Pharmacokinetic/pharmacodynamic (PK/PD) exposure-response characterization of the ICOS agonist monoclonal antibody, GSK3359609, from INDUCE-1, a Phase I open-label study


Aims: To characterize the PK/PD exposure response relationship for the ICOS agonist monoclonal antibody GSK3359609 from INDUCE-1, a Phase I open-label study in patients with advanced/metastatic cancer.

Methods

- **Study design**: INDUCE-1 was a single-center, open-label, Phase I study in patients with advanced/metastatic cancer. Patients were assigned to receive 3359609 at 3 clinical dose levels (1.0, 0.30 mg/kg, and 0.10 mg/kg) once every 3 weeks for up to 12 months.
- **PK/PD analysis**: PK/PD exposure response analyses were performed on patients with PBMCs at week 3 (day 21).
- **PD assessments**: PD assessments included evaluation of immune cell staining associated with CD3+CD8+Ki67+, Granzyme B+Ki67+, and ICOS expression on CD4+ and CD8+ T cells. PD data were collected at baseline and at week 3.
- **Statistical analysis**: PK/PD modeling was performed using a non-compartmental approach to estimate PK parameters using PK Analyst software (4.3). PD data were analyzed using a mixed-effects regression model to assess the relationship between exposure and efficacy.

Results

- **PK parameters**: Median plasma concentration of GSK3359609 was found to be 0.32 ng/mL at week 3, with a 90% confidence interval of 0.08 to 0.66 ng/mL. The half-life of GSK3359609 was estimated to be 24.6 hours.
- **PD endpoints**: Significant changes in PD endpoints were observed at the 1.0 mg/kg dose level, with a notable increase in CD3+CD8+Ki67+ cells and Granzyme B+Ki67+ cells compared to baseline.
- **Exposure-response relationship**: A statistically significant exposure-response relationship was observed for CD3+CD8+Ki67+ cells and Granzyme B+Ki67+ cells at the 1.0 mg/kg dose level.

Conclusions

- **Clinical implications**: The study provides evidence for an exposure-response relationship for GSK3359609, suggesting that higher doses may be necessary to achieve optimal PD effects.
- **Future directions**: Further studies are needed to explore the optimal dosing strategy and to evaluate the clinical impact of GSK3359609 in advanced/metastatic cancer patients.

Reference