**M-09**

**Time-to-event analysis of polatuzumab vedotin induced peripheral neuropathy to assist comparison of dosing regimen**

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**Objectives:** Peripheral neuropathy (PN) has been frequently observed in clinical studies of polatuzumab vedotin (PoV), an antibody-drug-conjugate containing monomethyl auristatin E (MMAE). Conjugate exposure has a trend of correlation with PN incidence. To further quantify the correlation of exposure and treatment duration with the risk of developing clinically significant PN to assist comparison of dosing regimen, a time-to-event model was needed.

**Methods:** A base model was selected from a range of plausible models based on Akaike information criterion and graphical predictive checks, using Phase I/II data for PoV as a single agent or in combination with rituximab for treating Non-Hodgkin’s lymphoma (N=155, 0.1-2.4 mg/kg every-three-week). Effects of ~ 10 covariates (demographics and potential PN risk factors) were further explored on the base model.

**Results:** The final model (Figure 1) suggests PN onset is delayed relative to conjugate plasma concentrations; major factors associated with the PN risk included conjugate exposure and treatment duration. A trend of higher risk for higher body mass patients is observed. The model-predicted Grade ≥2 PN risk ratio for nominal dose of 2.4 mg/kg versus 1.8 mg/kg (every-three-week, 8 cycles) was 1.33 (90% confidence interval [CI]: 1.25-1.49). However, when dose reductions were accounted (for 2.4 mg/kg), the risk ratio was 1.20 (90% CI: 1.16-1.28); the corresponding model-predicted incidence of Grade 2+ PN events was 35.1% (90% CI: 26.2%-41.7%) and 28.9% (90% CI: 21.3%-34.7%) for 2.4 and 1.8 mg (every-three-week, 8 cycles), respectively.

**Conclusions:** The PN risk increases with conjugate exposure and treatment duration. At clinically relevant doses, 2.4 mg/kg confers a higher PN risk than 1.8 mg/kg. However, capping the treatment duration to 8 cycles may reduce PN risk compared to treatment until progression.

*Figure 1: The model structure*