



Product-based Registries

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Case Study – Bavencio[®]

Merkel Cell Carcinoma

Disclaimer:

This presentation contains company proprietary information and the outcomes of the company's internal evaluations. The conclusions are my personal view and interpretation.





Background

Bavencio® (avelumab)

– FDA accelerated approval March 2017

- BAVENCIO is indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC).

– EC decision (conditional marketing authorization) September 2017

- Bavencio is indicated as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC).



Clinical Development

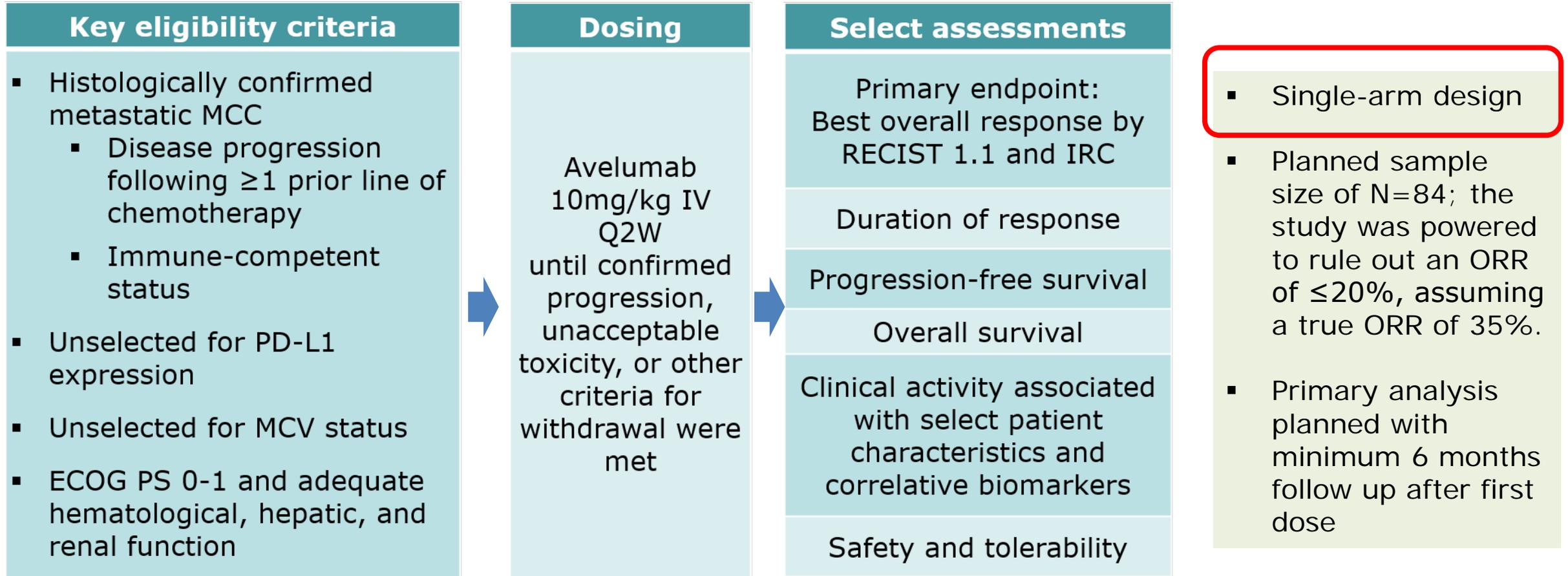
- MCC is a ultra-rare, aggressive skin cancer associated with poor survival outcomes ¹ and sparse treatment options
- Incidence of MCC ²
 - 0.6 per 100,000 in US in 2009
 - 1.6 per 100,000 in Australia, 2006–2010
 - 0.3 per 100,000 in Sweden in 2012
- Treatment Options (prior Bavencio[®]):
 - Stage I-III: surgery, radiation, adjuvant chemotherapy
 - Stage IV: 1L historic chemotherapy, 2L+ no standard treatment, however limited evidence of benefit

1. Harms KL et al. *Ann. Surg Oncol.* 2016;23:3564-3571

2. Becker JC et al. *Nature Rev* 2017;3:1-17



Pivotal Study Design: EMR100070-003 (JAVELIN Merkel 200)





Submission Strategy

EU: Conditional MAA
US: Accelerated Approval

Pivotal study: EMR100070-003 Part A (JAVELIN Merkel 200 (2L+))

- Single-arm design with BOR as primary endpoint (n=88)

