Population pharmacokinetic analysis of avelumab in different cancer types

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BACKGROUND

- 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 unresectable MCC, and platinum-treated advanced urothelial carcinoma (UC), and is in clinical development for other cancer indications
- Avelumab has shown promising clinical activity and manageable safety in multiple tumor types

METHODS

- Pharmacokinetic and covariate data from three clinical trials were used for PopPK analysis:
  - JAVELIN Solid Tumor (NCT01772004): A Phase I, Open-label, multinational, non-escalating dose escalation study to investigate the safety, tolerability, pharmacokinetics, and pharmacodynamic activity of avelumab in Subjects With Metastatic or Locally Advanced Solid Tumors and Expansion to Selected Indications (1,688 patients)
  - JAVELIN Solid Tumor JPN (NCT01944541): A Phase I Trial to Investigate the Safety, Tolerability, Pharmacokinetics, Biological and Clinical Activity of Avelumab (N80010171C) in Japanese Subjects With Metastatic or Locally Advanced Solid Tumors. With Expansion Part In Asian Subjects With Gastric Cancer (81 patients)
  - JAVELIN Merkel 200 (NCT01556647): A Phase II, Open-label, Multicenter Trial to Investigate the Clinical Activity and Safety of Avelumab (N80010171C) in Subjects With Merkel Cell Carcinoma (88 patients)

- This analysis includes 10,637 avelumab serum concentration observations from 1,927 patients with 14 different tumor types, which were obtained according to rich and sparse sampling schemes
- Patients received avelumab 1 mg/kg (n=4, 3 mg/kg (n=118), 10 mg/kg (n=1,778) or 20 mg/kg (n=217)) every 2 weeks by intravenous (IV) infusion administered over 1 hour

MODELING

- The PopPK model was built using nonlinear mixed effect modeling software package (NONMEM, v7.3)
- Two-compartment models with covariates including time-constant and time-varying clearance (CL) were tested

RESULTS

- No significant decrease in CL over time was seen in any of the other tumor types represented in the dataset
- In patients with MCC, this may reflect that they were typically followed longer than patients in other indications
- It could also be shown that time-varying CL is more prevalent in responders than non-responders
- Other significant covariates on CL included body weight (estimated exponential2.34, albumin, tumor burden, age, sex, race, estimated glomerular filtration rate (eGFR), immunogenicity, platelet count, creatinine, estimated creatinine clearance (CrCl), concomitant opioid use, and previous use of biologics producing small but statistically significant effects (Figure 4)

CONCLUSIONS

- The PopPK model incorporating time-varying CL described the observed data well
- Time-varying CL has also been observed in other anti-PD-1/PD-L1 antibodies such as nivolumab, pembrolizumab and atezolizumab
- It may be related to post-treatment effects of disease impacting exposure, such as infusional, cachexia, tumor dynamics, or treatment efficacy
- The identified covariates did not warrant dose adjustment

REFERENCES


ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams of each of the participating centers for the collection of data from avelumab trials. Darmstadt, Germany, and EMD Serono, Malvern, PA, USA (colleagues of Merck KGaA, Darmstadt, Germany). The full report on this analysis was prepared by Merck KGaA, Darmstadt, Germany, and the preparation was undertaken by Clinopharm Inc. Hamilton, NJ, USA, and funded by Merck KGaA, Darmstadt, Germany, and Pfizer Inc. New York, NY, USA.

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