

NKTR-102, a novel PEGylated-irinotecan conjugate, demonstrates improved pharmacokinetics with sustained exposure of irinotecan and its active metabolite

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Abstract

NKTR-102, a novel PEGylated-irinotecan conjugate, is currently in Phase I clinical development. PEGylation dominated the disposition kinetics of NKTR-102 as demonstrated in rat studies where the plasma kinetics of NKTR-102 mimicked that of the ¹⁴C-PEG itself used in NKTR-102.

PEGylation of irinotecan enhanced the pharmacokinetic and pharmacodynamic behavior of the active metabolite SN38. Intravenous administration of 260 mg/kg ¹⁴C-PEG to rats resulted in distribution primarily within the circulatory system. The main route of excretion of the ¹⁴C-PEG was via urine where 61.1% of the administered radioactivity was recovered over 10 days. Fecal excretion and other elimination routes accounted for 22.7% of the administered radioactivity over the same period.

Intravenous administration of either the ¹⁴C-PEG alone or NKTR-102 showed prolonged plasma exposure. At equivalent doses, the plasma clearances of the ¹⁴C-PEG alone or NKTR-102 were similarly small, 2.5 ml/h/kg and 9–30 ml/h/kg, respectively. In contrast, plasma clearance of irinotecan following irinotecan administration was 2320 ml/h/kg, 100–300 times greater than that following NKTR-102 administration. Unlike NKTR-102, irinotecan distributed extensively in the tissue compartment and minimally in the plasma compartment.

In the rat, NKTR-102 volume of distribution was comparable to the vascular compartment volume, which contributed to the observed high plasma exposure of NKTR-102.

In summary, the PEG component of NKTR-102 dominated its disposition kinetics, resulting in greater and sustained systemic exposure to irinotecan and SN38.

Background

- NKTR-102 is a PEGylated conjugate of irinotecan, an antineoplastic agent of the 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.
- Non-clinical studies have demonstrated the substantial anti-tumor activity and extended pharmacokinetics of NKTR-102 in mouse models of human tumors (see ECCO 14 Poster 722 for details).

Objectives

- Two studies in rats were conducted to investigate the contribution of the PEG moiety used in NKTR-102 to the observed greater and sustained exposure to irinotecan and the active metabolite SN38.

Materials and Methods

- In the first study, a 260 mg/kg IV dose of the PEG used in NKTR-102 labeled with ¹⁴C (¹⁴C-PEG) was administered to rats (1-min tail vein infusion) to determine the disposition of the PEG moiety. This dose of ¹⁴C-PEG was equivalent to the mass of PEG present in a 20 mg/kg irinotecan-equivalent dose of NKTR-102.
- Four male Sprague-Dawley rats each received a single IV dose and were placed singly in all-glass metabolic cages, and urine and feces were quantitatively collected for 240 h. A separate group of four rats received the same treatment followed by serial blood sampling for 168 h. Levels of total radioactivity were determined in all samples using a scintillation counter.
- In the second study, 20 mg/kg NKTR-102 was administered to rats via the tail vein and serial venous blood samples were collected for 168 h. Plasma samples were assayed for NKTR-102 and its metabolites irinotecan and SN38 using an LC/MS-MS method.

Reference

- Davies B, Morris T. *Pharm Res* 1993;10:1093–5.

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Results

- The main route of excretion of ¹⁴C-PEG was in the urine, with a mean of 61.1% of the administered radioactivity recovered over the 240-h collection period (Figure 1). Fecal excretion was 15.1%, and other elimination routes (expired air, gastrointestinal residual, cage wash) accounted for 7.7% of the administered radioactivity, with the remainder of the dose found in the carcass.
- Excretion of ¹⁴C-PEG was relatively slow, with 58.9% of the administered radioactivity recovered over the first 48 h post dose and evidence of continued excretion at the end of the 240-h observation period.
- A blood to plasma ratio of less than 1 indicated that the total radioactivity was not associated with cells in the blood compartment.
- Following administration of NKTR-102, the time–concentration profile of its metabolites, irinotecan and SN38, paralleled the pharmacokinetic profile of the ¹⁴C-PEG (Figure 2), suggesting the slowest step in their elimination was related to the PEG moiety of NKTR-102.

Figure 1. Mean ± SD cumulative recovery of total radioactivity after IV ¹⁴C-PEG.

