Introduction

Etirinotecan Pegol (NKTR-102) is a unique topoisomerase I inhibitor designed for improved pharmacokinetics and tolerability. After q21d dosing of etirinotecan pegol to patients with cancer, plasma SN38 exposure is increased and greatly prolonged compared to etirinotecan (elimination half-life 5 to 10-times less).

Background

In a phase 2 trial in heavily pretreated patients with platinum-resistant/ refractory ovarian cancer, etirinotecan pegol administered q14d or q21d demonstrated confirmed objective RECIST and GCIG response rates (CR, PR, SD) of 27% and 31%, respectively.

Model Building Steps

1. Predict the plasma SN38 concentration-time profile for each patient using our previously developed population PK model.
2. Investigate the relationship of predicted plasma SN38 concentration with serum CA-125 concentration.
3. Evaluate the impact of dosing schedules on CA-125 response.

Results

1. CA-125 concentration-time profiles were well described by the model independent of response pattern.
2. The half-life of CA-125 decline was 8.4 days, consistent with previous reports.4
3. The modelled population mean IC50 of SN38 was 1.1 ng/mL.
4. The minimum plasma SN38 concentration (Cmin) at steady state for the q14d regimen exceeded the EC50 in the absence of dose interruption as illustrated in Figure 6.
5. Model-predicted CA-125 profiles after q14d or q21d were very similar, with overlapping 95% prediction intervals. (Figure 4)
6. Predicted median CA-125 concentrations at steady state were 242 and 307 U/mL for the q14d and q21d schedules, respectively.

Conclusions

1. The PK/PD model described CA-125 profiles accurately, providing a tool to dose and monitor patients with CA-125 data.
2. The close correlation of CA-125 with tumor size and RECIST ORR in this dataset is consistent with historical use of CA-125 as a surrogate marker of tumor response.
3. Model-predicted CA-125 and GCIG response patterns for q14d and q21d were comparable, this strong correlation of CA-125 and RECIST response also supports use of the better-tolerated q21d regimen.

References