

# NKTR-102, a novel PEGylated-irinotecan conjugate, results in sustained tumor growth inhibition in mouse models of human colorectal and lung tumors that is associated with increased and sustained tumor SN38 exposure

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## Background

- NKTR-102 is a novel PEGylated conjugate of irinotecan, an antineoplastic agent of topoisomerase I inhibitor class that is widely used to treat colorectal cancer and other solid tumors. NKTR-102 was created using Nektar's small molecule PEGylation technology and is currently in Phase I clinical development.
- Adding a PEG moiety to anti-tumor drugs such as irinotecan is expected to lead to increased in exposure to active drug leading to greater inhibition of tumor growth (see AACR-NCI-EORTC poster C10 for details).

## Objectives

- To evaluate the relationship between drug and metabolite pharmacokinetics (PK) and tumor growth following NKTR-102 and irinotecan administration in two mouse xenograft models:
  - colorectal (HT29); and lung (NCI-H460).
- To develop PK/PD models relating tumor SN38 concentration-time data to relative tumor weight for both cell lines were developed and as an aid to selecting doses and dosing schedules for Phase I.

## Methods

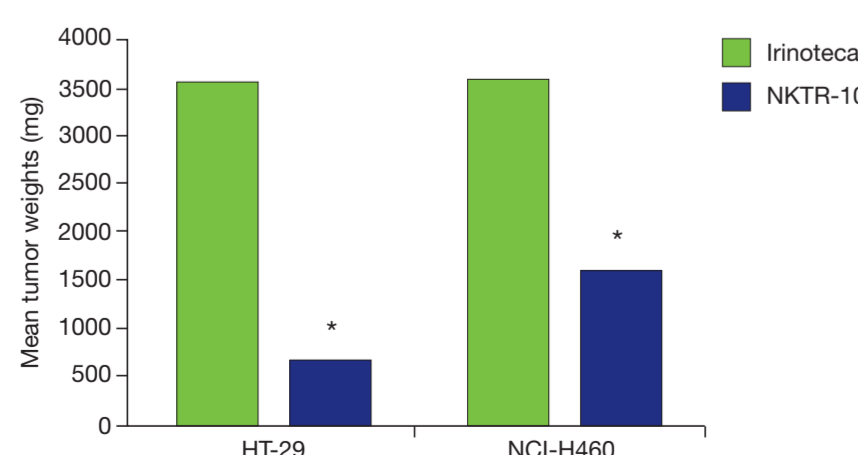
- In separate studies, female, athymic (Ncr:Nu) nude mice were implanted subcutaneously with HT29, which is inherently resistant to irinotecan, or NCI-H460 tumor fragments. Once measurable tumors were established, mice received 40 mg/kg irinotecan-equivalent doses of NKTR-102 or irinotecan intravenously on Days 0, 4 and 8 (q4d x3).
- Tumor weight was measured and plasma and tumor tissue were sampled serially at preselected timepoints for 60 days in the HT29 model and 30 days in the NCI-H460 model. At each timepoint, four mice were sacrificed and blood and tumor samples were collected.
- Plasma and tumor samples were assayed for irinotecan and SN38 using a sensitive, selective and validated liquid chromatographic mass spectrometric method.
- PK parameters were estimated by compartmental PK analyses using WinNonlin™ (Professional version 2.1; Pharsight Corp., Mountain View, CA).
- Differences in median tumor weights at the end of the study were analyzed by ANOVA.
- A pharmacokinetic/pharmacodynamic (PK/PD) model based on observed SN38 concentrations and anti-tumor activity was developed as an aid to selecting doses and dosing frequency for Phase I studies.

## Results

### Tumor growth delay/inhibition

- NKTR-102 treatment resulted in marked and statistically significant ( $p < 0.0001$ ) two- to five-fold inhibition of colorectal and lung tumor growth compared with irinotecan treatment (Figure 1; also see AACR-NCI-EORTC poster C10 for additional data).

