Alternative Endpoint(s)

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Case Study – Bavencio®

Merkel Cell Carcinoma (MCC)

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 and EU approved indications
  - Merkel Cell Carcinoma (MCC)
  - Renal Cell Carcinoma (RCC)
  - Urothelial Carcinoma (UC)

Primary Endpoint for approval

MCC: BOR and DRR

RCC: PFS; OS (BM+)

UC: OS (BM+)&OS (all)

BOR: Best Overall Response
DRR: Duration of Response Rate
PFS: Progression Free Survival
OS: Overall Survival
BM: Biomarker

https://www.ema.europa.eu/en/documents/product-information/bavencio-epar-product-information_en.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761049s005lbl.pdf

MCC Clinical Development

- Merkel Cell Carcinoma (MCC) is an 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: EMR100070-003 Part A (JAVELIN Merkel 200)

Patient Population

Participants with metastatic Merkel cell carcinoma (MCC) after failing first-line chemotherapy received Avelumab at a dose of 10 milligram per kilogram (mg/kg) as 1-hour intravenous infusion once every 2 weeks until therapeutic failure, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the trial or investigational medicinal product occurs.

Dosing

Avelumab 10mg/kg IV Q2W until confirmed progression, unacceptable toxcity, or other criteria for withdrawal were met

Select assessments

Primary endpoint: Best overall response **(BOR)** by RECIST 1.1 and IRC

Duration of response

Progression-free survial

Overall survival v

Clinical activity associated with select patient characteristics and correlative biomarkers

Safety and tolerability

Statistical Considerations

Single-arm design

Planned sample size N=84; the study was powered to rule out an ORR of <20%, assuming a true ORR of 35%.

Primary analysis planned with minimum 6 months follow after first dose.

https://clinicaltrials.gov/ct2/show/results/NCT02155647

https://www.ema.europa.eu/en/documents/product-information/bavencio-epar-product-information_en.pdf

Confirmatory Study: EMR100070-003 Part B (JAVELIN Merkel 100)

Patient Population

Participants received Avelumab as first-line treatment for metastatic or distally recurrent MCC at a dose of 10 mg/kg as 1-hour intravenous infusion once every 2 weeks until therapeutic failure, significant clinical deterioration, unacceptable toxicity, or any criterion for withdrawal from the trial or investigational medicinal product occurs.

Dosing

Avelumab 10mg/kg IV Q2W until confirmed progression, unacceptable toxcity, or other criteria for withdrawal were met

Select assessments

Primary endpoint: Duration of Response Rate **(DRR)** by RECIST 1.1 and IRC

ORR and DoR

Progression-free survial

Overall survival

Clinical activity associated with select patient characteristics and correlative biomarkers

Safety and tolerability

Statistical Considerations

Single-arm design

Planned sample size N=112; assuming a true DRR of 45% the probability to observe lower bound of the exact 95% CI above 20% would be>99% and above 30% would be 90%.

Primary analysis planned with minimum 6 months follow after first dose and 15 months after the accrual of the last subject.

https://clinicaltrials.gov/ct2/show/results/NCT02155647

https://www.ema.europa.eu/en/documents/product-information/bavencio-epar-product-information_en.pdf

Final 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)

EU: Conversion Annex II.E specific obligation Jan2020
US: Conversion planned

BOR : Best Overall Response
DRR: Duration of Response Rate (6 month)

Agency Interaction related to Design and Endpoint

Overview EMA and FDA interactions where the Endpoint discussed.

- *EMA: CHMP Scientific Advice (SA), indication mMCC*
  - *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)*
- *FDA: Type B meetings, indication mMCC*
  - *FDA Type B pre-IND/pre-Phase II meeting in 2014*
  - *FDA Type B meeting February 2016*
  - *FDA Type B meeting September 2016*

CDDF
Cancer Drug Development Forum

EMA/FDA interactions 2014

Purpose: Reach agreement that the proposed single-arm pivotal Phase II design and study endpoints are acceptable for conditional Marketing authorization or Accelerated Approval.

Topic	EMA	FDA
Single-arm trial (SAT) design	Not preferred, EMA stated a RCT would be most reasonable, but SAT acceptable under certain considerations.	A SAT evaluating ORR would not be sufficient to support a BLA.
BOR as primary endpoint	Acceptable, with at least 6months follow-up, and only with OS and PFS as secondary endpoints	There is no evidence that a ORR of 10% with immunomodulatory agents will reliably predict an effect on OS. Clinical benefit would require evidence of significant improvements in survival or PFS of substantial and clinical meaningful magnitude to support BLA.
Secondary endpoints	Duration of Response (DoR) at a defined time point, e.g. 1 year	Time-to-event endpoints, such as PFS, will not be interpretable in a single arm trial.

