REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND
REIMBURSEMENT OF MEDICINAL PRODUCTS

HEALTH TECHNOLOGY ASSESSMENT

Bavencio

20 mg/ml concentrate for solution for infusion 10 ml x 1 vial

Avelumab

Therapeutic indications	Monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (mMCC)
Start- end of the procedure	22.04.2019 – 24.10.2019
Final decision	Inclusion in Annex 2 for purchase by medical establishments with state and/or municipal participation and under Art. 5 of the Medical Establishments Act of the Positive Drug List (PDL) and paid by the National Health Insurance Fund (NHIF).

Summary of the report on the clinical and pharmacoeconomic evaluation of the health technology of the medicinal product Bavencio

Health problem

Merkel cell carcinoma (MCC) is a rare, aggressive and with a poor prognosis skin tumor that combines local infiltration of nonmelanoma skin tumors with regional and distant metastases characteristic for malignant melanoma.

Tumor origin – unclear histogenesis:

- neuroendocrine – probably from cutaneous mechano-receptors;

- pluripotent stem cells in the epidermis;

- lymphoid cells (also discussed by some authors);

- neural origin.

MCC has many common morphological, immunohistochemical and structural features with Merkel cells, without a proven direct histogenetic link.

MCC occurs mainly in people over 70 years of age with fair skin. Only 5% of all cases are in patients under 50 years of age. Population aging and an increase in older people with a history of chronic sun exposure are also factors in the increased incidence.

The etiology of MCC is likely to be multifactorial, with immunosuppression, UV-induced skin damage, and some viral factors are referred as contributing factors to MCC development.

MCC is clinically manifested by rapidly growing, hard, red, livid, or with color on the surrounding skin asymptomatic node. It is most common in photoexposed areas, mainly on the neck and head. In 15% of cases there may be lymphatic or visceral metastases in the absence of a clinically recognizable primary tumor. Even without there is clinical evidence of lymph node involvement, in 32% of cases detected microscopic metastases. For an exact staging is necessary a biopsy of sentinel lymph nodes to be performed. Five-year survival at histologically verified negative lymph nodes was 76%.

For the determination of the therapy of MCC the staging according to the TNM classification is important. The main therapeutic approaches include surgery, radiotherapy, conventional chemotherapy and immunotherapy. Due to the

aggressive nature of the MCC, patients need to be monitored every 3-6 months for the first two years and every 6-12 months thereafter.

Recommendations for treatment by stage of the disease can be summarized as follows:

- **In patients with MCC stage I or II, without nodal or distant metastases (local disease):** most guidelines recommend radical excision of up to 1-2 cm of healthy tissue, accompanied by adjuvant radiotherapy in at-risk patients. Some guidelines suggest larger excision limits of up to 3 cm.
- **In patients with stage III MCC, with regional metastases (regional disease) or unresectable tumor:** lymph node dissection and/or radiotherapy are usually recommended.
- **In patients with stage IV MCC, with distant metastases (metastatic disease):** treatment options are palliative and include participation in clinical trials and immunotherapy (avelumab, pembrolizumab or nivolumab). Chemotherapy is only acceptable as an option in patients with contraindications to immunotherapy and in individual cases where it is clinically justified.
- **In patients with recurrent disease:** there is no standard approach and treatment should be individualized according to the stage of the disease.

Epidemiological data

MCC is an extremely rare skin cancer worldwide. According to data from the large-scale European project to study the epidemiology of rare tumors RARECARE, the incidence of MCC is about 0.13 per 100,000. This makes approximately 600 new cases of MCC per year in the EU. **Extrapolated to Bulgaria (with a population of 7 million), this incidence would mean about 9 newly diagnosed patients with MCC per year and includes all stages of the disease.**

Bavencio is indicated for use in cases of metastatic MCC (mMCC) (stages III and IV). From the studies available to date, it can be summarized that the relative proportion of patients with stage III and IV MCC represents about one third of the total newly diagnosed patient population. Additionally, about one third of cases diagnosed in stage I or II are expected to metastasize within 1 to 3 years thereafter.