Historic Control: Comparative quality-controlled retrospective RWD

- Retrospective Observational Study with 2 cohorts in US and EU

Confirmatory study: EMR100070-003 Part B (JAVELIN Merkel 100 (1L))

- Single-arm design with DRR as primary endpoint (n=116)



Real World Data used as Evidence for Control

Supportive Retrospective RWD: Observational Study (100070-Obs001)

- Objective: Study 100070-Obs001 provides a comparative historic reference for the pivotal Merkel 200 clinical study results. Recognizing that literature on outcomes for patients with metastatic MCC (mMCC) in general remains sparse and may be subject to reporting bias.
- Source: Part A (US; Nov 2004 – June 2015; n=20 (2L; 14 immunocompetent(ic)) + n=67 (1L; 51 ic))^{1/2}
 - Part A: US Oncology Network (USON) outpatient medical oncology practices across the United States (US) (19 states)
 - Data were obtained from iKnowMed, an oncology-specific electronic health record (EHR) system.
 - The data represent multisite treatment patterns and outcomes.
 - Records from 1 November 2004 to 30 September 2014 were searched, and qualifying patients were followed up to the end of the study period (30 June 2015)
- Source: Part B (EU (DACH; Nov 2004 – Dec 2015; n=34 (2L; 29 immunocompetent(ic))^{1/3}
 - Retrospective anonymized patient-level information was extracted from an observational, real-world MCC specific registry that was established in 2005 in German speaking countries.
 - Patients were identified through a collaboration between IMS Health and the German Cancer Research Center (Deutsches Krebsforschungszentrum).
 - Data in the registry were collected from 56 clinical sites (53 in Germany, 2 in Austria, and 1 in Switzerland),

Design discussed prior initiation with Health Authorities.

¹EU EPAR:

https://www.ema.europa.eu/en/documents/assessment-report/bavencio-epar-public-assessment-report_en.pdf



²Part A: Cowey CL, Mahnke L, Espirito J, Helwig C, Oksen D, Bharmal M. Real-world treatment outcomes in patients with metastatic Merkel cell carcinoma treated with chemotherapy in the USA. *Future Oncol.* 2017;13(19):1699-1710.

³Part B: Becker JC, Lorenz E, Ugurel S, Eigentler TK, Kiecker F, Pföhler C, Kellner I, Meier F, Kähler K, Mohr P, Berking C. Evaluation of real-world treatment outcomes in patients with distant metastatic Merkel cell carcinoma following second-line chemotherapy in Europe. *Oncotarget.* 2017;8(45):79731.



Real World Data used as Evidence for Control

Supportive Retrospective RWD: Observational Study (100070-Obs001)*

*Based on Module 2 information submitted during initial MAA.

