Appendix A. Comment from Merck/Pfizer Alliance on HTA application of avelumab (BAVENCIO®) for mMCC

The Alliance appreciates the opportunity to comment on the HTA report provided by the Norwegian Medicine Agency. There are mainly four points we would like to emphasize:

1. We have done our utmost to provide NoMA with a best possible decision basis. Metastatic Merkelcell carcinoma (mMCC) is an ultra-rare disease, and JAVELIN Merkel 200 is the largest current clinical trial for this patient population. . In absence of clinical data for the comparator treatment on the relevant patient population, the Alliance has constructed an observational study to obtain such data.
2. Our approach, including detailed information on the relevant studies (both the JAVELIN and the Obs001), were presented in detail at the pre-submission meeting with NoMA. No significant objections were raised at the meeting, or prior to the HTA submission.
3. NoMA has not offered an achievable alternative approach they would find satisfactory. There are no randomized studies with mMCC patients and as a rare indication of high unmet need there are no planned trials for randomization of avelumab or other investigational agents vs. chemotherapy, as the medical community considers such a trial design to be unethical.
4. The same analysis and clinical documentation which we have submitted has been recognized as sufficient by other HTA bodies. The UK NICE recommends avelumab for both naïve and treatment experienced patients, thus making an effective treatment available to all UK patients with metastatic MCC. Avelumab has also been made available to patients in Finland, Denmark, Sweden, Germany, Austria, Switzerland and the Netherlands, among others.

According to NCCN guidelines and European clinical guidelines from 2015[1] there was no defined standard for 2L+ therapy of metastatic MCC, and 1L chemotherapy for metastatic MCC there was not the preferred treatment recommendation. An editorial, published in September 2016 by clinical leaders in MCC, reported that the primary endpoint data published from 2L+ avelumab therapy for metastatic MCC and early data of another PD-1 blockade for therapy of metastatic MCC showed promising results and consequently stated that it was now unethical to randomize to treatment with

[1] *LEBBE, C., BECKER, J. C., GROB, J.-J., MALVEHY, J., DEL MARMOL, V., PEHAMBERGER, H., PERIS, K., SAIAG, P., MIDDLETON, M. R., BASTHOLT, L., TESTORI, A., STRATIGOS, A. & GARBE, C. 2015. Diagnosis and treatment of Merkel Cell Carcinoma. European consensus-based interdisciplinary guideline. European Journal of Cancer, 51, 2396-2403.*

chemotherapy, if these options were available. Therefore, conducting any future randomized trials in chemotherapy or best supportive care would not be feasible[2].

In lieu of conducting a randomized trial, and given the sparse literature with no randomized trials and no prospective trials, the Alliance conducted a two-part observational study to collect retrospective data regarding response to chemotherapy from patients with mMCC.

In the absence of any other large prospective datasets in metastatic MCC and the difficulty in conducting a randomized study, as this is considered unethical by the clinical community, this observational data set in Obs001 represents the most robust approach to generating comparator data.

The Alliance has provided the available data and justification from the literature for use of available historical data as a reference to demonstrate the clinical relevance of the response duration observed with checkpoint inhibition with avelumab. The response rates and response duration data with avelumab for mMCC in treatment-naive and previously treated patients with mMCC demonstrate the clinically meaningful response which has not been observed with historical off-label use of chemotherapy agents. The prolonged durable responses translate into prolonged progression-free survival and potential prolonged overall survival rates not observed with chemotherapy.

The Alliance held a pre-submission meeting with NoMA in November 2017 where we presented our intended approach, and detailed information on the JAVELIN study and the two-part observational study, Obs001. Since no objections were raised on either our approach or our data, the Alliance proceeded with the strategy and the HTA application was submitted in December 2017. The base case in our analysis resulted in the following ICERs per QALY:

- 1. line treatment: **NOK 526.345** (deterministic) or **NOK 503.954** (probabilistic)
- 2. line treatment: **NOK 414.012** (deterministic) or **NOK 402.199** (probabilistic)

Following recommendations from Magnussenutvalgets report on prioritization from 2015, the relevant willingness-to-pay threshold for this patient population is NOK 495.000.

The analysis we have submitted indicates that Bavencio is a cost effective treatment option with a very limited budget impact. We hope for a constructive dialog with Beslutningsforum going forward, so that we together can ensure that patients with metastatic merkelcell carcinoma can receive a better treatment option.

[2] *Hauschild and Schadendorf, 2016*