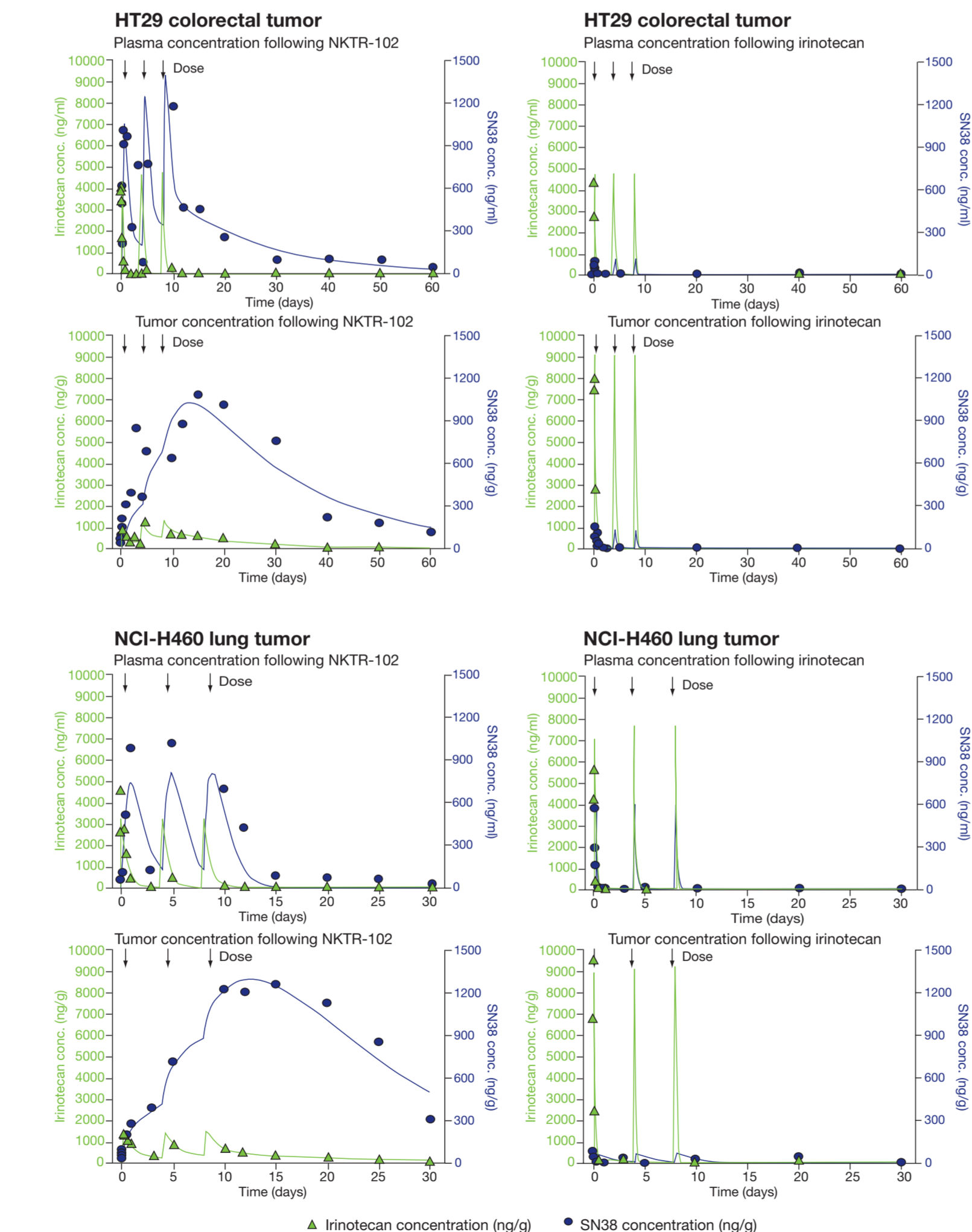
Figure 1. Median tumor weight at Day 30 (NCI-H460) or Day 60 (HT-29) following treatment with NKTR-102 and irinotecan (40 mg/kg qd on Days 0, 4 and 8). \* $p < 0.0001$  versus irinotecan



### Multi-analyte PK/PD results

- NKTR-102 administration results in a substantially greater and more prolonged plasma and tumor exposure to irinotecan and SN38 relative to irinotecan administration, which is secondary to the metabolism of NKTR-102 to irinotecan and its established metabolites (Figure 2). A previous preclinical study showed that the concentration-time profile of NKTR-102 and its metabolites parallel the pharmacokinetic profile of the PEG moiety of NKTR-102, suggesting the slowest step in their elimination is controlled by the PEG component (ECCO 14 – the European Cancer Conference. Barcelona, Spain, 23–27 September 2007; abstract P#727)

Figure 2. Plasma and tumor concentrations of irinotecan and SN38 in the HT29 colorectal tumor and NCI-H460 lung tumor models following treatment with NKTR-102 and irinotecan (40 mg/kg qd on Days 0, 4 and 8).



- Colorectal- and lung-tumor tissue SN38 exposure was increased by 390-fold and 58-fold, respectively, following NKTR-102 versus irinotecan administration (Figure 3). Similarly, plasma exposure to SN38 in the colorectal and lung models was increased by 580-fold and 13-fold, respectively, following NKTR-102 versus irinotecan administration (Figure 3).

