

NKTR-102, A NOVEL PEGYLATED-IRINOTECAN, HAS A SUPERIOR ACUTE SAFETY, TOLERABILITY, AND PHARMACOKINETIC PROFILE COMPARED TO IRINOTECAN IN RATS AND DOGS

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Background:

- NKTR-102, a novel conjugate of irinotecan created using Nektar's small molecule PEGylation technology, is currently in clinical development as a second-line colorectal cancer therapy.
- At equivalent doses to irinotecan, NKTR-102 has demonstrated superior tumor growth inhibition in mouse xenograft models of colorectal, lung, and breast cancer. This was associated with prolonged systemic and tumor SN38 exposure.^{1,2}
- NKTR-102 administered as a single dose at 20 mg/kg in rats resulted in an 80-fold increase in the plasma AUC of SN38 (the active metabolite of irinotecan) relative to irinotecan at an equivalent dose. The apparent SN38 plasma half-life was extended to 40 hours (h) compared with 3.5 h for irinotecan.³ Data in dogs were lacking.
- Adding a PEG moiety to irinotecan has been demonstrated to increase exposure to SN38 and is expected to reduce C_{max}, thereby potentially improving the toxicity profile.

Objectives:

- Determine the acute (single-dose) maximum tolerated dose (MTD) of NKTR-102 in rats and dogs.
- Compare the acute toxicity of NKTR-102 with that of irinotecan.
- Provide toxicokinetic data in dogs.

Methods:

- Groups of rats and dogs were administered single doses of NKTR-102 (test article) or irinotecan (control) and were evaluated for 14 days. Treatment and dose groups are summarized in Table 1.

Table 1: Study design.

Species	N	Dose (mg/kg) ¹	
Rat	6	NKTR-102	30, 60, 90, 120
		Irinotecan	30, 60, 90, 120
Dog	2	NKTR-102	6, 30, 40, 60
		Irinotecan	6, 20, 30

¹ All doses expressed as irinotecan-equivalent doses (normalized for % irinotecan by weight).

Rats

- NKTR-102 or irinotecan was administered over 30 minutes by continuous intravenous infusion.
- Clinical observations were recorded twice daily.
- Hematologic analyses were performed 24 hours after dosing.
- All animals were subject to gross necropsy; no tissues were retained.

Dogs

- NKTR-102 or irinotecan was administered over 70 minutes by continuous intravenous infusion.
- Clinical observations were recorded twice daily (once daily on weekends).
- Severe diarrhea was defined as bloody diarrhea and/or diarrhea lasting 3 or more days.
- Hematologic analyses were performed before dosing on Day 1, and subsequently on Days 2, 3, 4, 6, 8, 11, and 15.
- Moribund animals sacrificed prematurely were subjected to necropsy and histopathological examination of relevant tissues. All other dogs were terminated without further examination.
- Samples for toxicokinetic analyses were collected prior to dose, immediately after infusion, and at 1, 3, 6, 8, and 24 hours postdose. Samples were also collected on Days 6, 8, 11, and immediately prior to sacrifice on Day 15.
- Toxicokinetic parameters of NKTR-102 and irinotecan were determined by noncompartmental analysis using WinNonlin-Pro (Version 4.1, Pharsight Corporation, Mountain View, CA).

Results:

Rats

Mortality

- Irinotecan treatment resulted in death or moribund sacrifice in 2/6 rats at 90 mg/kg and 1/6 rats at 120 mg/kg (Table 2).
- NKTR-102 treatment was associated with death or moribund sacrifice in only 1/24 rats and only at the highest dose (1/6 at 120 mg/kg).
- In rats, the Maximum Tolerated Dose (MTD), defined as the dose with not greater than 10% mortality, was 90 mg/kg for NKTR-102 and 60 mg/kg for irinotecan.