US Part A: 1L/2L+ Population - Identification Scheme

EU Part B: 2L+ Population - Identification Scheme

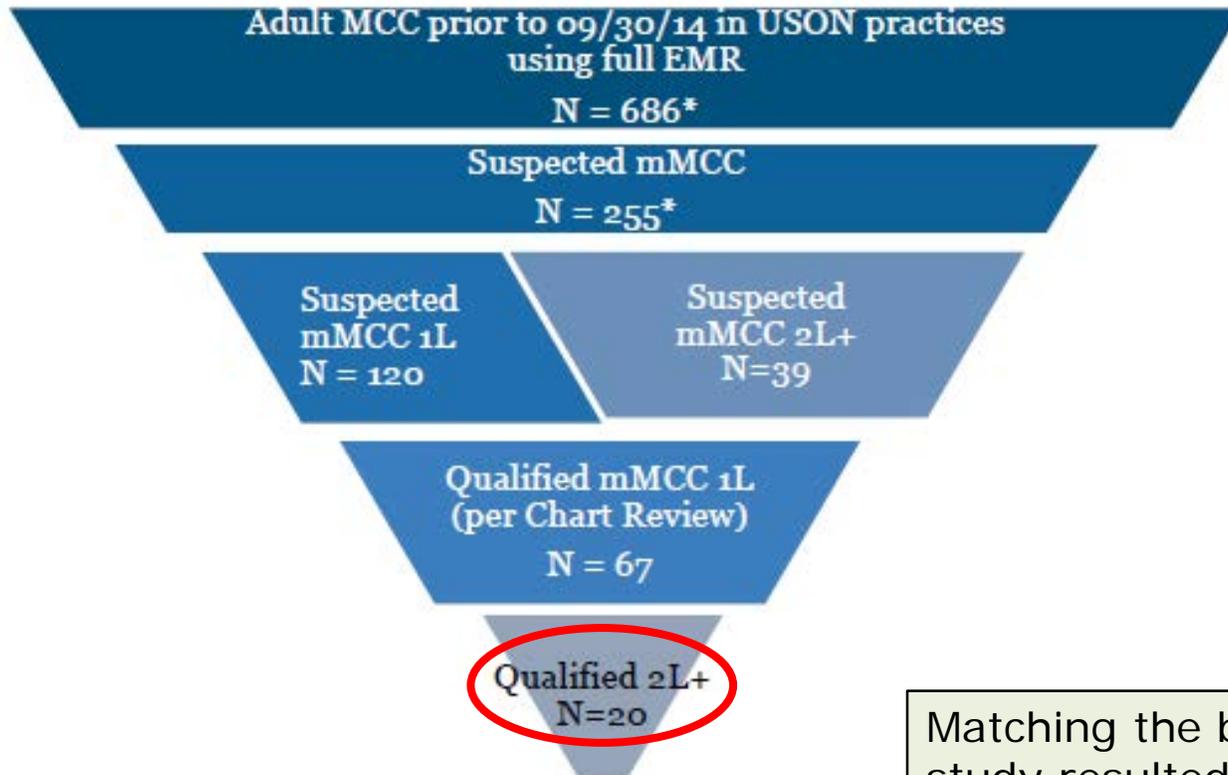


Table 30 Overview of Subject Selection for Subjects with Metastatic Merkel Cell Carcinoma Receiving Second-line or Later Chemotherapy- Part B

	Subjects Excluded		Subjects Remaining	
	N	%	N	%
Subjects with MCC 01 Nov 2004 – Sep 2015			971	100
Subjects with advanced metastatic disease only	645	66.4	326	33.6
Attrition reasons among metastatic MCC (n=326)				
Subjects with Stage IV distant metastases	84	25.8	242	74.2
Subjects s treated with systemic therapy (e.g., interferons, somatostatin analogues, kinase inhibitors, radiopeptides, chemotherapy)	18	7.4	224	92.6
Subjects treated with chemotherapy (e.g., cisplatin, carboplatin, etoposide, anthracyclins, or taxanes)	53	23.7	171	76.3
Subjects with 1L and 2L chemotherapy	137	80.1	34	19.9
Subjects available for analysis ^a (same as above)			34	

Source: Study 100070-Obs001 study report Table 4.

Matching the baseline characteristics from the pivotal study resulted in a very low sample size.



Real World Data used as Evidence for Control

Supportive Retrospective RWD: Observational Study (100070-Obs001)*

2L+ Population

Table 35: Demographic and baseline characteristics for patients with second line or late chemotherapy

Parameter	Part A		Part B	
	All Qualified (N = 20)	Immunocompetent (N = 14)	All Qualified (N = 34)	Immunocompetent (N = 29)
Gender, n (%)				
Male	14 (70.0)	11 (78.6)	22 (64.7)	18 (62.1)
Female	6 (30.0)	3 (21.4)	12 (35.3)	11 (37.9)
Race, n (%)				
Caucasian	9 (45.0)	8 (57.1)		
ND	11 (55.0)	6 (42.9)	34 (100)	29 (100)
Age at index in years				
average (SD)	73.3 (10.4)	72.5 (11.7)	64.4 (11.3)	64.4 (11.6)
median	73.5	75.2	67.5	67.0
(25th, 75th percentiles)	(66.0, 81.1)	(63.6, 81.1)	(61.0, 72.0)	(61.0, 73.0)
ECOG, n (%)			N/A	N/A
0	1 (5.0)	0		
1	16 (80.0)	13 (92.9)		
2	1 (5.0)	0		
Unknown	2 (10.0)	1 (7.1)		
Metastatic status ^a				
Visceral metastases	14 (70.0)	10 (71.4)	20 (58.8) ^b	16 (55.2) ^b
Not noted or missing	4 (20.0)	2 (14.3)	7 (20.6)	6 (20.7)
Non visceral metastases (bone / lymph node only)	2 (10.0)	2 (14.3)	7 (20.6) ^c	7 (24.1) ^c

ECOG = Eastern Cooperative Oncology Group, N/A = not available, ND = not documented, and SD = standard deviation

^a For Part A, based on documented location of target lesions. If a patient did not have a target lesion identified or site not noted, it was classified under not noted. Non-visceral = bone or lymph node metastases only (no other sites); visceral = any other metastatic site other than bone or lymph node only.