- NKTR-102 SN38 tumor area under the curve (AUC) values were two- to four-fold greater than those in plasma, indicating accumulation in tumor tissue (Figure 3). Following irinotecan administration, tumor AUC was 3-fold higher than plasma AUC in the colorectal tumor model, but there was no accumulation in tumor tissue in the lung tumor model (Figure 3).
- The effective half-life of SN38 in colorectal- and lung-tumor tissues following NKTR-102 administration was increased 90-fold (from 4 h to 15 days) and approximately 10-fold (from 15 h to 6 days), respectively, compared with irinotecan administration (Figure 4). The effective plasma half-life of SN38 was increased by 204-fold (from 2 h to 17 days) and 12-fold (from 2 h to 12 days) following administration NKTR-102 and irinotecan, respectively (Figure 4).
- Together, these data demonstrate that NKTR-102 treatment substantially increased SN38 exposure of the colon- and lung-tumor tissue and tumor SN38 effective half-lives versus irinotecan administration.

Figure 3. Mean plasma and tumor SN38 Day 1 AUC values following administration of NKTR-102 and irinotecan (40 mg/kg qd on Days 0, 4 and 8).

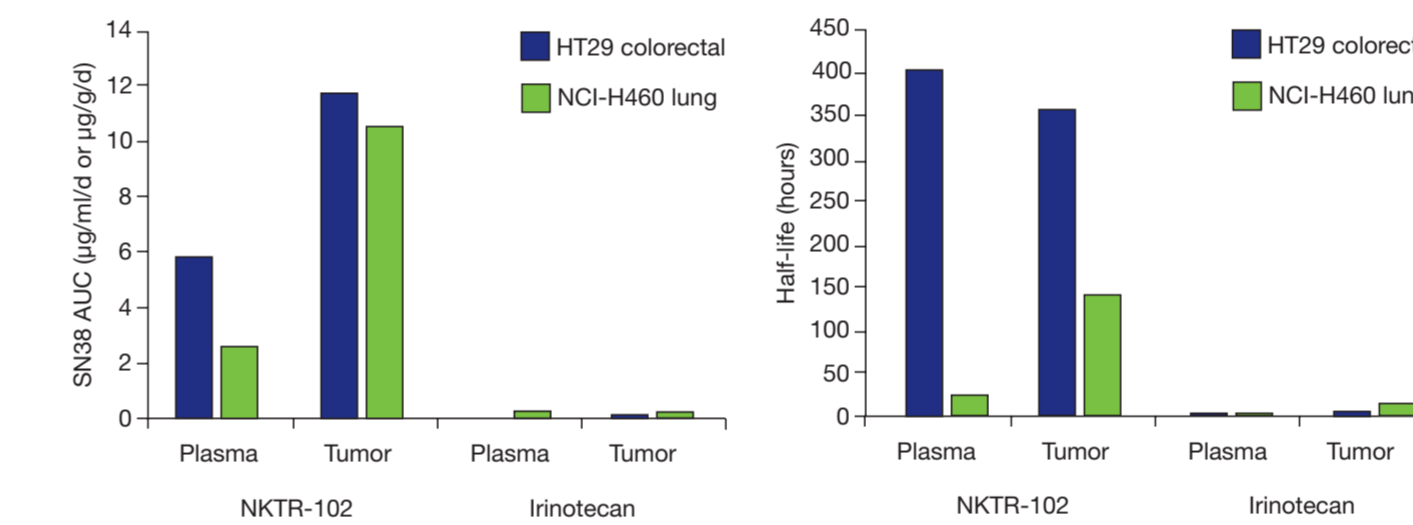
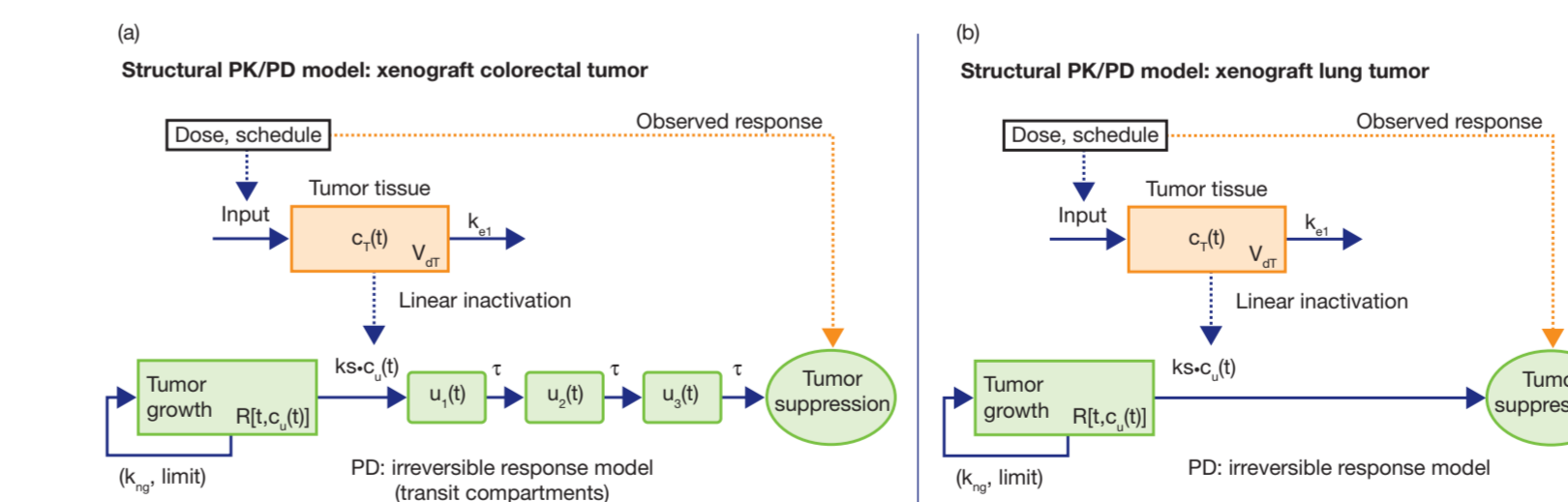