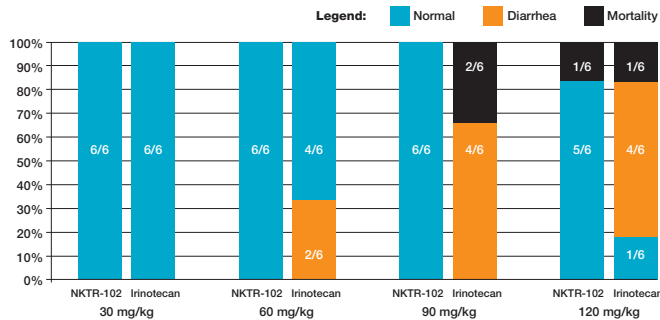
Table 2: NKTR-102 demonstrates a 1.5-fold higher single-dose MTD than irinotecan in rats.

Dose (mg/kg)	Morbidity/Mortality		Neutropenia at 24 h postdose		Diarrhea	
	NKTR-102	Irinotecan	NKTR-102	Irinotecan	NKTR-102	Irinotecan
30	0/6	0/6	0/6	4/6	0/6	0/6
60	0/6	0/6	1/6	6/6	0/6	2/6
90	0/6	2/6	0/6	2/4	0/6	4/4
120	1/6	1/6	0/5	2/5	0/5	4/5

Diarrhea

- NKTR-102-treated rats did not exhibit diarrhea at any dose during the study period.
- Irinotecan-treated rats exhibited diarrhea on study Day 1 at 60 mg/kg and higher (Figure 1).

Figure 1: NKTR-102-treated rats do not exhibit diarrhea.



Neutropenia

- NKTR-102 treatment was associated with neutropenia in only 1/24 rats (1/6 at 60 mg/kg).
- At 24 hours postdose, neutropenia was present in all irinotecan-treated dose groups in a non-dose related manner.

Dogs

Mortality

- Irinotecan resulted in moribund sacrifice in 2/2 dogs at 30 mg/kg (Table 3).
- The irinotecan-equivalent dose of NKTR-102 (30 mg/kg) was not associated with morbidity.
- NKTR-102 resulted in moribund sacrifice in 1/2 dogs at 60 mg/kg.
- In dogs, the MTD, defined as the dose at which there was no mortality, was 40 mg/kg for NKTR-102 and 20 mg/kg for irinotecan.

Table 3: NKTR-102 demonstrates a 2-fold higher single-dose MTD than irinotecan in dogs.

Dose (mg/kg)	Treatment	Neutropenia		Diarrhea		Moribund Sacrifice
		Incidence	ANS Nadir ^b (10 ³ /μL)	Incidence	Severe Diarrhea ^c	
6	NKTR-102	0/2	—	0/2	—	0/2
	Irinotecan	1/2	1.79	0/2	—	0/2
20	Irinotecan	2/2	0.82	2/2	1/2	0/2
	NKTR-102	1/2	1.40	2/2	0/2	0/2
30	Irinotecan	1/2	0.20	1/2	1/2	2/2
	NKTR-102	2/2	1.18	1/2	0/2	0/2
60	NKTR-102	1/2	1.20	2/2	1/2	1/2

— = not applicable.

^b ANS nadir: due to small group size, mean ANS (absolute count of segmented neutrophils) nadir is not reported, but absolute nadir is reported for each group.

^c Severe diarrhea: defined as bloody diarrhea and/or diarrhea of 3 or more days in duration.

Diarrhea

- NKTR-102 resulted in no severe diarrhea at 30 or 40 mg/kg and in 1/2 dogs at the highest dose of 60 mg/kg.
- Irinotecan treatment resulted in severe diarrhea at the 20 and 30 mg/kg doses.

