

NKTR-102, A NOVEL PEGYLATED-IRINOTECAN, HAS AN ENHANCED PHARMACOKINETIC PROFILE WITH REDUCED GASTROINTESTINAL AND HEMATOPOIETIC TOXICITY COMPARED TO IRINOTECAN WITH REPEAT DOSING IN DOGS

Abstract #5741

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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 demonstrates a single-dose maximum tolerated dose (MTD) in dogs of 40 mg/kg, compared with a single-dose MTD of 20 mg/kg for irinotecan.³
- A previous pilot study of 4 weekly doses (Days 1, 8, 15, 22) of NKTR-102 at 6, 20, 30, or 40 mg/kg identified a repeat-dose MTD of less than 40 mg/kg and possibly less than 30 mg/kg. Therefore, the current study was designed at doses of 20 mg/kg or 25 mg/kg NKTR-102.
- Adding a PEG moiety to irinotecan has been demonstrated to increase exposure to SN38 and is expected to reduce C_{max}, thereby improving the toxicity profile.

Objectives:

- Evaluate the repeat-dose tolerability of NKTR-102 in dogs compared with irinotecan.
- Determine the toxicokinetic profile of SN38 on repeat dosing of NKTR-102 relative to irinotecan.

Methods:

- NKTR-102, irinotecan, or vehicle control was administered to dogs via intravenous infusion on Days 1, 8, 15, and 22.
- Irinotecan was administered at doses of 20 mg/kg or 25 mg/kg. NKTR-102 was administered at doses equivalent to 20 mg/kg or 25 mg/kg irinotecan (normalized for % irinotecan by weight).
- Treatment and dose groups are summarized in Table 1.

Table 1: Study design.

Treatment	Dose ^a	Number of Dogs	
		Main Study (terminated at Day 26)	Recovery Group (terminated at Day 40)
Vehicle Control ^b	0 mg/kg	6	2
NKTR-102	20 mg/kg	6	0
Irinotecan	20 mg/kg	6	0
NKTR-102	25 mg/kg	6	2
Irinotecan	25 mg/kg	6	0

^aAll doses expressed as irinotecan-equivalent doses.
^bVehicle = 5% dextrose in water.

- Clinical observations were recorded twice daily. Detailed clinical examinations were performed weekly and immediately prior to necropsy.
- Severe diarrhea was defined as bloody diarrhea and/or diarrhea lasting 3 or more study days.
- Analysis of clinical pathology was performed prior to initiation of the study and before necropsy, with hematologic analysis performed more frequently:
 - Hematologic analyses were performed prior to dosing on Day 1 and subsequently on Days 2, 4, 6, 8, 11, 13, 15, 18, 20, 22, and 26. Hematologic samples collected on Days 8, 15, and 22 were drawn prior to dosing.
- Samples for toxicokinetic analysis were collected at the following intervals:
 - NKTR-102: 8, 48, 96, 168 hours post-dose on Days 1 and 22; pre-dose on Days 1, 15, 22; Day 40.
 - Irinotecan: 3, 8, 12, 24, 48 hours post-dose on Days 1 and 22; pre-dose on Days 1, 15, 22; Day 40.
- Animals were subjected to necropsy (Day 26) and histopathologic examination of relevant tissues.
- Noncompartmental toxicokinetic parameters were estimated using WinNonlin 4.0.1 software (Pharsight Corporation, Mountain View, CA). Homogeneous data were analyzed using Analysis of Variance, while heterogeneous data were analyzed using Kruskal-Wallis tests.

Results:

Mortality

- Irinotecan treatment resulted in mortality in 1/6 dogs at the 20 mg/kg dose and 4/8 at 25 mg/kg (found dead or moribund sacrifice), with a probable cause of death of severe bone marrow hypocellularity and enteric pathology.
- NKTR-102 treatment was not associated with mortality at any dose.
- Under the conditions of this study, the MTD, defined as the dose at which mortality was not observed, was >25 mg/kg and <20 mg/kg for NKTR-102 and irinotecan, respectively, due to the absence of death at 25 mg/kg NKTR-102 and the occurrence of death in 1/6 dogs at 20 mg/kg irinotecan. However, the MTD is nominally designated as 25 mg/kg and 20 mg/kg for NKTR-102 and irinotecan, respectively.

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Poster presented at the 2008 AACR Annual Meeting, April 12-16, 2008, San Diego, CA, USA.

References: 1. 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. 2. 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. 3. Persson H, Barker T, Eldon M, Wolff R. NKTR-102, a novel PEGylated-irinotecan, has a superior acute safety and tolerability profile compared to irinotecan in rats and dogs. Poster presented at the 2008 AACR Annual Meeting, April 12-16, 2008, San Diego, CA, USA. Abstract no. 5742.