Figure 4. Mean effective half-life values for SN38 in plasma and tumor tissue following administration of NKTR-102 and irinotecan (40 mg/kg qd on Days 0, 4 and 8).

- To aid in selecting doses and dosing schedules for Phase I studies, PK/PD models relating drug/metabolite concentration-time data to tumor growth rate were developed.
- An irreversible response model with 3 transit compartments (Figure 5, diagram a) sufficiently described both the intra-tumoral SN38 concentration profiles and resulting effects on colorectal tumor growth in mice (Figure 6, top row).
- For the more rapidly growing lung-tumor model, an irreversible response model (Figure 5, diagram b) sufficiently described intra-tumoral SN38 concentration-time profiles and resulting effects on lung-tumor growth in mice (Figure 6, bottom row).

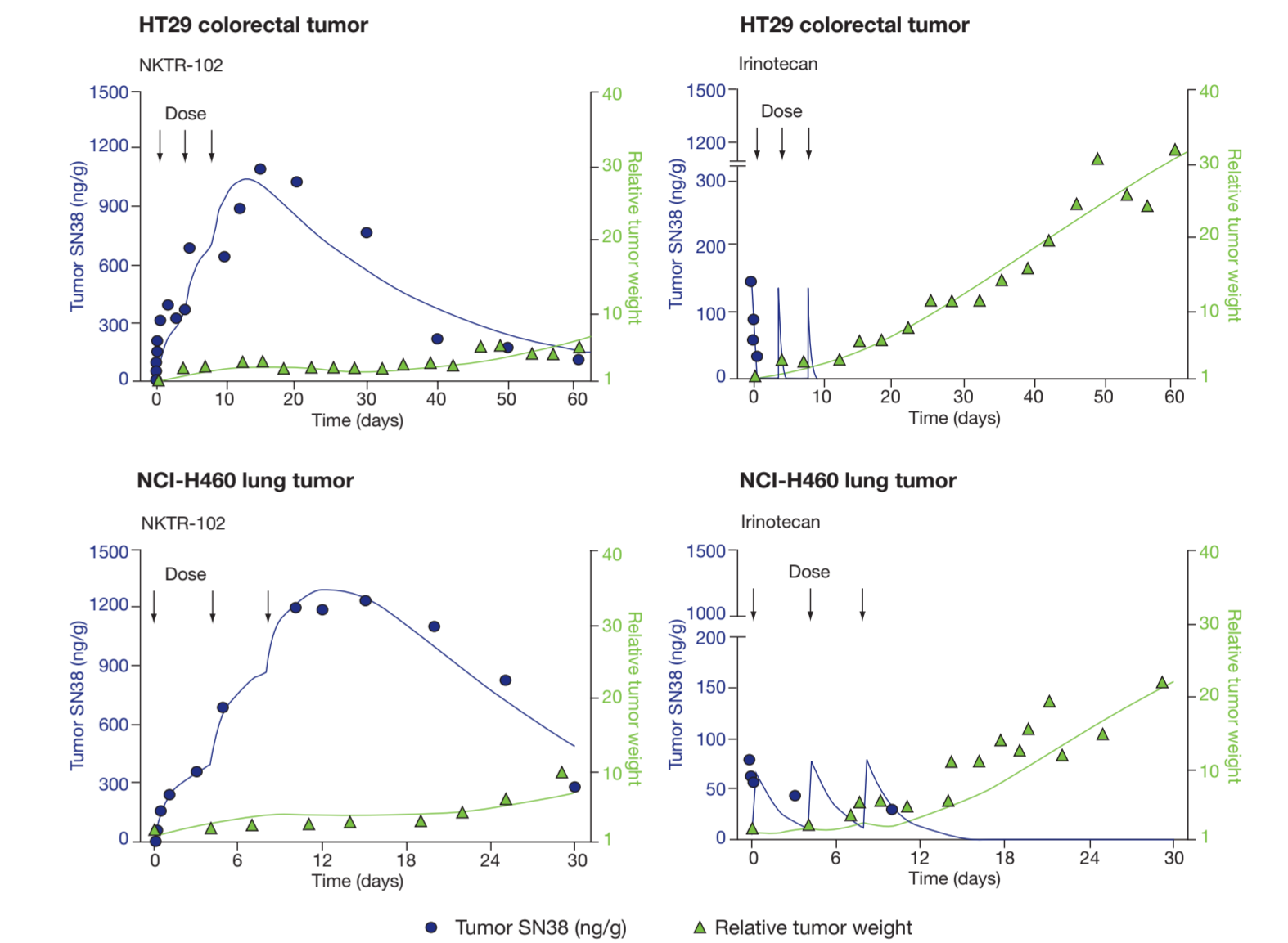
Figure 5. Schematics of colorectal- and lung-tumor PK/PD models.



