Quantitative clinical pharmacology considerations for the development of Avelumab

International Workshop on Clinical Pharmacology of Anticancer drugs (IACPD) 8-9 November 2018, Amsterdam

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Note to reviewers

This is an invited presentation at International workshop on Clinical Pharmacology of Anticancer drugs (IACPD) 8-9 November 2018, Amsterdam

The data and conclusions in this presentation are based on published data and at times verbatim. Abstract/publications used to draft slide deck is included in reference slide # 26

Slide #24 flat dose will be substituted with US PI excerpt if we hear back from FDA before the presentation and conclusion will be changed accordingly.
Contents

• Mechanism of action
• Time-varying clearance
• Label examples based on PopPK
• Exposure-response MCC, UC & NSCLC
• Simulations for alternate dosing
• Summary
Merck / Pfizer Global Strategic Alliance

Avelumab Development and Marketing Approvals

• Merck and Pfizer are co-developing avelumab in global strategic alliance

• Avelumab is currently approved as monotherapy
  • in the US, the EU, Australia, Canada, Israel and Switzerland for metastatic Merkel Cell carcinoma (mMCC)
  • in Japan for curatively unresectable MCC
  • in the US and Israel for locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-containing chemotherapy or disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
Avelumab (Bavencio®)
Mechanism of action

- Human immunoglobulin G1 (IgG1) monoclonal antibody that selectively targets programmed death-ligand 1 (PD-L1), a protein expressed on immunoinfiltrating cells and tumors in a variety of human cancers.

- Inhibition of PD-1/PD-L1 signaling results in restoration of cytotoxic T-cell activity, T-cell proliferation, cytokine production, and antitumor immune responses.

- Avelumab also retains an intact fragment crystallizable (Fc) region and, therefore, has the potential to engage the immune system to induce innate effector function against tumor cells.
Characterizing the PK of avelumab and its relation to response

Support dose and regimen selection for intended indications and populations

NCA: non-compartmental analysis
ADA: anti-drug antibody
popPK: population pharmacokinetics
TO: target occupancy
TMDD: target-mediated drug disposition
BOR: best overall response
DDI: drug-drug interaction

- Intrinsic/extrinsic factors (including DDI)
- TMDD
- Special populations: pediatrics, renal/hepatic impairment
- Manufacturing process changes
- Dosing regimens: flat dosing
Trials
Population PK Model

- **EMR100070-001**: Various cohorts of JAVELIN Solid Tumor (NCT01772004) including different tumor types, a phase 1, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab (MSB0010718C) in patients with metastatic or locally advanced solid tumors and expansion to selected indications.

- **EMR100070-002**: JAVELIN Solid Tumor JPN (NCT01943461), a phase 1, open-label trial of avelumab in Japanese patients with advanced solid tumors, including dose escalation in patients with various tumors, and dose expansion in patients with adenocarcinoma of the stomach or gastroesophageal junction progressed after prior treatment.

- **EMR100070-003**: JAVELIN Merkel 200 part A (NCT02155647), a phase 2, open-label trial of avelumab in patients with stage IV Merkel cell carcinoma progressed after prior chemotherapy for metastatic disease.
## Data

### Population PK Model

<table>
<thead>
<tr>
<th>Nominal dose</th>
<th>EMR100070-001</th>
<th>EMR100070-002</th>
<th>EMR100070-003</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mg/kg</td>
<td>4 (0.237%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4 (0.219%)</td>
</tr>
<tr>
<td>3 mg/kg</td>
<td>13 (0.77%)</td>
<td>5 (9.8%)</td>
<td>0 (0%)</td>
<td>18 (0.985%)</td>
</tr>
<tr>
<td><strong>10 mg/kg</strong></td>
<td><strong>1650 (97.7%)</strong></td>
<td><strong>40 (78.4%)</strong></td>
<td><strong>88 (100%)</strong></td>
<td><strong>1778 (97.3%)</strong></td>
</tr>
<tr>
<td>20 mg/kg</td>
<td>21 (1.24%)</td>
<td>6 (11.8%)</td>
<td>0 (0%)</td>
<td>27 (1.48%)</td>
</tr>
</tbody>
</table>
where $CL$ is clearance (L/hour); $TVCL$ is CL at baseline (L/hour); $I_{max}$ is the logarithm of maximal change in $CL$ relative to baseline; $T50$ is time required to reach 50% of $I_{max}$ (days); $\gamma$ is shape parameter; and $Time$ is time in days; TSPK is Time Stationary Pharmacokinetic model; TDPK is Time Dependent Pharmacokinetic model;
### Change in CL from baseline

