the best supportive care (BSC) in metastatic Merkel cell carcinoma, an assumption was made in the economic analysis that BSC and chemotherapy have the same efficacy;
- The same values of progression-free survival were adopted for the first-line treatment model as for the second-line treatment model, and the HR of overall survival in the second-line vs. first-line equal to 0.8 was adopted (which means an increase in overall survival in the naive arm in comparison with patients treated with avelumab in second-line or subsequent lines). This assumption cannot be verified due to a lack of relevant clinical data;
- There is a lack of long-term data on the use of the technology in question, which makes it necessary to extrapolate health results beyond the period of the studies and thus is associated with uncertainty;
- Alternative values of utilities of particular health conditions were not tested in the analysis, which in the context of recorded differences in relation to the results presented in the Bullement 2019 publication (a publication describing the results using a similar economic model), reduces the credibility of the presented results.

Indication whether the circumstances referred to in Article 13, paragraph 3 of the Act of 12 May 2011 on the reimbursement of medicines, foodstuffs for particular nutritional uses and medical devices apply (Journal of Laws of with 2019 item 784 as amended);

In case the applicant's clinical analysis does not include randomised clinical trials, which prove the superiority of the medicine over the medical technologies which are currently reimbursed in the particular indication, it is the ex-factory price of the medicine which must be calculated in such a way that the cost of using the medicine applying for reimbursement is not higher than the cost of the health technology with the most favourable ratio of health effects to the cost of obtaining them.

The circumstances referred to in Article 13 (3) of the Act on reimbursement apply in the present case because a randomised trial has not been presented to prove the superiority of the technology in question over the reimbursed comparator.

The values of the ex-factory prices of Bavencio, at which the cost of its use does not exceed the cost of using the reimbursed optional technology with the most favourable ratio of health effects to the costs of obtaining them, were:

- For the comparison with chemotherapy: PLN 199.19 (gross wholesale price: PLN 225.88);
- For the comparison with BSC: PLN 68.19 (gross wholesale price: PLN 77.53).

Analysis of the effects on the healthcare system, including budget impact analyses (BIA)

The analysis of the effects on the healthcare system consists of two important parts.

Firstly, the analysis of the impact on the payer's budget allows for estimating potential expenditure related to the financing of a new therapy from public funds.

The estimated expenditure related to the new therapy (the "tomorrow" scenario) is compared with how much currently is spent on the treatment of a particular health problem (the "today" scenario). On that basis it is possible to assess whether the new therapy will require a higher level of funding for the treatment of a particular health problem or whether it will involve savings in the payer's budget.

The budget impact assessment makes it possible to determine whether the payer possesses the necessary resources to finance a particular technology.

The second part of the analysis of the effects on the healthcare system raises the question on how the decision to finance a new therapy can affect the organisation of the provision of services (especially in the context of adjustments necessary for the new therapy to be used) and the availability of other healthcare services.

Results of the budget impact analysis carried out by the applicant were presented in a two-year horizon. The analysis was carried out from the payer's perspective, the results of which are similar to the common perspective. in line with the applicant's estimates, the number of patients who will be newly enrolled in the pharmaceutical programme in question will amount to:

[information protected as a trade secret]

The following direct medical costs were included in the analysis:

- the costs of active substances – avelumab and comparators;
- the costs of hospitalisation associated with the administration of medicines;
- the costs of treatment monitoring;
- the costs of BSC;
- the costs of palliative radiotherapy;

- the costs of treating adverse events;
- the costs of palliative care.

The financing of the health technology in question by the public payer will contribute to the increase in expenditure:

- in the variant taking the RSS into account:
  - by approx. PLN *[information protected as a trade secret]* in the first year;
  - by approx. PLN [*information protected as a trade secret]* in the second year.
- in the variant not taking the RSS into account:
  - by approx. PLN 4.08 million in the first year;
  - by approx. PLN 5.82 million in the second year.

The incremental costs estimated under a scenario including *[information protected as a trade secret]*

In addition, the applicant tested the impact on the results of assumptions related to *[information protected as a trade secret]* and the relative dose intensity (RDI) of the included medicines. The following conclusions refer to the results of the RSS variant.

[information protected as a trade secret]

- The relative dose intensity (95.4% for avelumab and 66.7% for chemotherapy as part of the basic analysis):
  - the adoption of RDI for both technologies at 100% – *[information protected as a trade secret]*

Limitations

The size of the target population has not been estimated on the basis of epidemiological data and is not possible to extract NHF's data for patients with Merkel cell carcinoma, which makes proper verification impossible.

Moreover, the limitations of the budget impact analysis are also influenced by the limitations identified in the clinical and economic analysis.

