Clearance over time and effect of response in the pharmacokinetics of avelumab

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BACKGROUND

- Avelumab is a human anti–PD-L1 IgG1 antibody that has shown clinical activity and acceptable safety in patients with various tumor types[1–5]
  - Avelumab has a half-life of ≈6.1 days and achieves 90% target occupancy with 10 mg/kg dosing every 2 weeks (Q2W)[1]
  - Doses of up to 20 mg/kg Q2W were safely administered in a phase 1a dose-escalation study, and the maximum tolerated dose was not reached[1]
- Avelumab has been approved by the United States Food and Drug Administration (US FDA), the European Medicines Agency (EMA), the Swiss Agency for Therapeutic Products (SwissMedic) and the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) for the treatment of patients with Merkel cell carcinoma (MCC) at a dose of 10 mg/kg Q2W[6]
  - In a phase 2 study of patients with metastatic MCC progressed on chemotherapy (N=88), the objective response rate (ORR) with avelumab treatment after ≥1 year of follow-up was 33.0%, including complete response (CR) in 11.4%[2]
- In a phase 1b study of patients with platinum-refractory metastatic urothelial carcinoma (UC) (N=249; ≥6 months of follow-up), the ORR with avelumab treatment was 17.3%, comparable to findings with other anti–PD-1/PD-L1 antibodies in this setting[3]
  - Avelumab has also been approved by the US FDA for the treatment of patients with this indication[6]
- Time-dependent clearance (CL) has been reported recently for some immune checkpoint inhibitors[7]
- Here, we present comparisons between several population pharmacokinetic models (PopPK) of avelumab, investigating time-varying clearance (CL_{tv}), covariate effects,[8] and impact of response status

METHODS

- Data from three clinical trials involving 1,827 patients were used for PopPK analysis using nonlinear mixed effect modeling (NONMEM)
  - Various cohorts of patients with different tumor types enrolled in JAVELIN Solid Tumor (NCT01772004), a phase 1, open-label, multiple-ascending dose trial investigating 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
  - 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[9,10]
  - JAVELIN Merkel 200 part A (NCT02155647), a phase 2, open-label trial of avelumab in patients with stage IV MCC progressed after prior chemotherapy for metastatic disease[2]
- In all 3 trials, general eligibility criteria included: Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, estimated life expectancy of ≥3 months, ≥1 measurable lesion by RECIST v1.1, and availability of tumor samples for analysis of PD-L1 expression
- All patients included in the efficacy analyses were treated with avelumab 10 mg/kg by 1-hour intravenous infusion Q2W
  - Patients were treated until confirmed disease progression (although additional dose levels were used in building the PK model), unacceptable toxicity, or any other protocol-specified criterion for withdrawal occurred
- Clinical activity was assessed every 6 weeks by investigator per RECIST v1.1
- Serum samples were obtained at various time points for pharmacokinetic (PK) analysis
- Two time-varying clearance model approaches for describing CL_{tv} were used[7,11]
  - Seven model variants were compared: 4 two-compartment base models (1 single-dose [SD] and 3 multiple-dose [MD] models, with and without CL_{tv}), and 3 of these models after covariate inclusion (**Table 1**)
- CL from the final SD and MD models was compared by objective response status (RECIST 1.1)

Table 1. Model variants used in this analysis

No.	Description	N/Obs.
1	Single-dose data only, no covariates	1,827/3,651
2	Single-dose data only, covariates included (full model approach)*	1,827/3,651
3	Multiple-dose data, time-invariant CL, effect of weight on CL, V_1, V_2	1,827/10,637
4	Multiple-dose data, time-varying CL (Gibiansky method), effect of weight on CL, V_1, V_2	1,827/10,637
5	Multiple-dose data, time-varying CL (Liu method), effect of weight on CL, V_1, V_2	1,827/10,637
6	Multiple-dose data, time-varying CL (Liu method), covariates included (full model approach)*	1,827/10,637
7	Multiple-dose data, time-invariant CL, covariates included (stepwise approach)	1,629/10,220

* Final models

Patients and treatment

- Doses of 1 mg/kg (n=4 [0.2%]), 3 mg/kg (n=18 [1.0%]), 10 mg/kg (n=1,778 [97.3%]) and 20 mg/kg (n=27 [1.5%]) were given Q2W; total population N=1,827
- Efficacy data for responders (CR + partial response [CR + PR]) and nonresponders (stable disease + progressive disease + not evaluable [SD + PD + NE]) according to RECIST 1.1
  - MCC: N=88
  - UC: N=249