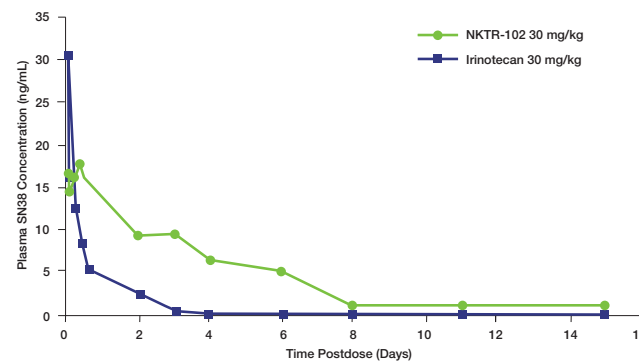
Neutropenia

- NKTR-102 resulted in less neutropenia compared with irinotecan at equivalent doses; nadir values were 7-fold higher for NKTR-102 than irinotecan-treated dogs at 30 mg/kg.
- NKTR-102 demonstrated a no observed effect level (NOEL) for neutropenia of 6 mg/kg.

Toxicokinetics

- SN38 concentrations resulting from NKTR-102 administration declined at a much slower rate (terminal t_{1/2}) than with irinotecan administration while yielding greater exposure (AUC) (Table 4).
- NKTR-102 30 mg/kg demonstrates an approximately 2-fold lower SN38 C_{max} compared with irinotecan treatment at the same dose.

Figure 2: NKTR-102 achieves greater and sustained SN38 exposure in dogs relative to irinotecan.



Each data point is the average of 2 dogs; error bars not shown.

Plasma SN38 concentrations were below the limit of quantitation (BLQ; limit of quantitation = 1 ng/ml) for irinotecan-treated dogs at Days 4, 6, 8, 11, and 15.

Table 4: NKTR-102 30 mg/kg achieves a 2-fold lower SN38 plasma C_{max} than irinotecan 30 mg/kg.

Dose (mg/kg)	Treatment	SN38 C _{max} (μg/mL)	SN38 AUC _{0-∞} (μg•hr/mL)	Apparent SN38 T _{1/2} (hr)
6	NKTR-102	0.003	0.401	102.5
	Irinotecan	0.004	0.033	6.4
20	Irinotecan	0.009	0.049	3.4
	NKTR-102	0.018	1.9	112.5
30	Irinotecan	0.031	0.321	11.3
	NKTR-102	0.013	1.8	149.0
60	NKTR-102	0.028	3.1	112.5

Average of 2 animals per group.

Conclusions:

- NKTR-102 demonstrated a superior acute safety profile compared with irinotecan in rats and dogs.
- The single-dose MTD in rats and dogs was 1.5-fold and 2-fold higher, respectively, for NKTR-102 compared with irinotecan.
- Diarrhea was not observed in rats treated with NKTR-102 up to 120 mg/kg, but was observed at 60 mg/kg and higher in rats treated with irinotecan. Dogs treated with irinotecan at 20 mg/kg and 30 mg/kg exhibited severe diarrhea, while severe diarrhea was observed only at the highest dose of NKTR-102 (60 mg/kg).
- Neutropenia was observed in only 1 rat treated at the highest dose of NKTR-102, whereas neutropenia was observed in all irinotecan dose groups. Dogs treated with NKTR-102 exhibited milder neutropenia than dogs treated with equivalent doses of irinotecan.
- NKTR-102 in dogs exhibited a superior tolerability profile compared with irinotecan while achieving a 6-fold greater exposure (AUC) to SN38.

References:

- Persson H, Antonian L, Staschen C-M, et al. NKTR-102, a novel polyethylene glycol conjugate of irinotecan, has improved anti-tumor activity in three mouse xenograft models. Poster presented at the 2007 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Oct 22-26, 2007, San Francisco, CA, USA. Poster no. C10.
- Eldon MA, Staschen C-M, Viegas T, et al. 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. Poster presented at the 2007 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Oct 22-26, 2007, San Francisco, CA, USA. Poster no. C157.
- Eldon MA, Antonian L, Burton K, et al. NKTR-102, a novel PEGylated irinotecan-conjugate, demonstrates improved pharmacokinetics with sustained exposure of irinotecan and its active metabolite. Presented at the 14th European Cancer Conference (ECCO 14), September 23-27, 2007, Barcelona, Spain. Poster no. 727.