Company implementation:

- SAT Phase II EMR100070-003 Part A (JAVELIN Merkel 200 (2L+)) started. IND submission in Q2 2014.
- BOR as independent readout with DoR (6months), OS and PFS as secondary endpoints (see slide 4).

EMA/FDA interactions 2015/2016

Purpose: Reach feedback that the design of the planned Phase III study in 1L MCC is acceptable as confirmatory trial.

Topic	EMA Jul 2015	FDA Jan 2016
Randomized placebo-controlled study design	RCT placebo-controlled maintenance design is seen acceptable.	A well-designed, well conducted, internally consistent, randomized trial demonstrating a statistically robust and clinically meaningful improvement in PFS would be adequate. FDA has concern that a single-arm study with historical control is difficult to interpret with response rate as primary endpoint.
PFS as primary endpoint	PFS with sufficient magnitude. The proposed type I error 1-sided 5% is not acceptable.	PFS assessed by independent review committee (IRC) as the primary endpoint is acceptable.
Secondary endpoints	OS and PFS2 should be considered as secondary endpoints	Durable of response should be in hierarchical testing as secondary endpoint if considered for label claim

company implementation:

- A RCT Phase III EMR100070-006 as confirmatory study initiated (IND submission in Q2 2016).
- PFS as primary endpoint based on independent readout with OS and ORR as secondary endpoints.
- Statistical assumption PFS type I error 1-sided 2.5%.

EMA/FDA interactions 2016/2016

Purpose: Reach agreement that the proposed RCT Phase III Study (EMR100070-006) is not feasible anymore and changed to a SAT design is the only option for a confirmatory study.

Topic	EMA June 2016	FDA Sep 2016
Single-arm confirmatory study	Replication of the single-arm pivotal Phase II in a 1L population might be reasonable to convert the initial CMA into full MAA. However, the number of patients should be >100 to provide sufficient evidence and potential determinants of response in subgroups.	A single arm, open label trial, even if compared to historical controls, will not likely meet the regulatory requirements. FDA again encourages to conduct the proposed RCT study that will assess PFS (submitted to the IND Q2 2016). FDA acknowledged that the RCT Phase III Study 006, PFS primary endpoint, will not be initiated at this time.
DRR as primary endpoint	The primary endpoint 6months DRR with 40% (estimated effect) could appear reasonable target. The results should demonstrate convincingly the positive B/R in context of the high-quality historical data.	In order to verify clinical benefit a confirmatory trial demonstrating a treatment effect on OS or an improvement in PFS of a substantial and clinically meaningful magnitude would be acceptable.

Company implementation:

- RCT Phase III 006 was terminated and SAT 003 was extended by a 1L mMCC cohort, Part B, (n=112).
- Primary endpoint DRR (6-months) based on IRC with OS, PFS and ORR as secondary endpoints.
- Statistical assumption 40% DRR (6 months) in n=112 patients (see details slide 5)