<table>
<thead>
<tr>
<th>ACC</th>
<th>CRC</th>
<th>CRPC</th>
<th>GEJ</th>
<th>Head &amp; neck</th>
</tr>
</thead>
</table>
| ![Graph showing change in CL from baseline](image)

- **MCC**
- Melanoma
- Mesothelioma
- Metastatic breast
- NSCLC

- **Ovarian**
- RCC
- Solid
- UC

*Wilkins et al American conference pharmacometrics 2017*
Interplay between disease status, pharmacokinetics, and response

- Lower clearance relative to baseline in responders compared to non-responders

- Impact of disease response alters distribution of CL from baseline to steady state. At steady state responders have lower CL compared to Non-responders

**MCC**: Merkel cell carcinoma  
**UC**: Urothelial carcinoma
• None of the identified covariates require dose adjustment
Elimination
The primary elimination mechanism of avelumab is proteolytic degradation. Based on population pharmacokinetic analyses in patients with solid tumors, the total systemic clearance was 0.59 L/day and the terminal half-life was 6.1 days in patients receiving 10 mg/kg. In a post hoc analysis, avelumab clearance was found to decrease over time in patients with MCC, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline value of approximately 41.7% (40.0%).

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761049s000lbl.pdf
Specific populations
Body weight was positively correlated with total systemic clearance in population pharmacokinetic analyses. No clinically meaningful differences in pharmacokinetics were observed in the clearance of avelumab based on age; sex; race; PD-L1 status; tumor burden; mild [calculated creatinine clearance (CLcr) 60 to 89 mL/min, n=623 as estimated by the Cockcroft-Gault formula], moderate [CLcr 30 to 59 mL/min, n=320] or severe [CLcr 15 to 29 ml/min, n=4] renal impairment; and mild [bilirubin less than or equal to ULN and AST greater than ULN or bilirubin between 1 and 1.5 times ULN, n=217] or moderate [bilirubin between 1.5 and 3 times ULN; n=4] hepatic impairment. There are limited data from patients with severe hepatic impairment [bilirubin greater than 3 times ULN, n=1], and the effect of severe hepatic impairment on the pharmacokinetics of avelumab is unknown.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761049s000lbl.pdf
US PI - Pediatrics

8.4 Pediatric Use
The safety and effectiveness of BAVENCIO have not been established in pediatric patients age 12 years and older. Use of BAVENCIO in this age group is supported by evidence from adequate and well-controlled studies of BAVENCIO in adults with additional population pharmacokinetic data demonstrating that age and body weight had no clinically meaningful effect on the steady state exposure of avelumab, that drug exposure is generally similar between adults and pediatric patients age 12 years and older for monoclonal antibodies, and that the course of MCC is sufficiently similar in adult and pediatric patients to allow extrapolation of data in adults to pediatric patients. The recommended dose in pediatric patients 12 years of age or greater is the same as that in adults [see Dosage and Administration (2.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]

Figure to be replaced with high resolution image

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761049s000lbl.pdf
Challenges in Exposure-Response Modeling

• Generally, exposure is assumed to be the cause (independent variable) and response as outcome (dependent variable) in exposure-response analysis

• In case of Avelumab and other immunoncology drugs, the response can affect exposure and hence the relationship becomes mutual rather than causal

• Exposures at later time point could be affected by treatment outcome
  o Higher concentration at steady state could be the “result” rather than “cause” of a better treatment effect
  o This would make exposures at later time-points less informative for estimating causal effects between exposure and efficacy

• Analysis using steady state exposure metric can lead to biased estimate of exposure-response relationship.
  o Therefore, exposures derived from first dose data is recommended (Liu et al 2017)
Exposure-Response Analysis

**Exposure-Efficacy**

Endpoint: Best overall response (BOR) according to RECIST 1.1
- Responder (complete response and partial response)
- Non-responder (all the others)

Endpoint: Progression Free Survival (PFS) and Overall Survival (OS)

<table>
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<tr>
<th>Indication</th>
<th>Dose</th>
<th>N</th>
<th>ORR(%)</th>
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<tbody>
<tr>
<td>MCC</td>
<td>10 mg/kg</td>
<td>88</td>
<td>31.8</td>
</tr>
<tr>
<td>UC</td>
<td>10 mg/kg</td>
<td>249</td>
<td>17.3</td>
</tr>
<tr>
<td>2L NSCLC</td>
<td>10 mg/kg</td>
<td>184</td>
<td>14.1</td>
</tr>
</tbody>
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**Exposure-Safety (N=1629)**

Endpoints:
- irAE: Occurrence of at least one treatment-emergent immune-related adverse event (grade 1)
- IRR: Occurrence of at least one IV infusion reaction
- teAE: Occurrence of at least one treatment-emergent adverse event (grades 1-3)
Differences in avelumab exposure were not associated with overall rates of AEs (grade ≥1 or grade ≥3) or with different types of AEs.