Epidemiological assessment for Bulgaria

For the period 1996–2015, a total of 68 patients with MCC were registered. A tendency of increasing incidence is reported. By the end of 2015, 38 of these 68 patients had died.

Table 1. Main methodological considerations in assessing the epidemiology of the MCC in Bulgaria.

Incidence of MCC	**0.13 per 100,000**
Expected number of newly diagnosed patients with MCC per year	9
Relative proportion of newly diagnosed patients with metastatic MCC	30%
Expected number of newly diagnosed patients with metastatic MCC per year	3
Relative proportion of newly diagnosed patients with non-metastatic MCC	70%
Expected number of new patients with non-metastatic MCC per year	6
Expected number of patients treated per year with non-metastatic MCC, developing metastases	1
Five-year overall survival in patients with metastatic MCC	20-30%

Efficacy data

Following the applied search strategy according to the requirements of the PRISMA standard, the final analysis of the efficacy, therapeutic effectiveness and safety of Bavencio in the treatment of mMCC included one clinical trial - JAVELIN Merkel 200 (EMR100070-003), which was performed in two parts. Part A (2L + cohort) included patients with histologically confirmed stage IV MCC and refractory to chemotherapy (defined as cases in which the disease had progressed after at least one previous line of chemotherapy for metastatic disease). Part B includes patients with mMCC who have not previously been treated with systemic therapy in the metastatic setting. Part B is an ongoing, multicenter, single-arm, open-label, phase II study of Bavencio in patients with

mMCC who have not been previously treated with systemic therapy in the metastatic setting.

For the analysis of the efficacy, therapeutic effectiveness and safety of Bavencio in the treatment of mMCC, the observational study 100070-Obs001 was included. Part A (conducted in the US as 2 cohorts, one for 2L+ and one for 1L) and Part B (conducted in the EU as one cohort for 2L+) are designed to mimic the inclusion criteria for Bavencio treatment in adult patients with mMCC. The study analyzed historical data on chemotherapy and its response in patients with mMCC based on electronic patient records and registries in the United States, Germany, Austria, and Switzerland.

A key indicator of efficacy and therapeutic effectiveness is the best overall response, defined as a complete or partial response to the RECIST tumor response criteria (version 1.1), obtained from the start of therapy to documented disease progression and evaluated every 6 weeks. The complete or partial response should be confirmed at a subsequent evaluation of the tumor, preferably at the next scheduled 6-week evaluation, but not earlier than 5 weeks after the initial documentation of the response.

The results of the JAVELIN Merkel 200 trial due to the long follow-up period in patients receiving second and subsequent line treatment with Avelumab - 24 months showed that Bavencio has sufficient data on efficacy, therapeutic effectiveness and safety in patients with mMCC.

Regarding the tumor response in patients in group A, 33% of them showed a high frequency of the best response compared to RECIST v.1.1. Responses were reported during the first tumor reassessment –at week 7, indicating the rapid tumor response achieved with Avelumab treatment.

Secondary goals of the study were freedom from progression and overall survival. The median duration of treatment was 3.9 months. The Kaplan-Mayer curves for progression-free survival at months 12, 15, and 18 are identical - 29%. Thus, the mean progression-free survival is 2.7 months. The overall survival at month 12 in these patients was 50%, while at month 24 - 36%. The median for overall survival was 12.6 months.

In group B patients, those receiving Avelumab treatment as the disease progressed after a single line of cytostatic therapy, the best response rate to RECIST 1.1 for a 3-month follow-up was 50%; in addition, progression-free survival was 61%, 46%, and 40% at months 3, 6, and 9, respectively.

The subgroup analysis of efficacy and therapeutic effectiveness showed a definite benefit in earlier line therapy with Avelumab. Patients in whom immunotherapy was initiated after progression to only one cytostatic regimen had a statistically better response to treatment than those in whom this treatment was initiated after several previous regimens: 40.4% versus 19.4%. In regard to stratification depending on PDL1 and MCPyV status, no statistically significant differences were observed in the two arms. The data from the post-hoc analysis are presented in **Figure 1**.