Adapted from (a) Sun & Jusko. J Pharm Sci 1998; (b) Jusko. J Pharm Sci 1971.

- The PK/PD modeling results indicate that the increased and prolonged exposure to SN38 in both tumor types following administration of NKTR-102 is associated with significant reductions in tumor growth rate compared with irinotecan.

Figure 6. Relationship between tumor SN38 concentration and relative tumor weight following NKTR-102 (left) and irinotecan (right) treatment (40 mg/kg qd on Days 0, 4 and 8).



- Simulations using the HT29 tumor PK/PD model indicate that administration of irinotecan to achieve comparable SN38 tumor exposure and tumor growth inhibition as the 40 mg/kg NKTR-102 q4d x3 regimen used in this study would require a continuous IV infusion of 240 mg/kg/day irinotecan for 60 days.
- This required daily dose is twice the irinotecan single-dose LD<sub>10</sub> in mice of ~120 mg/kg and thus would be expected to cause significant drug related mortality.
- In contrast, NKTR-102 at the 90 mg/kg irinotecan-equivalent dose q4d x3 in mice with HT29 tumors was well tolerated with 5% loss in mean body weight and no deaths due to drug toxicity, further indicating the significant safety and efficacy advantages of NKTR-102 over irinotecan in mouse models of human tumors.

## Conclusions

- NKTR-102 significantly inhibited tumor growth in mouse models of human colorectal and lung tumors compared with irinotecan ( $p < 0.0001$ , see AACR-NCI-EORTC poster C10 for additional information).
- Colorectal- and lung-tumor tissue SN38 exposure was increased by 390-fold and 58-fold, and tumor SN38 effective half-life was increased from 4 h to 15 days and from 15 h to 6 days, respectively, following NKTR-102 versus irinotecan administration.
- PK/PD models demonstrated an association between increased and prolonged exposure to SN38 following administration of NKTR-102, and improved anti-tumor responses in lung and colorectal models compared with irinotecan.
- PK/PD simulations indicate that a continuous infusion of irinotecan at twice the single-dose LD<sub>10</sub> would be required to equal the tumor SN38 exposure and tumor growth inhibition achieved with NKTR-102.
- Using Nektar's small molecule PEGylation technology, NKTR-102 was created to improve the time-concentration profile and the anti-tumor activity of irinotecan. The safety and tolerability of NKTR-102 are currently being evaluated in clinical trials.

## References

Sun YN, Jusko WJ. J Pharm Sci 1998;77:732-7. Jusko WJ. J Pharm Sci 1971;60:892-5.

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