RESULTS

The predicted CL at steady state was similar using either full model (model 3) or stepwise modeling approach (model 7)

Figure 1. Linear clearance vs nonlinear clearance: models with time-varying CL predicted lower CL at steady state for MCC

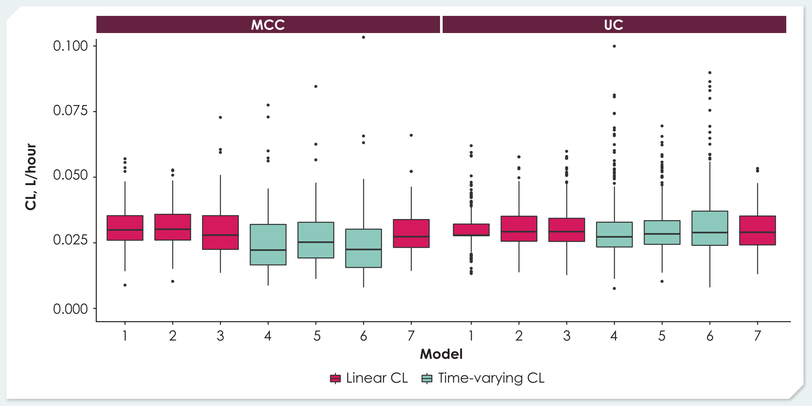


Figure 2. Linear clearance vs nonlinear clearance: models with time-varying CL predicted higher AUC at steady state for MCC