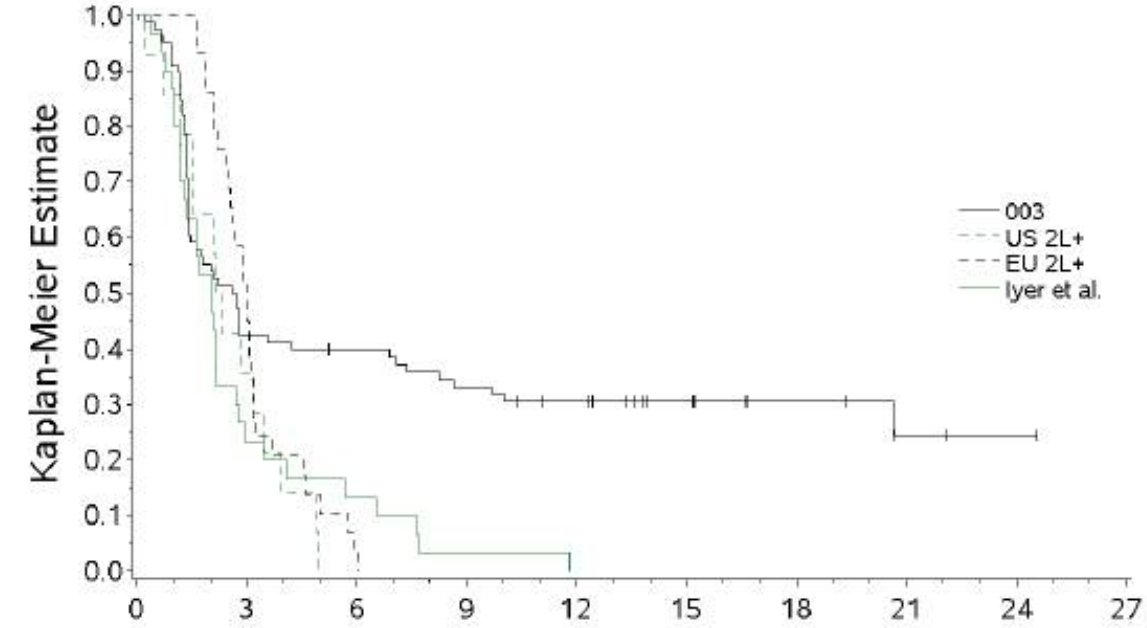
Results*

EPAR*: …An apparent plateau of the Kaplan-Meier PFS curve, observed in the 6-months analysis, is maintained in the updated 12-months analysis, possibly reflecting the proportion of subjects with durable responses (extract from dossier 2.7.3).

…

Indeed, PFS rates with avelumab 2L+ was 40%, 30% and 30% at 6, 12 and 15 months respectively, while it was between 0 and 13% at 6 months, and 0% at 12 and 15 months with chemotherapy.

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



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.

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

EMA – EPAR discussion

Section 2.5.3 – Context of BOR with secondary endpoints

*[…]The primary endpoint (ORR) as well as secondary endpoint (DoR, PFS and OS) were also considered acceptable considering that MCC is a rare tumour and there are few patients that can be recruited in order to appropriately power a randomised controlled trial with the conventional endpoints of PFS and OS[...]

*[…]Although ORR is not very impressive, the duration of response is considered clinically relevant advantage over chemotherapy. The duration of response with avelumab therapy in 2L+ is favourable when placed in context with chemotherapy[…]

*[…]Compared to chemotherapy in 2L+, while the median PFS is numerically similar (2.7 months), long-term PFS rates exceed results with 2L chemotherapy […]

*[…]The reported ORR (33%) for avelumab in the next-line treatment of mMCC is not considered outstanding, however, durability of responses is convincing[…]

**[…]Despite the lower effect estimates, the data still support a positive Benefit/Risk (B/R) for Bavencio both in the first line and the previously treated mMCC. […]

Effects Table – Results of PFS plateau was highlighted!

*https://www.ema.europa.eu/en/documents/product-information/bavencio-epar-product-information_en.pdf
**https://www.ema.europa.eu/en/documents/variation-report/bavencio-h-c-004338-ii-0013-epar-assessment-report-variation_en.pdf

FDA Review

FDA Summary of Review March 2017*

*[…] The primary efficacy endpoint was overall response rate with duration of response being the key secondary endpoint. […]

*[…] Study 003 demonstrated a clinically meaningful ORR that was significantly more durable than response rates observed for salvage chemotherapy, which is the current treatment standard[…]

*[…] 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[…]

*[…] Durable objective response rate of sufficient magnitude is a surrogate endpoint that is reasonably likely to predict clinical benefit (i.e., improved survival) in patients with metastatic MCC.

*[…] The durability of responses provides an advance over that observed with off-label use of chemotherapy which produces nondurable response rates (reported and observed median durations of response less than 3 months).

[…] A trial of avelumab which will characterize the durable response rate in chemotherapy-naïve patients is ongoing, the results will provide confirmatory evidence of clinical benefit for avelumab in patients with metastatic MCC[…]

*https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761049Orig1s000MultidisciplineR.pdf

Conclusion

- In first interactions a RCT was seen as the most acceptable design based on the sparse historical control data for this disease to bring the results in clinical context.
- Based on evolving knowledge in the clinical evidence of this rare disease from various immune-checkpoint inhibitor study results, a RCT with standard time-to-event endpoints was agreed with agencies not anymore seen feasible.
- Continuous interaction with the agencies to present and agree on the study design was crucial to find most pragmatic way.
- With company initiated historical control data and available literature, the SAT design and alternative endpoints were acceptable and could be placed in clinical context, to generate an adequate benefit/risk balance.
- The SAT study design was agreed for pivotal and confirmatory study with alternative primary endpoints BOR and DRR after several agency interactions.
- Finally, both agencies accepted the data for a “conditional” and “accelerated” approval. In the EU the conditional could be converted into a full approval in 2020.
- Importantly, overall survival data, duration of response, and long-term PFS data showing the “tail” of the curve were key aspects to demonstrate the clinical benefit as the results of the primary endpoints BOR and DRR would have been alone not sufficient.

In summary, the alternative endpoints best overall response and duration of response rate were acceptable in this rare disease especially that the SAT design was the only feasible ethical study set-up to keep the equipoise for patients.