^b Visceral metastases and/or elevated lactate dehydrogenase according to classification of malignant melanoma.

^c Distant soft tissue and lymph node metastases according to classification of malignant melanoma.

1L Population

Table 36: Demographic and baseline characteristics for patients with first line chemotherapy (Part A only)

Parameter	All Qualified (N = 67)	Immunocompetent (N = 51)
Gender, n (%)		
Male	53 (79.1)	43 (84.3)
Female	14 (20.9)	8 (15.7)
Race, n (%)		
Caucasian	43 (64.2)	34 (66.7)
Other or ND	24 (35.8)	17 (33.3)
Age at index in years		
average (SD)	74.4 (10.5)	75.8 (10.7)
median	75.8	78.1
(25th, 75th percentiles)	(67.1, 82.3)	(67.9, 83.7)
ECOG, n (%)		
0	14 (20.9)	11 (21.6)
1	32 (47.8)	25 (49.0)
2 or 3 ^a	8 (9.0)	5 (5.9)
Unknown	13 (19.4)	10 (19.6)
Metastatic status, ^a n (%)		
Visceral metastases	46 (68.65)	34 (66.67)
Non visceral metastases (bone/lymph node only)	14 (20.90)	10 (19.61)
Not noted	7 (10.45)	7 (13.72)

ECOG = Eastern Cooperative Oncology Group, ND = not documented, and SD = standard deviation

^a Based on documented location of target lesions. If a patient did not have a target lesion identified or site not noted, it was classified under not noted. Non-visceral = bone or lymph node metastases only (no other sites); visceral = any other metastatic site other than bone or lymph node only.



Real World Data used as Evidence for Control

Supportive Retrospective RWD: Observational Study (100070-Obs001)*

2L+ Population

Table 33 Best Overall Response and Objective Response Rate for Subjects Receiving Second-line or Later Chemotherapy, Study 100070-Obs001

Response	Part A		Part B	
	All Qualified (N = 20)	Immunocompetent ^{a,b} (N = 14)	All Qualified (N = 34)	Immunocompetent ^{a,b} (N = 29)
Best Overall Response, n (%)				
Complete response	0	0	0	0
Partial response	4 (20.0)	4 (28.6)	3 (8.8)	3 (10.3)
Stable disease	2 (10.0)	2 (14.3)	3 (8.8)	3 (10.3)
Progressive disease	8 (40.0)	5 (35.7)	28 (82.4)	23 (79.3)
Not evaluable	6 (30.0)	3 (21.4)	0	0
No baseline information and no F/U information	1 (16.7)	0		
No F/U information and no target lesions	2 (33.3)	1 (33.3)		
No F/U information	3 (50.0)	2 (66.7)		
Objective Response Rate (95% CI)^{c,d}	20.0 (5.7 – 43.7)	28.6 (8.4 – 58.1)	8.8 (1.9 – 23.7)	10.3 (2.2 – 27.4)

Source: Study 100070-Obs001 study report, Table 13.

*Based on Module 2 information submitted during initial MAA.

1L Population

Table 37 Efficacy Results for First-line Treatment with Avelumab and Treatment with Chemotherapy

Efficacy Parameter	Study 100070-Obs001 Part A (US) Immunocompetent 1 st Line ^a N=51	Study 100070-Obs001 Part A (US) All Eligible 1 st Line ^a N=67
ORR, confirmed BOR, % (95% CI)	29.4 (17.5, 43.8)	31.3 (20.6, 43.8)
Median DOR, months (95% CI)	6.7 (1.2, 10.5)	5.7 (2.6, 8.7)
6-month DRR, % (95% CI)	15.7 (7.0, 28.6)	14.9 (7.4, 25.7)
6-month PFS rate, % (95% CI)	47.1 (33.0, 59.9)	44.8 (32.7, 56.2)
12-month PFS rate, % (95% CI)	24.78 (13.8, 37.4)	21.8 (12.7, 32.4)
15-month PFS rate, % (95% CI)	17.34 (8.1, 29.5)	NA
6-month OS rate, % (95% CI)	66.7 (52.0, 77.8)	70.1 (57.5, 79.5)

Potentially due to sample size, there was a large difference in efficacy based on ORR across the two 2L+ cohorts in US vs EU, which made the agencies question the validity of the data.

However, the duration of response from both 2L+ cohort was consistent, providing confidence on the poor efficacy of chemotherapy in 2L+.