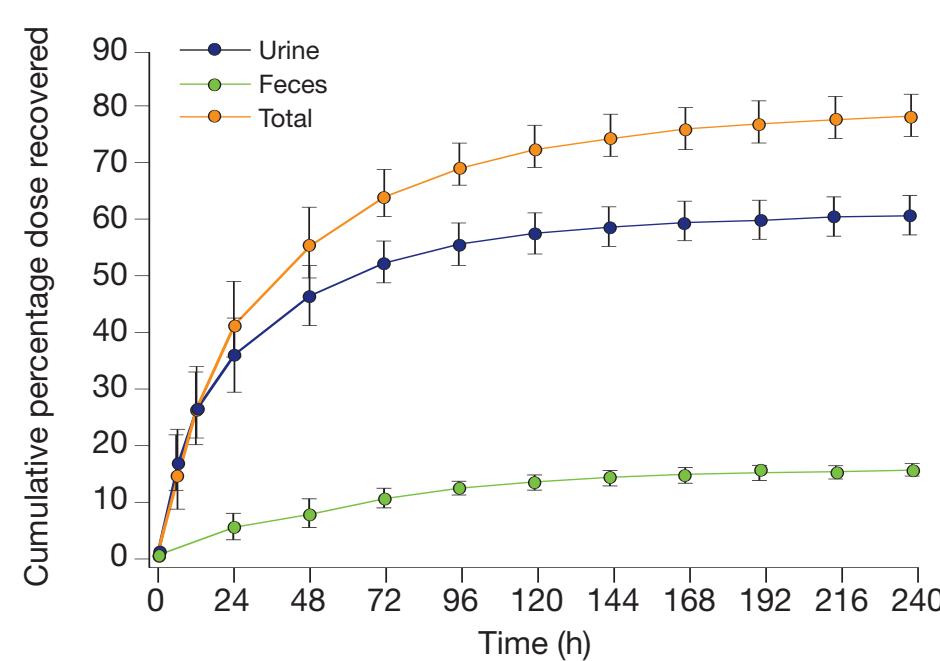
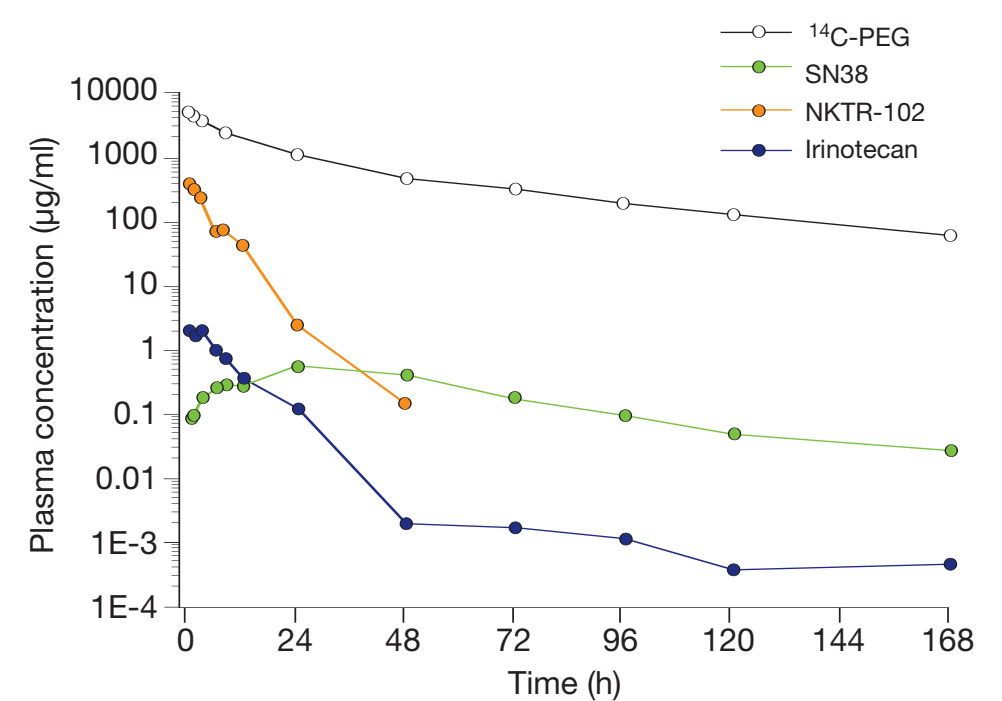


Figure 2. Mean plasma total radioactivity after IV ¹⁴C-PEG and NKTR-102 and metabolites after IV NKTR-102.



- The Vd of total radioactivity associated with ¹⁴C-PEG was 146 ml/kg (Table 1), greater than the blood volume but less than the total body water in rats (~ 600 ml/kg)¹, indicating limited distribution of the PEG moiety.
- Clearance of total radioactivity associated with ¹⁴C-PEG was not precluded by either hepatic (13.8 ml/min) or renal (9.2 ml/min) blood flow, as plasma clearance was much lower than blood flow to either the liver or kidneys¹. In contrast, the clearance of irinotecan in rats is approximately 7 times that of hepatic blood flow (Table 1).
- Plasma clearance and Vd of ¹⁴C-PEG and NKTR-102 in the rat were much lower than that of irinotecan, suggesting that the disposition kinetics of NKTR-102 and its active metabolites irinotecan and SN38 are dominated by the disposition properties of the PEG moiety.
- Systemic exposure to SN38 (plasma AUC) after dosing rats with 20 mg/kg NKTR-102 is ~80 times greater than that after 20 mg/kg irinotecan (Figure 3; Table 1).
- When taken together, these results suggest that the PEG moiety of NKTR-102 serves as a circulating reservoir of irinotecan that is slowly metabolized in vivo, resulting in significantly greater and sustained systemic exposure to irinotecan and the active metabolite SN38.
- The findings of these studies are consistent with and support the observation of marked, prolonged tumor growth suppression in athymic mice implanted with HT-29, as reported in Poster 722 of this meeting.

