ELECTRONIC SUPPLEMENTARY MATERIAL

Nonclinical pharmacokinetics and activity of etirinotecan pegol (NKTR-102), a long-acting topoisomerase 1 inhibitor, in multiple cancer models

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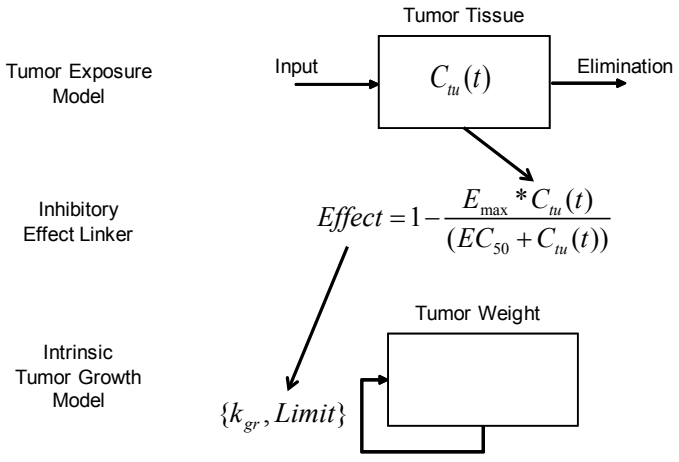
Electronic Supplementary Material – Figure Legends

Online Resource 1 Schematic of tumor PK/PD model

Online Resource 2 Observed and model-predicted plasma and tumor concentration-time profiles of analytes after intravenous administration of three doses (Days 0, 4, 8) of irinotecan and etirinotecan pegol to NCI-H460 tumor-bearing mice

a, b, After administration of conventional irinotecan, plasma (a) and tumor (b) irinotecan concentrations rapidly declined to below measurable concentrations within 12 hrs of dosing. **c,** After administration of etirinotecan pegol, plasma etirinotecan pegol concentrations also declined rapidly; however, the decline was less rapid than that observed for irinotecan, and concentrations remained measurable throughout each dosing interval and for the duration of the study. **d,** In contrast to plasma, etirinotecan pegol tumor concentrations continued to accumulate with each dose, reached a maximum after the last administration, and was followed by a slow decline. Starting 24 hrs after each dose, etirinotecan pegol concentrations in the tumor exceeded those in the plasma, consistent with tumor targeting through the enhanced permeation and retention effect. N=4 animals/timepoint. Etirinotecan pegol and irinotecan were administered as an intravenous bolus at 40-mg/kg irinotecan equivalents. Symbols, mean concentration values; solid lines, model-predicted concentration values.



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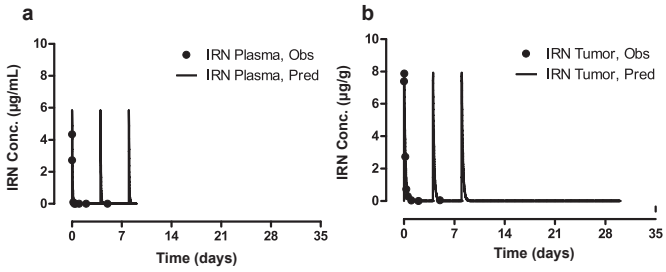
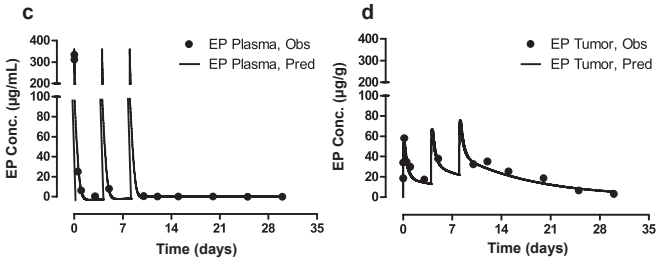
Conventional Irinotecan Administration



Etirinotecan Pegol Administration



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