Avelumab is a human monoclonal antibody that selectively binds PD-L1, which is expressed on many different tumor cells. Avelumab is approved in the US and EU for treatment of metastatic Merkel cell carcinoma (MCC), in Japan for cutaneous un melanoma, and for platinum-treated advanced urothelial carcinoma (US) and is in clinical development for other cancer types.[10] Avelumab has shown promising clinical activity and manageable safety in multiple tumor types.[11]

Methods

Patients and treatment

Pharmacokinetic and covariate data from three clinical trials were used for PopPK analysis:

- JAVELIN Solid Tumor (NCT01772004): A Phase I, Open-label, Multiple-ascending Dose Trial to Investigate the Safety, Tolerability, Pharmacokinetics, Biological and Clinical Activity of Avelumab (MSB0010718C) in Subjects With Metastatic or Locally Advanced Solid Tumors and Extension to Selected indigents (1,688 patients)
- JAVELIN Solid Tumor JPN (NCT01943441): A Phase I Trial to Investigate the Tolerability, Safety, Pharmacokinetics, Biological and Clinical Activity of Avelumab (MSB0010718C) in Japanese Subjects With Metastatic or Locally Advanced Solid Tumors, With Expansion Part in Asian Subjects With Gastric Cancer (51 patients)
- JAVELIN Merkel 200 (NCT01556647): A Phase II, Open-label, Multicenter Trial to Investigate the Clinical Activity and Safety of Avelumab (MSB0010718C) in Subjects With Merkel Cell Carcinoma (88 patients)

This analysis included 10,637 avelumab serum concentration observations from 1,927 patients with 14 different tumor types, which were obtained according to rich clinical and tumor characteristics. Patients received avelumab 1 mg/kg (n=3), 3 mg/kg (n=18), 10 mg/kg (n=17), or 20 mg/kg (n=3) every 2 weeks (Q2W) by iv infusion (99% infusion administered over 1 hour).

Modeling

The PopPK model was built using nonlinear mixed effect modeling software package (NONMEM; v7.3.0).

- Two-compartment models with covariates including time-constant and time-varying clearance (CL) were tested
- Changes in CL over time were considered using the model according to eq. (1):
  \[ CL = TVCL \times \text{exp}(\theta + PAR_i) \]

\( i \) is the value of the CL in individual subjects; \( TLVCL \) is the typical value of CL in the population; \( \theta \) and \( PAR_i \) are parameters describing the shape of the relationship of the CL to the parameters.

CAategorical variables were used defining a linear function, as follows:

- PARCOV = PAR \times (1 + DCOV _{PARCOV})

where PARCOV is the parameter value for individual i / PAR is the typical value of the parameter in the population / DCOV is the inter-individual variability of the unique value of the categorical covariate in individual i / the bagged category, \( a \), is defined as follows:

- Continuous variables were defined by a power function, as follows:

\( PARCOV = PAR \times \text{power}(\theta, PARCOV) \)

where PARCOV and PAR are as previously defined, \( \text{power}( \) ) is the value of the covariate in individual i / the power function describes the shape of the relationship of the covariate to the parameter.

- Alternatively, time-varying covariates were included in the two-compartment model for CL according to Wanby et al.:

\[ CL_{COV} = TVCL \times \text{exp}(\theta + PAR_i) \]

where TVCL is the value of the CL (in individual i); of interest are TVCL; \( \theta \) is the typical value of CL in the population; \( PAR_i \) is a parameter describing the shape of the relationship of the covariate to the parameter.

- Significant decreases in CL over time were in seen in any of the other tumor types represented in the dataset.
- Other significant covariates on CL, included body weight (estimated exp(maximal 0.24), albumin, tumor burden, age, sex, race, estimated development of hepatic function rate (ASCt), immunogenicity, platelet count, creatinine aminotransferase (AST) levels, C-reactive protein (CRP), concomitant opioid use, and previous use of biologics producing small but statistically significant effects (Figure 4).

**Figure 4.** Relationships between covariates and PK parameters (CL, V1, and Imax).

- Time-varying CL has also been observed in other anti-PD-1/PD-L1 antibodies such as nivolumab, pembrolizumab and alemtuzumab[7,8].
- It may be related to post-treatment effects on disease impacting exposure, such as inflammation, cachexia, tumor dynamics, or treatment efficacy[9].
- The identified covariates did not warrant dose adjustment.

**References**


**Conclusions**

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