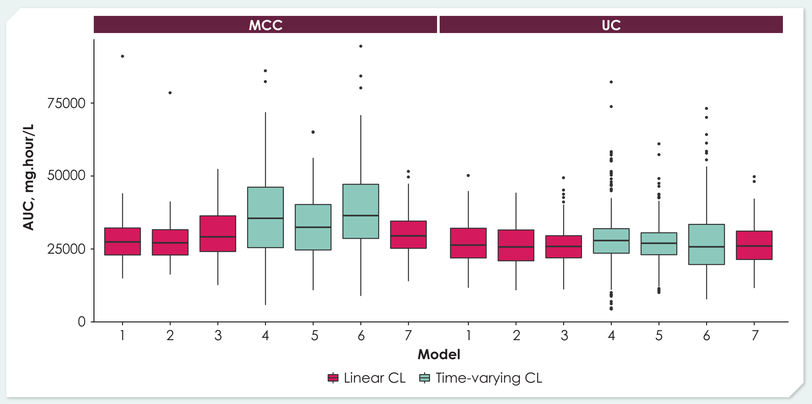


Figure 3. Clearance relative to baseline stratified by response using model 6

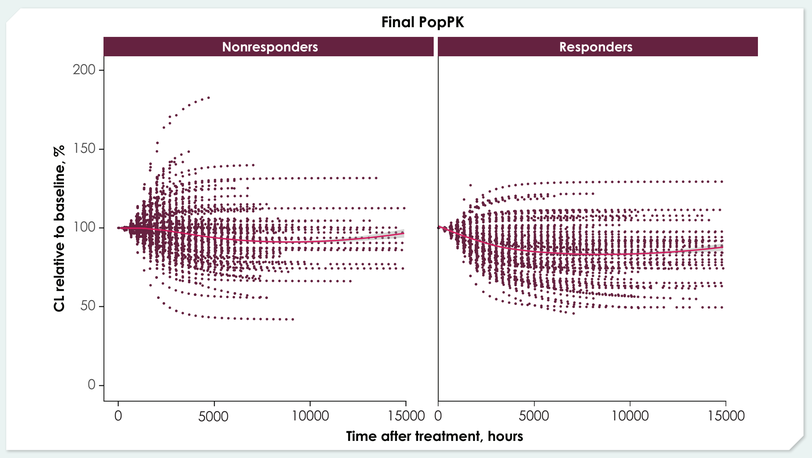


Figure 4. Clearance stratified by tumor type using model 6

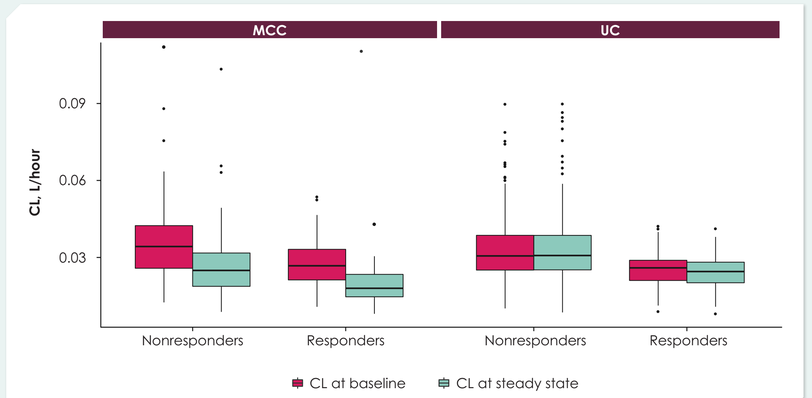


Figure 5. Clearance multiple-dose (model 6) vs clearance first cycle (model 2) stratified by response

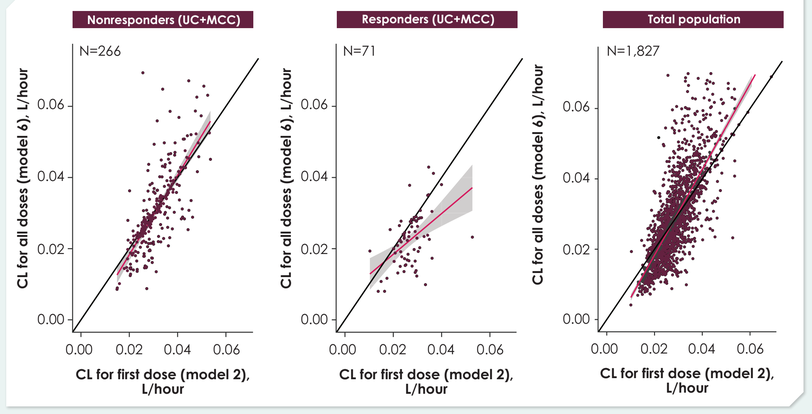
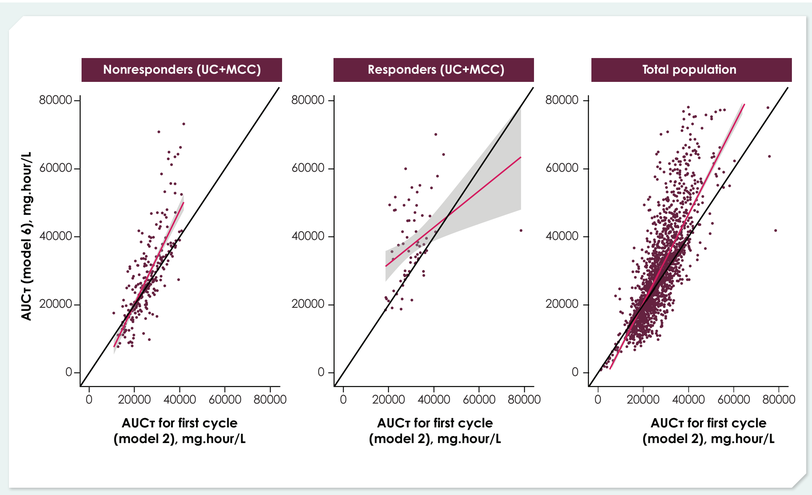


Figure 6. AUC at steady state all dose (model 6) vs first cycle (model 2) stratified by response



CONCLUSIONS

- **Model 2 is considered final PopPK model for single dose data and model 6 is considered final PopPK model for multiple dose data using time varying CL**
- **For patients with UC and MCC, responders tended to have lower baseline clearance**
- **CL tends to decrease further for responders with increasing time**
- **It is clear that, for MCC and UC, time-varying CL is more prevalent in responders than nonresponders**
- **Time-varying CL was identified most strongly for MCC, potentially as a result of other post-treatment effects altering the CL distribution between baseline and steady state in MCC**
- **Accounting for time variation in CL was critical for adequately characterizing the avelumab dose-exposure relationship**
- **Avelumab shows time-varying CL similar to nivolumab,[7] pembrolizumab,[13] and atezolizumab,[12] particularly for responders**
- **AUC_T at steady state from final first cycle model (model 2) and final nonlinear model (model 6) are highly correlated for the total population (Pearson r=0.81)**
  - **Results suggested that exposure metrics derived after the first dose, while not without disadvantages, were nonetheless more appropriate than metrics derived at steady state for subsequent exposure-response analysis[7,12,13]**

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