Table 1. Pharmacokinetic parameters after IV administration of ¹⁴C-PEG, NKTR-102 and irinotecan to rats.

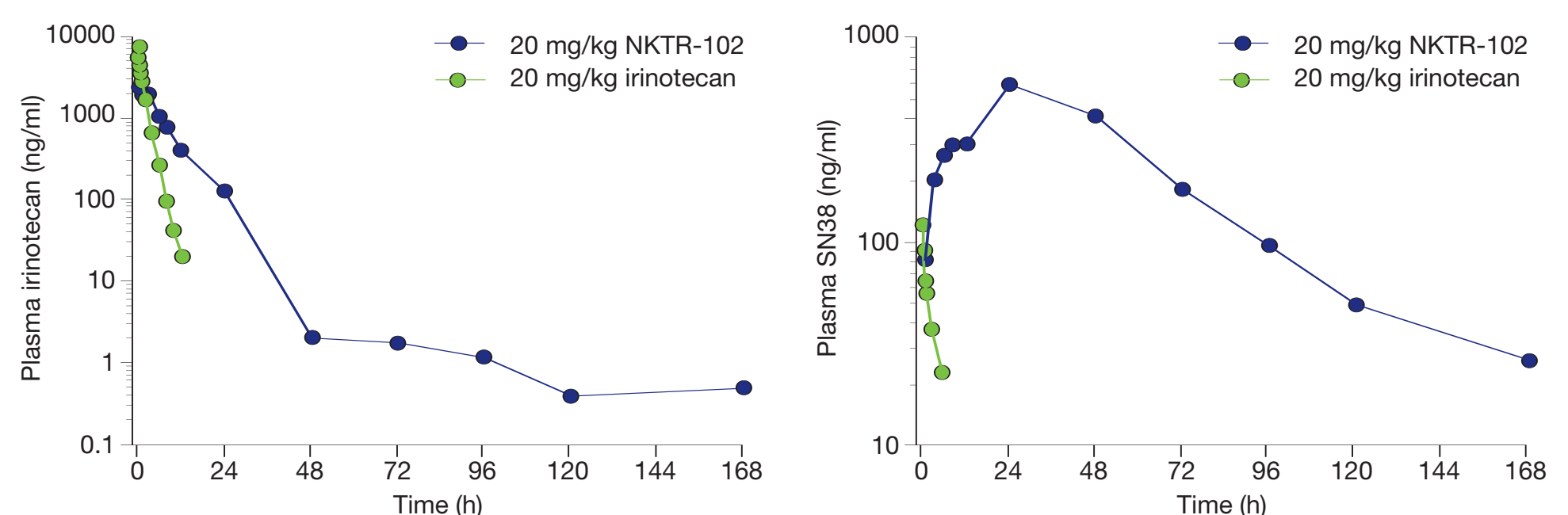
Drug	260 mg/kg IV ¹⁴ C-PEG*	20 mg/kg IV NKTR-102		20 mg/kg IV irinotecan [†]		
Analyte	¹⁴ C-PEG	NKTR-102	Irinotecan	SN38	Irinotecan	SN38
AUC/dose (µg/h/ml/[mg/kg])	394	110	1.0	1.6	0.6	0.02
CL (ml/h/kg)	2.5	9.2	ND	ND	1680	ND
Vd (ml/kg)	146	78	ND	ND	4389	ND
Terminal phase t _{1/2} (h)	41	5.9	123	40	1.9	3.5

* Equivalent to the mass of PEG present in a 20 mg/kg irinotecan-equivalent dose of NKTR-102.

[†]Data from Kaneda N, Yokokura. *Cancer Res* 1990;50:172.

ND = Not determined for metabolites measured after administration of parent drug.

Figure 3. Comparison of irinotecan and SN38 plasma concentration–time profiles in rats after IV dosing of 20 mg/kg of NKTR-102 or irinotecan.



Conclusions

- NKTR-102 administration to rats results in an 80-fold increase in SN38 plasma AUC versus irinotecan and an extended SN38 plasma half-life of 40 h compared to 3.5 h for irinotecan at equivalent doses.
- NKTR-102 disposition kinetics are dominated by the PEG moiety, resulting in significantly greater and sustained systemic exposure to irinotecan and the active metabolite SN38.
- Total radioactivity associated with ¹⁴C-labeled PEG used in NKTR-102 is excreted slowly, predominantly in the urine, and persists in the systemic circulation for more than 7 days after a single dose.
- 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.

For information on the anti-tumor activity of NKTR-102, see ECCO 14 Poster P-0722

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