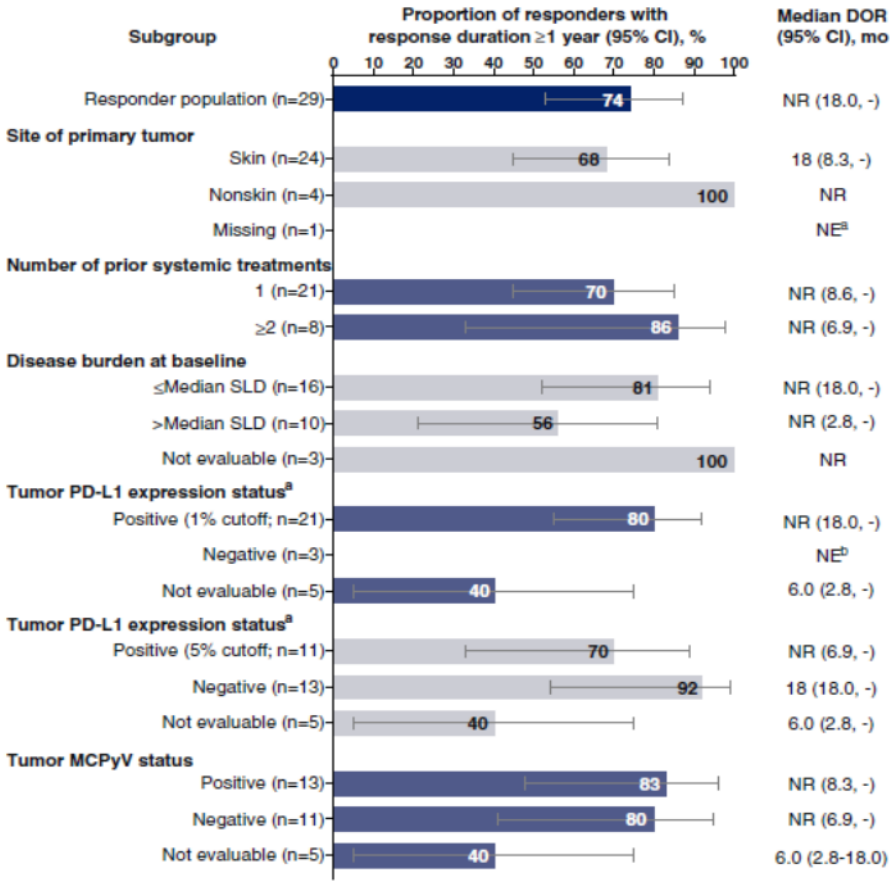

Figure 1. Subgroup analysis of responses with a duration of at least 1 year in group A

When comparing the data from this study to the observational study 100070-Obs001, a statistically significant advantage of Avelumab as a second and subsequent line over standard second line therapy was demonstrated.

Part B of the JAVELIN Merkel 200 trial is an ongoing, multicenter, phase II study that evaluates the effect of Avelumab in untreated MCC patients. A total of 112 patients were included. The results regarding the tumor response show that an objective response occurred early - at week 6 of the treatment. The average progression-free survival is 4.2 months, with 40% of patients without disease progression for at least 9 months. Comparing the results of the observational study 100070-Obs001, it is proved that the best response to immunotherapy occurs in 51.3% of patients, while in cytostatic treatment it is only 29.4%, i.e. an indirect comparison between the two studies showed an advantage for immunotherapy in terms of tumor response over chemotherapy. The assessment of median progression-free survival was similar: it was not achieved with Avelumab, while it was only 6.7 months with chemotherapy.

In 2L+ therapy of patients with mMCC:

- In two thirds of those treated (65.5%), Bavencio resulted in a sustained long-term response. Kaplan-Meier's estimate of the expected relative proportion of responses lasting at least 18 months was 67% (95% CI: 46, 81);
- Bavencio demonstrated a high frequency of best response on the RECIST scale in 2L+ mMCC therapy - 33.0% (95% CI: 23.3, 43.8);
- Overall survival with Bavencio therapy was 50% (95% CI: 39, 60) at month 12, 43% (95% CI: 32, 53) at month 15, 39% (95% CI: 29, 49), and 36% (95% CI: 26, 46) at month 24. The Kaplan-Meier overall survival curve stabilizes over time with the addition of new study data;
- The safety data of Bavencio as 2L+ therapy in patients with mMCC show a standard, manageable safety profile of therapy.