Agency Interaction related to RWD

- Overview EMA and FDA interactions where the RWD study Obs001 discussed
 - *EMA: CHMP Scientific Advice (SA), indication MCC*
 - *EMA 22 May 2014: EMEA/H/SA/2771/1/2014/II (MCC)*
 - *EMA 23 July 2015: EMEA/H/SA/2771/1/FU/1/2015/III (MCC)*
 - *EMA 23 June 2016: EMEA/H/SA/2771/1/FU/2/2016/PA/II (MCC)*
 - *CHMP Co-Rapporteur Meeting June 24, 2016*
 - *CHMP Rapporteur Meeting June 28, 2016*
 - *FDA:*
 - *FDA Type B meeting February 2016*
 - *FDA advice letter based on a new protocol submission of OBS001 in March 2016*
 - *FDA Type B meeting September 2016*



EMA Interactions

Evolution of
acceptability

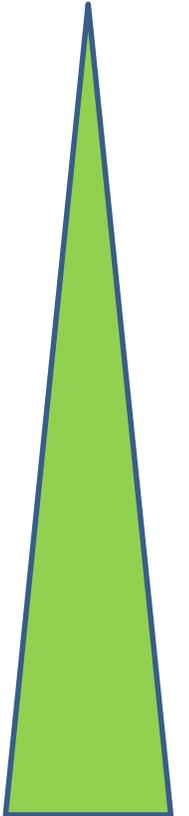
- **EMA CHMP SA meeting 22May2014**
 - The agency would like to see a good quality comparative control.
- **EMA CHMP FU-SA meeting 23July2015**
 - The agency agreed that the proposed observational study with the presented ENCePP template and the prospective planned analysis could provide good quality information to help assess the single-arm results of the pivotal study.
 - The prospective planned interim analysis with a comparison to the observational study results could be acceptable for an conditional approval.
- **EMA CHMP FU-SA 23June2016**
 - The information that the patient numbers in the observational study are really limited based on the algorithm to identify matching patients would request further sources to substantiate the data for a descriptive comparison.
- **EMA Rapporteur meeting 24June2016**
 - The process and method of patient selection for the observational study should be in detail described in the dossier.
 - The results from the observational study should be presented in Module 2.
 - The agency stated that the clear criteria to match the pivotal single-arm study eligibility criteria explained the limited final numbers and confirmed the ultra-rare nature of the patient population in metastatic Merkel Cell Carcinoma.
- **EMA Co-Rapporteur meeting 28June2016**
 - The presented data especially the limited numbers should be clearly described in the dossier with the detailed method and process of patient identification.
 - The additional 1L data from the observational study should be described as well to provide the clinical context for the single-arm 1L confirmatory study.



FDA Interactions

Evolution of
acceptability

- **FDA interaction February 2016:**
 - FDA mentioned that it would be challenging to set up such a study and especially to control the medical care over the historically-controlled population.
 - FDA advised to have an alternative approach to the single-arm plus historical control proposal for a confirmatory study.
 - The proposal that the observational study is only described in Module 5 would be not acceptable and results should be in the Module 2 documents, respective the Summary of Efficacy.
 - In addition, FDA pointed out that the data would be not considered for comparative labeling claims.
- **FDA interaction April 2016:**
 - FDA pointed out that they would not be utilizing the data from the observational study during their review of the MCC BLA.
 - The FDA acknowledged only that the applicant will submit the results as a historical comparator.
- **FDA interaction September 2016:**
 - FDA pointed out that the results of the pivotal single-arm study would be only convincing if the enrolled patients would reflect the population identified in the observational study.





Data*

1L&2L+ Population

2L+ Population

Table 37 Efficacy Results for First-line Treatment with Avelumab and Treatment with Chemotherapy