Higher avelumab exposure was associated with a modest increase in immune-related irAEs of grade ≥1, although data are sparse at higher exposure levels.

The benefit–risk balance for avelumab appears favorable at all levels of avelumab exposure.

Gulley et al, 2017 American Society of Clinical Oncology Annual Meeting, Abstract # 9086
Exposure Efficacy relationship

MCC (univariate model)

MCC first cycle popPK model

Apparent increase in response with increase in exposure

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761049Orig1s000MultidisciplineR.pdf
Exposure Efficacy relationship

UC (univariate model)

Apparent increase in response with increase in exposure

Vugmeyster et al American conference pharmacometrics 2018
Exposure Efficacy relationship
Advanced NSCLC progressed after platinum doublet chemotherapy (n=184)

Gulley et al., 2017 American Society of Clinical Oncology Annual Meeting, Abstract # 9086

Apparent increase in response with increase in exposure
Relationship between ORR and PD-L1 expression level according to avelumab exposure (Ctrough first-dose) in patients with advanced NSCLC progressed after platinum doublet chemotherapy (n=142)

Potential association between higher ORR and both higher avelumab exposure and increasing level of PD-L1 expression

Gulley et al, 2017 American Society of Clinical Oncology Annual Meeting, Abstract # 9086
Assess the effects of different dosing schedules on avelumab exposure based on PopPK Simulation

- The simulated median C\text{\textsubscript{trough-first-dose}} with 10 mg/kg weekly dosing is above the lower cut-off for the highest quartile of C\text{\textsubscript{trough-first-dose}} measured in patients with NSCLC treated with avelumab 10 mg/kg Q2W.

- The simulated maximum concentration (C\text{\textsubscript{max}}) at steady state with avelumab 10 mg/kg administered QW or Q2W was notably lower than with 20 mg/kg Q2W dosing.

PopPK Simulation derived exposures were used to inform dose for Phase III trial

Gulley et al, 2017 American Society of Clinical Oncology Annual Meeting, Abstract # 9086
Flat dose simulations – 10 mg/kg Q2W vs 800 mg Q2W

**Exposure**

- Reduced variability with flat dosing (27.1% Vs 29%)
- Higher exposures simulated for flat dosing (median ~12% increase) but within exposure range shown to be clinically efficacious with manageable safety profile
- For weight-based dosing, the lowest weight quartile is associated with the lowest exposure. The opposite is true for the flat dosing

Novakovic et al Population Approach Group Europe, 2018
Summary

• Population PK modeling was used to support label statements in approved indications.

• PopPK simulations were performed to avoid conducting a clinical trial to compare the weight-based and flat dosing regimens. A flat dose regimen is currently being evaluated in several trials.

• The interpretation of the apparent exposure–response association for avelumab is confounded by the study design, single dose level data, imbalance in the distribution of covariates, immortal bias and selection bias. Therefore, these observations do not confirm that a dose/exposure–response relationship exists.

• These analyses provide a rationale for studies of more intensive avelumab dosing regimens in NSCLC populations with different levels of tumor PD-L1 expression to assess the potential for further increased clinical benefit with avelumab, and to confirm the existence of an exposure–response relationship.¹

• The ongoing phase 3 JAVELIN Lung 100 trial (NCT02576574) is comparing 2 regimens of avelumab vs platinum doublet chemotherapy as first-line treatment for patients with PD-L1+ NSCLC, and will therefore investigate the effects of higher avelumab exposure.¹

¹Gulley et al, 2017 American Society of Clinical Oncology Annual Meeting, Abstract # 9086
References

- **Wilkins et al.**, Clearance over time and effect of response in the pharmacokinetics of avelumab. American conference pharmacometrics 2017
- **Wilkins et al.**, Population pharmacokinetic analysis of avelumab in different cancer types. American conference pharmacometrics 2017
- **Vugmeyster et al.**, Exposure-response analysis of avelumab in patients with advanced urothelial carcinoma via a full-model approach. American conference pharmacometrics 2018
- [https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761049s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761049s000lbl.pdf)
- [https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761049Orig1s000MultidisciplineR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761049Orig1s000MultidisciplineR.pdf)
## Acknowledgements

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