In 1L therapy of patients with metastatic MCC:

- Bavencio demonstrated an impressively high frequency of best response on the RECIST 1.1 scale in 1L mMCC therapy for 3-month follow-up - 50.0% (95% CI: 35.5, 64.5). This result remained stable at 6-month follow-up - 51.3% (95% CI: 34.8, 67.6);
- Bavencio leads to a relatively rapid therapeutic response. A response was found extremely early - 22 out of 25 confirmed responses were reported during the first evaluation of the tumor. The expected relative share of responses lasting at least 3 months is 84% (95% CI: 59, 95);

- Bavencio progression-free survival was high and clinically significant - 61% (95% CI: 48, 73), 46% (95% CI: 32, 59) and 40% (95% CI: 25, 54) at months 3, 6 and 9, respectively. The assessment at month 12 remains stable - 36% (95% CI: 22, 51);
- The safety data of Bavencio as 1L therapy in patients with mMCC show a standard, manageable safety profile of therapy.

Bavencio therapy in mMCC was associated with a significant improvement in quality of life in treated patients, with the therapeutic response leading to clinically significant higher quality of life outcomes (as measured by EQ-5D) compared to non-responders. A dependence between tumor reduction with Bavencio therapy and clinically significant improvement in the quality of life of treated patients were reported;

In conclusion, the results of the present analysis of efficacy, therapeutic effectiveness and safety in 1L and 2L+ Bavencio therapy in metastatic MCC demonstrate a significant and long-lasting therapeutic response in treated patients. These data fully support the application of the evaluated health technology in mMCC, regardless of the line of therapy.

Safety data

Table 2. Summary of reported immune-related adverse events within JAVELIN Merkel 200 (EMR100070-003) - Part A

Immune-related adverse reactions	**Total, n (%)**	**Degree ≥3, n (%)**
Patients with one or more adverse reactions affecting the immune system	15 (17.0)	4 (4.5)
Immune-mediated rash	8 (9.1)	0
Erythema	2 (2.3)	0
Pruritus	1 (1.1)	0
Rash	5 (5.7)	0
Maculopapular rash	1 (1.1)	0
Immune-mediated colitis	2 (2.3)	0
Diarrhea	2 (2.3)	0
Immune-mediated thyroid disorder	3 (3.4)	1 (1.1)
Hypothyroidism	3 (3.4)	1 (1.1)
Immune-mediated hepatitis	2 (2.3)	2 (2.3)
Elevated alanine aminotransferase	1 (1.1)	1 (1.1)
Elevated transaminases	1 (1.1)	1 (1.1)

Elevated aspartate aminotransferase	1 (1.1)	0
Immune-mediated nephritis and renal dysfunction	1 (1.1)	0
Tubulo-interstitial nephritis	1 (1.1)	0
Other immune-mediated adverse reactions	1 (1.1)	1 (1.1)
Autoimmune disorder	1 (1.1)	1 (1.1)

Based on the presented data in terms of effectiveness, efficacy and safety, it can be concluded that treatment with Avelumab in patients with MCC leads to significantly better outcomes in regard to tumor response and survival, in good quality of life and in lack of seriously adverse effects.

Comparators data

Bavencio is indicated for use in adult patients with metastatic MCC (stages III and IV). Patients with mMCC (newly diagnosed with metastases or diagnosed at an earlier stage and metastasized thereafter) have very limited and poorly effective treatment options. Bavencio is the first officially approved drug therapy with an indication of mMCC and meets significant unmet health needs.

Therapeutic options for MCC include surgery, radiotherapy, chemotherapy, and a combination of these. Chemotherapy is the only comparator for evaluation of Bavencio in mMCC.

Until Bavencio was approved for use, all other therapies for these stages of the disease had a palliative focus.

The most commonly used combination for chemotherapy in mMCC is carboplatin + etoposide according to the approved Pharmacotherapeutic Guidelines in Medical Oncology in Bulgaria. According to these guidelines, the standard chemotherapeutic approach in patients with MCC is a combination of carboplatin + etoposide or cisplatin + etoposide.