Remarks on the proposed risk-sharing scheme

[information protected as a trade secret]

Remarks on the pharmaceutical programme

The Agency draws attention to the lack of precision in the provisions concerning the eligibility criteria for the assessed pharmaceutical programme in terms of the line of treatment under which the medicine in question is to be used.

It is not clear from the provisions of the inclusion criteria that a patient may be qualified to third-line and subsequent lines of treatment (point 4 of the eligibility criteria for the MP)

Review of the solutions proposed in the rationalisation analysis

The objective of the rationalisation analysis is to identify a mechanism which, if introduced, will result in a release of public funds in an amount at least corresponding to the increase in costs resulting from a positive decision to reimburse the intervention in question.

A rationalisation analysis is submitted if the budget impact analysis of the public payer demonstrated that the cost of reimbursement would increase.

In the rationalisation analysis, the applicant proposed solutions to release funds in the budget for the reimbursement of Bavencio: The proposed solution consists in disseminating information to patients about the equivalents of medicines which are cheaper than the basis of the limit, and the benefits of using such products.

In line with the information provided by the applicant, the estimated savings would compensate the NHF's expenditure related to the reimbursement of avelumab in the indication in question (the savings indicated in the rationalisation analysis are higher than the maximum additional expenditure of the public payer estimated in the budget impact analysis).

Review of recommendations issued in other countries in relation to the technology in question

As a result of the search for clinical guidelines, the following documents were identified:

- PTOK 2018 (Polish Society of Clinical Oncology);
- NCCN 2019 (National Comprehensive Cancer Network);
- NICE 2018 (National Institute for Health and Care Excellence);
- EDF/EADO/EORTC 2015 (European Dermatology Forum/European Association of Dermato-Oncology/ European Organization for Research and Treatment of Cancer).

The identified clinical guidelines demonstrate that it is currently not possible to set a standard procedure for metastatic MCC. As most of the therapies used are palliative therapies, the importance of including patients in clinical trials is underlined. The PTOK 2018, NCCN 2019 and NICE 2018 guidelines recommend the use of immunotherapy in the form of PDL1/PD-1 inhibitors, which include avelumab and pembrolizumab; additionally, US guidelines mention nivolumab therapy. PTOK 2018 recommends avelumab after the failure of systemic chemotherapy, while pembrolizumab is recommended without prior systemic therapy. In addition, Polish experts have pointed out that immunotherapy in MCC should be the first-line treatment of choice. NICE 2018 also recommends using avelumab in patients who underwent one or more lines of chemotherapy. The EDF/EADO/EORTC 2015 guidelines do not mention the use of avelumab in metastatic Merkel cell carcinoma, probably due to the fact that they were developed at a time when no treatment was registered for MCC by either the EMA or the FDA.

6 reimbursement recommendations have been identified (presented in 4 documents), 4 of which were positive, one conditionally positive and one negative. All recommendations referred to patients in second-line and subsequent lines of treatment, the SMC (Scottish Medicines Consortium) 2018 did not distinguish populations according to treatment-lines, while NICE 2018 and HAS (Haute Autorité de Santé) 2018 additionally presented recommendations for patients in the first-line treatment. NICE 2018 gave a positive opinion on the above-mentioned population, while HAS 2018 gave a negative opinion on first-line avelumab treatment.

[information protected as a trade secret]

Legal basis for the recommendation

The recommendation was prepared on the basis of a commission of the Minister of Health of 11/09/2019 (reference number: PLR.4600.645.2019. IV.PB), with regard to preparation of the recommendation of the President of the AOTMiT on Bavencio (avelumab) under the following pharmaceutical programme: "Treatment of Merkel cell carcinoma with avelumab (ICD-10 C44" under Article 35 sec. 1 of the Act of 12 May 2011 on the reimbursement of medicines, foodstuffs for particular nutritional uses and medical devices (Journal of Laws of 2019, item 784, as amended), after having read the Position of the Transparency Council No. 108/2019 of 02

December 2019 on the evaluation of Bavencio (avelumab) under the following pharmaceutical programme: "Treatment of Merkel cell carcinoma with avelumab (ICD-10 C44"

References

1. The Position of the Transparency Council No. 108/2019 of 02 December 2019 on the evaluation of Bavencio (avelumab) under the following pharmaceutical programme: "Treatment of Merkel cell carcinoma with avelumab (ICD-10 C44"
2. Report No. OT.4331.53.2019. Application for reimbursement and setting of the ex-factory price of Bavencio (avelumab) in the following pharmaceutical programme: "Treatment of Merkel cell carcinoma with avelumab (ICD-10 C44". Verification analysis