Gastrointestinal Effects

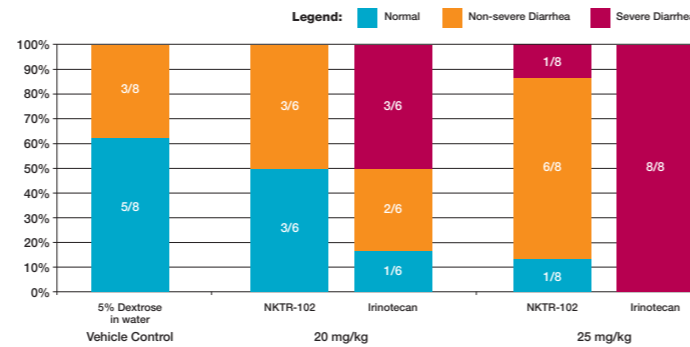
Diarrhea

- NKTR-102 treatment resulted in no severe diarrhea episodes at 20 mg/kg and 1 severe diarrhea episode at 25 mg/kg characterized by diarrhea lasting 3 or more days. Bloody diarrhea was not observed with NKTR-102 treatment (Table 2, Figure 1).
- Irinotecan treatment resulted in 2 severe diarrhea episodes at 20 mg/kg and 9 severe diarrhea episodes at 25 mg/kg. One of two severe episodes at 20 mg/kg and all severe episodes at 25 mg/kg involved bloody diarrhea.

Table 2: NKTR-102 results in less severe diarrhea than irinotecan at equivalent doses.

Dose	Group Size	Treatment	No. Dogs With Diarrhea During Study	Total No. Episodes Observed	Total Episodes of Severe Diarrhea
0 mg/kg	8	Vehicle Control	3	5	0
20 mg/kg	6	NKTR-102	3	8	0
		Irinotecan	5	27	3
25 mg/kg	8	NKTR-102	7	20	1
		Irinotecan	8	46	9

Figure 1: NKTR-102 20 mg/kg diarrhea frequency and severity are comparable to control.



Enteric Pathology

- NKTR-102 at 20 mg/kg or 25 mg/kg did not result in significant enteric pathology.
- Irinotecan treatment at both doses was associated with severe enteric pathology.

Table 3: NKTR-102 demonstrates minimal enteric pathology.

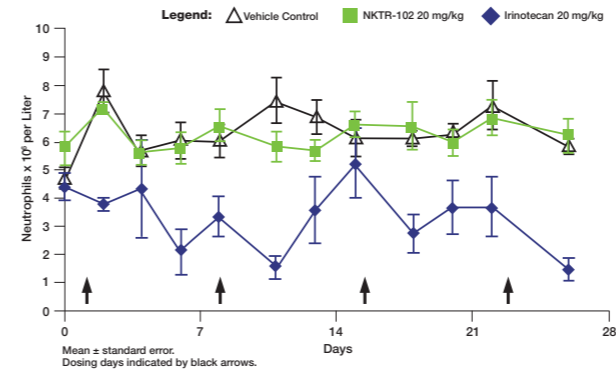
	Irinotecan	NKTR-102
Gut-Associated Lymphoid Tissue	Variable (minimal to severe) atrophy of the gut-associated lymphoid tissue (GALT or Peyer's patches) in 4/6 at 20 mg/kg and 6/6 at 25 mg/kg.	Minimal to mild atrophy of GALT in 5/6 at 20 mg/kg and 6/6 at 25 mg/kg.
Small Intestine Mucosa	Severe villous atrophy and minimal to moderate cryptal necrosis of the small intestinal mucosa (jejunum, ileum) in the four 25 mg/kg dogs that died or were terminated prematurely on study. The frequency and severity of pathology were lower in dogs surviving to terminal sacrifice.	Normal
Large Intestine Mucosa	Glandular necrosis with mucosal hyperplasia (mild to severe) in 3/4 25 mg/kg dogs that died or were terminated prematurely on study. The frequency and severity of pathology was lower in dogs surviving to terminal sacrifice.	Normal

Hematopoietic Effects

Hematology

- NKTR-102 demonstrates a smaller decrement in neutrophil counts than irinotecan dogs at the same dose (group means 20 mg/kg shown in Figure 2).