Pharmacoeconomic indicators

Published assessments of health technology performed by state institutions for the purposes of another national health care system

Positive assessments of health technology from the United Kingdom (NICE), Germany (IQWIG), France (HAS), Sweden (SKL) for the treatment of

mMCC are presented and the medicinal product in these countries is reimbursed.

Applied analysis

A cost-effectiveness analysis (CEA) of the interventions in patients with mMCC was applied. The interventions are avelumab as monotherapy and a combination of chemotherapy - carboplatin + etoposide. A simulation of a probabilistic discrete Markov model was performed, which presents the transition between health conditions and related to health, quality of life and cost. The results are presented as incremental cost-effectiveness ratios (ICER) for both quality-adjusted life years (QALYs) and life-years gained (LYG). In accordance with the current pharmacotherapeutic guidelines for medical oncology in our country, the standard chemotherapeutic approach in patients with MCC is a combination of carboplatin + etoposide or cisplatin + etoposide. The perspective of the present analysis is from the point of view of the National Health Insurance Fund (NHIF). Benefits and costs are discounted by 3.5% on an annual basis. The time horizon is 40 years, with a cycle length of one week.

Modeling the cost-benefit ratio

A mMCC survival model has been developed to evaluate the cost-effectiveness of avelumab compared to the alternative - chemotherapy in combination of carboplatin + etoposide. A three-step disease-to-death (no-recovery) model is applied, which includes a solution for each possible transient probability.

Results of the cost-effectiveness analysis of the baseline case

The results of the baseline case demonstrate that avelumab therapy results in a higher number of life-years gained and quality-adjusted life years compared to chemotherapy and is associated with increased costs, with an additional cost for a year of life adjust to quality exceeding 3 times Gross Domestic Product (GDP) per capita.

The uncertainty of the parameters related to the cost-effectiveness analysis was investigated by probabilistic and deterministic one-way sensitivity analysis.

The results of the probabilistic sensitivity analysis show that the results are most sensitive to patients' Health-Related quality of Life (HRQL) and predict long-term survival outcomes.

Costs for the assessed health technology

Direct drug costs and cost of applicable clinical pathways/procedures are included.

The cost of treatment with alternative chemotherapy is based on a maximum duration of treatment of 18 weeks.

Budgetary impact analysis

The analysis was performed from the point of view of the paying institution NHIF with a time horizon of 5 years. The expected number of patients with metastatic MCC varies from 4 patients in the first year to 8 in the fifth year. This epidemiological prognosis is based on an expected 3 newly diagnosed cases per year, as well as 1 diagnosed case at an earlier stage but metastasizing thereafter. The annual number of patients treated with Bavencio will remain the same due to the expected two-year maximum duration of therapy - patients who start treatment in the first year will discontinue this therapy in the third year.

The parameters number of treated patients and duration of therapy were subjected to sensitivity analysis. The introduction of the new therapy leads to an increase in the costs of the NHIF, as risk-sharing agreements and patient access schemes are not taken into account.

Moral and ethical aspects

MCC is a rare, aggressive skin cancer that combines local infiltration of nonmelanoma skin tumors with regional and distant metastases characteristic of malignant melanoma. The disease is characterized by rapid progression and low survival rates. Patients with metastatic MCC (newly diagnosed with metastases or diagnosed at an earlier stage and metastasized thereafter) have very limited and poorly effective treatment options. The risks of chemotherapy treatment outweigh the benefits in metastatic MCC. The clinical response is limited and short-term, chemotherapy does not improve

survival in these patients and is associated with significant decrease in quality of life. The number of people affected by this rare disease in Bulgaria is small, which makes patients with MCC particularly vulnerable.

Conclusion

Bavencio is the first and only approved therapy with an indication of metastatic MCC. Health technology has the status of an orphan drug, supported by a large amount of clinical data on safety, efficacy and therapeutic effectiveness. Bavencio demonstrated 51% one-year survival in treated patients with metastatic MCC with a rapid and sustained therapeutic response. Bavencio is associated with clinically significant improvements in quality of life, is well tolerated and has a good safety profile, and is a therapy for unmet medical need in a small number of patients.