Efficacy Parameter	EMR100070-003 2L+ (Part A) 12-month minimum follow-up analysis N=88	EMR100070-003 1L (Part B) ≥13-week follow-up N=16	Study 100070-Obs001 Part A (US) Immunocompetent 1 st Line ^a N=51	Study 100070-Obs001 Part A (US) All Eligible 1 st Line ^a N=67	Iyer 2016 1 st line Immunocompetent N=48 ^b	Iyer 2016 1 st Line N=62 ^b
ORR, confirmed BOR, % (95% CI)	33.0 (23.3, 43.8)	62.5 (35.4, 84.8)	29.4 (17.5, 43.8)	31.3 (20.6, 43.8)	58.3 (43.2, 72.4)	54.8 (41.7, 67.5)
Median DOR, months (95% CI)	NE (18.0, NE)	NE (All 10 confirmed responses ongoing)	6.7 (1.2, 10.5)	5.7 (2.6, 8.7)	NA	2.8
6-month DRR, % (95% CI)	30.6 (20.9, 40.3)	ND	15.7 (7.0, 28.6)	14.9 (7.4, 25.7)	NA	17.7 (9.2, 29.5)
6-month PFS rate, % (95% CI)	40 (29, 50)	ND	47.1 (33.0, 59.9)	44.8 (32.7, 56.2)	27.1 (15.5, 40.0)	25.8 (15.7, 37.1)
12-month PFS rate, % (95% CI)	30 (21, 41)	ND	24.78 (13.8, 37.4)	21.8 (12.7, 32.4)	8.33 (2.7, 18.2)	6.5 (2.1, 14.4)
15-month PFS rate, % (95% CI)	30 (21, 41)	ND	17.34 (8.1, 29.5)	NA	6.25 (1.6, 15.5)	4.8 (1.3, 12.2)
6-month OS rate, % (95% CI)	70 (59, 78)	ND	66.7 (52.0, 77.8)	70.1 (57.5, 79.5)	NA	NA

Source: Study EMR100070-003 Addendum 2 (12 months minimum follow-up analysis): Table 15.2.1.1.1; Table 15.2.2.1, Table 15.2.13.1, Table 15.2.3.1, Table 15.2.4.1; Study EMR100070-003 Technical Report 1 Table 15.2.1.1.1b, Table 15.2.2.1b; Study 100070-Obs001 study report: Table 14, Table 17; refer to Iyer et al 2016 (with additional data from personal communication with P. Nghiem and calculations by the Sponsor).

*Submitted Module 2 documents for initial approval.

Iyer et al. Response rates and durability of chemotherapy among 62 patients with metastatic Merkel cell carcinoma Cancer Medicine 2016, 1-8.

Table 32 Results of Pivotal Study EMR100070-003, Part A and Observational Study 100070-Obs001 in Second-line or Later Subjects

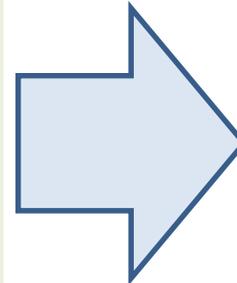
Efficacy Parameter	Study EMR100070-003 12-month minimum follow-up analysis N=88	Study 100070-Obs001 Part A (US) Immunocompetent ^a N=14	Study 100070-Obs001 Part B (EU) Immunocompetent ^a N=29
BOR per RECIST 1.1, n (%)			
Complete Response	10 (11.4)	0	0
Partial Response	19 (21.6)	4 (28.6)	3 (10.3)
Stable Disease	9 (10.2)	2 (14.3)	3 (10.3)
Progressive Disease	32 (36.4)	5 (35.7)	23 (79.3)
Non-CR /Non-PD	0	0	0
Not Evaluable	18 (20.5)	3 (21.4)	0
Objective Response Rate			
Response rate (CR+PR), n (%) (95% CI)	29 (33.0) (23.3, 43.8)	28.6 (8.4, 58.1)	10.3 (2.2, 27.4)
Duration of Response^b			
Median, months (95% CI)	NE (18.0, NE)	1.7 (0.5, 3.0)	1.9 (1.3, 2.1)
Durable response rate^a			
6-months, %, (95% CI)	30.6 (20.9, 40.3)	0 (0.0, 23.2)	0 (0.0, 11.9)
Progression-free survival			
Median, months (95% CI)	2.7 (1.4, 6.9)	2.2 (1.2, 3.5)	3.0 (2.5, 3.2)
6-month PFS rate by KM, % (95% CI)	40 (29, 50)	0	3.4 (0.3, 14.9)
12-month PFS rate by KM, % (95% CI)	30 (21, 41)	0	0
15-month PFS rate by KM, % (95% CI)	30 (21, 41)	0	0
Overall survival			
6-Month OS rate by KM, %	70 (59,78)	26.8 (7.3, 51.5)	27.5 (13.0, 44.2)

The historical and observational control demonstrate that the most relevant endpoint is the duration of response (blue circles).