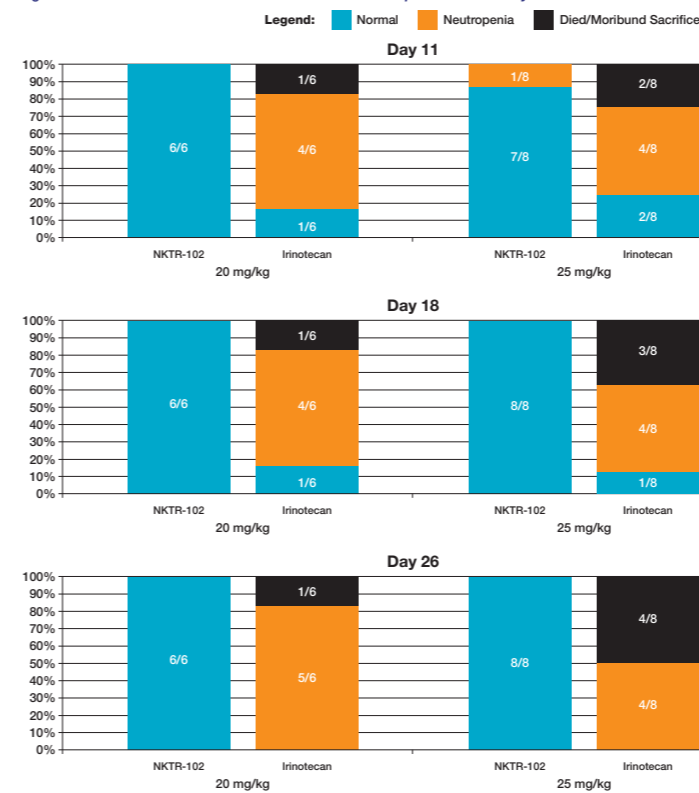
Figure 2: NKTR-102 group mean neutrophil counts are comparable to control.



- A secondary analysis assessed neutropenia on an individual-animal basis.

- NKTR-102 treatment was associated with a single observation of neutropenia in 1 dog at 1 timepoint (Day 11, 25 mg/kg) (Figure 3).
- Irinotecan treatment was associated with persistent neutropenia that was observed in 100% of dogs by Day 26 at both 20 mg/kg and 25 mg/kg.

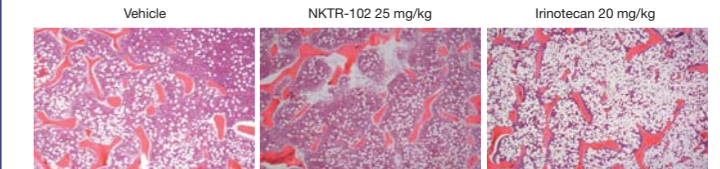
Figure 3: NKTR-102 treatment is associated with less neutropenia and mortality.



Bone Marrow Histology

- NKTR-102 treatment resulted in minimal bone marrow hypocellularity at both 20 mg/kg and 25 mg/kg (Figure 4, Table 4).
- Irinotecan treatment resulted in mild to severe bone marrow hypocellularity at the 20 mg/kg dose and moderate to severe hypocellularity at the 25 mg/kg dose.

Figure 4: At MTD, NKTR-102 demonstrates minimal bone marrow hypocellularity.



Normal bone marrow is characterized by trabeculae (pink), large numbers of hematopoietic cells (purple) and large lipid containing fat cells (white). At MTD, NKTR-102 is characterized by minimal bone marrow hypocellularity, while at MTD of irinotecan bone marrow toxicity is more severe.

Table 4: Summary of bone marrow histology.

Dose	NKTR-102	Irinotecan
20 mg/kg	Bone marrow exhibits minimal hypocellularity of the hematopoietic compartment.	Bone marrow exhibits mild to severe hypocellularity of the hematopoietic compartment and proportional increase in area occupied by fat cells.
25 mg/kg	Bone marrow exhibits minimal hypocellularity of the hematopoietic compartment.	Bone marrow exhibits moderate to severe hypocellularity of the hematopoietic compartment.

Toxicokinetics

Day 1

- NKTR-102 treatment was associated with a mean peak plasma SN38 concentration (C_{max}) that was 4-fold lower than comparable doses of irinotecan (Table 5).

Day 22

- NKTR-102 treatment was associated with mean SN38 exposure (AUC) that was 6-fold higher than irinotecan at both 20 mg/kg and 25 mg/kg (Table 5).

Table 5: NKTR-102 achieves 4-fold lower C_{max} and 6-fold higher exposure (AUC) of SN38 than irinotecan.

Dose (mg/kg)	Treatment	SN38 C _{max} at Day 1 (µg/mL)	SN38 AUC (0-48 h after Day 22 dose) (µg·hr/mL)
20	Irinotecan	0.0135	0.034
	NKTR-102	0.0034	0.191
25	Irinotecan	0.0217	0.040
	NKTR-102	0.0049	0.223

Conclusions:

- NKTR-102 demonstrated a superior repeat-dose safety profile compared with irinotecan in dogs.
- The repeat dose MTD for NKTR-102 in dogs was at least 25% higher than the MTD for irinotecan.
- Severe diarrhea and neutropenia in NKTR-102-treated dogs were markedly less than in dogs treated with irinotecan.
- NKTR-102 peak plasma SN38 concentration (C_{max}) was 4-fold lower than that seen with an equivalent dose of irinotecan and was associated with an 8-fold lower incidence of neutropenia and a 9-fold lower incidence of severe diarrhea.
- Repeat administration of NKTR-102 to dogs achieved a 6-fold greater exposure (AUC) to SN38 with less gastrointestinal and hematopoietic toxicity than comparable doses of irinotecan.

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