Data*

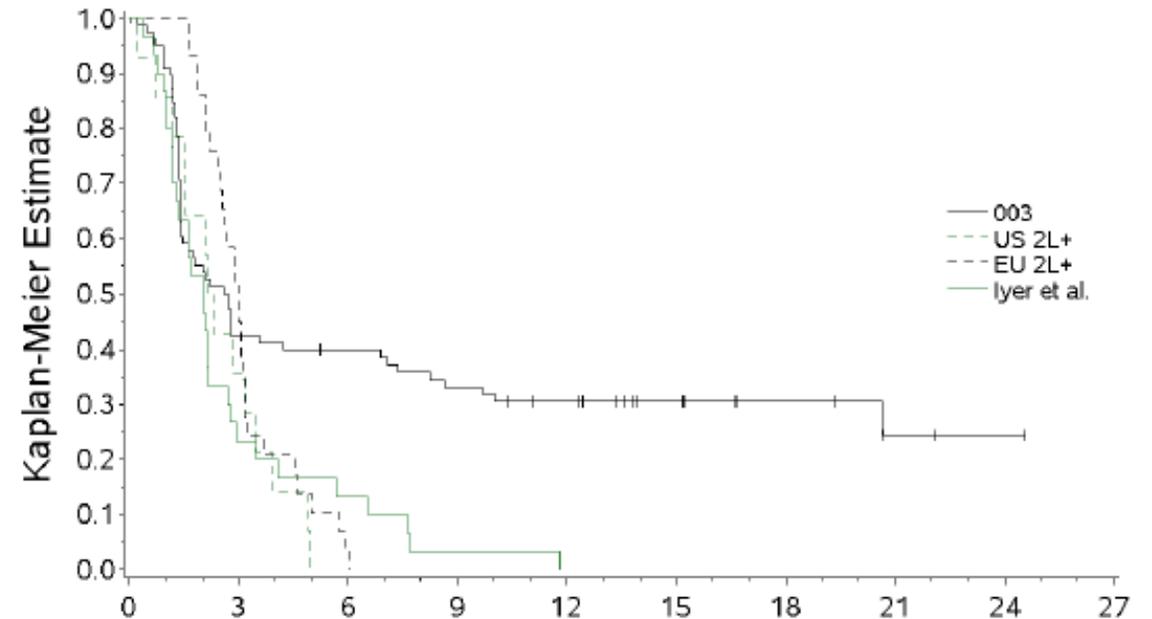
Important that the observational study match the baseline characteristics and endpoint determination with the pivotal study for a descriptive comparison!



Optimal would be a statistical comparison, however in this case also the descriptive analysis that duration of response is the main benefit was transferred in a clear way.

Figure 16

Kaplan-Meier Estimates for PFS in Pivotal Study EMR100070-003 Part A (12-month minimum follow-up analysis), Study 100070-Obs001 (Immunocompetent Subjects), and Iyer 2016 – All Second-line or Later



At Risk	Progression-Free Survival Time (months)									
	0	3	6	9	12	15	18	21	24	27
003	88	33	30	25	21	11	6	2	1	0
US 2L+	14	5	0	0	0	0	0	0	0	0
EU 2L+	29	15	1	0	0	0	0	0	0	0
Iyer et al.	30	7	4	1	0	0	0	0	0	0



Legend: 003: Study EMR100070-003; EU 2L+: Study 100070-Obs001 Part B (EU), 2L+ chemotherapy; Iyer et al: refer to Iyer et al 2016; US 2L+: Study 100070-Obs001 Part A (US), 2L+ chemotherapy.

*Submitted Module 2 documents for initial approval.



EMA – EPAR discussion*

Section 2.5.3 – Declared as supportive data but not as high quality comparative control as discussed in the CHMP SA meetings

- ... **The retrospective observational study was intended to address a lack of information on reliable historical data and also the lack of a comparator arm** in the Phase II trial EMR100070-003.
- ...**In addition, the data was supplemented with recent literature citing response rates** and duration of response for subjects with distant metastatic MCC (Stage IV) in the 1L and 2L chemotherapy disease settings. **Taking into account the caveats with registries and observational studies, the data can only be considered as supportive as there were divergences observed in terms of objective response rates in the registry study and in published clinical experience in first line treatment...**
- ...Combined with an ultra-orphan disease with no approved therapy or consensus guideline on the most appropriate chemotherapy, the **observational results cannot be used as intended by the advice**, which required good quality comparative controls and a compelling difference between a comparative analysis of the clinical effect observed in the chemotherapy group vs avelumab treated patients that would be indisputably positive. **The limited data showed marked geographic differences reflective of the lack of consensus regarding therapy.** ...

Section 2.5.4 – “...Challenges to compare the results with data from historical controls and in the literature...”

- ...Taking into account the intrinsic limitation of single arm studies, the rarity of the disease and **the challenges to compare the results with data from historical controls and in the literature, the currently available data are deemed to support the efficacy of avelumab** in both pre-treated and chemotherapy-naïve patients...
- ...The CHMP considers **that additional supportive data on efficacy will be provided also from the following post-authorisation safety study:**
PASS: German real-world cohort study should be submitted as additional PhV activity to address the missing information of safety and efficacy in immune compromised patients.

PASS/RWD

Effects Table – Results of observational study included as comparator arm

*EU EPAR:
https://www.ema.europa.eu/en/documents/assessment-report/bavencio-epar-public-assessment-report_en.pdf



FDA Review

FDA Summary of Review March 2017²- the observational study were considered exploratory and are used for clinical context

- The results of Study 003 were considered **in the context of an external population** that included treatment-naïve or previously-treated patients with metastatic MCC who were treated with chemotherapy **in observational Study 100070-Obs001 (Obs001), a retrospective, chart review...** No formal statistical comparisons were made between Studies 003 and Obs001.

Section Benefit/Risk assessment:

- **The results of the study are considered in the context of outcomes for previously-treated patients with metastatic MCC who had been treated with chemotherapy in observational Study Obs001, a retrospective chart review ... The data from Study Obs001 are subject to selection bias, therefore no formal statistical comparisons were undertaken and the data are considered for informational purposes.**

FDA B/R table:

- Study 003 was a well-conducted trial demonstrating a clinically meaningful response rate for a serious and life threatening rare disease and **with significantly longer response durations observed (Study Obs001) or reported with first-line chemotherapy.**

Section 7.1:

- **The descriptive analyses and results of Study Obs001 were considered exploratory and reviewed only in order to further characterize the risk: benefit profile of avelumab in metastatic MCC in the context of the natural history of MCC and treatment outcomes with cytotoxic chemotherapy.**

Section 7.6 “Conclusion and Recommendations”:

- **Acknowledging the limitations of the small sample size and selection bias inherent in the use of historical control data, the ORR and DOR results of Study Obs001 in immunocompetent patients with metastatic MCC treated with second line chemotherapy [ORR 28.6% (95% CI: 8.4, 58.1); median DOR 1.7 months (95% CI: 0.5, 3.0)], provided context for the natural history of MCC with chemotherapy.**

FDA Podcast May 2017¹

- *Moderator: I heard about some novel supportive data that were incorporated into the review. **Real-world data** are going prime-time?*
- *FDA: You're right, Abhi. **A retrospective, observational study**—a chart review of electronic medical records obtained in community and academic centers—**was submitted to describe the natural history of metastatic Merkel Cell tumor.** This supportive study collected information on the outcomes of patients with metastatic Merkel Cell carcinoma treated in the first line and beyond. **The data describe the relatively poor treatment outcomes following administration of cytotoxic chemotherapies.***

1. <https://www.fda.gov/drugs/resources-information-approved-drugs/fda-disco-avelumab-merkel-cell-carcinoma-transcript>.
2. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761049Orig1s000Mu1tidisciplineR.pdf



Conclusion

- The acceptance of RWD by the agencies is undergoing an evolution.
- Early interaction to present the purpose, method and layout of the protocol of the RWD study is crucial for clarity and final acceptance.
- In first interactions the data were not seen as acceptable to replace the active control of an adequate well-controlled study, however with more details and first results the agencies were more open for the approach.
- With better understanding the disease science and treatment options over time the acceptance increased and finally seen, although based on limited numbers, as the only option to substantiate the sparse existing historical control data, and place the results of the single-arm pivotal and confirmatory study in clinical context, to generate an adequate benefit/risk balance.
- In addition, both agencies accepted the data not for the label claims but as supportive data to place it in clinical context in case of incomplete well-controlled study results.
- In the EU EPAR the observational study is declared as comparator arm in the effects table.



Potential Challenges with RWD

- In case of regional investigations differences in patient data collection may impact the results.
 - Solution pooled analysis if feasible.
- If RWD should be used for historical control statistical direct comparison would be very helpful, however rarely feasible.
 - Upfront planning of RWD together with clinical study protocol substantiated by real world epidemiology data
- Descriptive statistical evaluation is helpful however will not replace a comparator arm completely.
 - Ensure that the descriptive evaluation is very close to the clinical study and has sufficient sample size.
- Early conceptual discussion with agencies are important however the final eligible patient sample number is very limited based on the requested matching criteria.
 - Run upfront an epidemiology study if the matching of the clinical study protocol would ensure sufficient data for the RWD investigation.