

NKTR-102 in Development to Treat Solid Tumors

About NKTR-102

Nektar is developing NKTR-102, a novel pro-drug form of irinotecan created using Nektar's advanced polymer conjugate technology. The product is currently in Phase 2 clinical studies being evaluated in multiple tumor settings. Irinotecan is an important chemotherapeutic agent used for the treatment of solid tumors, including colorectal cancer. However, its pharmacokinetic profile and half-life are sub-optimal. NKTR-102 is designed to overcome these limitations to create a potentially superior agent.

Irinotecan typically is cleared from the body within a few hours of dosing, resulting in a low time-concentration profile that may limit its efficacy. The addition of Nektar's proprietary and uniquely-designed polymer conjugate to irinotecan has been shown in preclinical studies to increase the half-life and exposure profiles of irinotecan, which results in improved anti-tumor activity in animal models. These data suggest that a novel and potentially superior half-life and pharmacokinetic profile of irinotecan could improve outcomes for patients whose cancers are typically treated with this chemotherapeutic agent. Nektar plans to study the drug in additional tumor settings beyond those of conventional irinotecan use where NKTR-102 has shown activity in a Phase 1 study.

NKTR-102 Improved Pharmacokinetics Profile and Mechanism of Action

Irinotecan is a pro-drug that is metabolized to its active form, SN-38, is an inhibitor of topoisomerase 1.

Inhibition of topoisomerase 1 blocks both DNA replication and transcription, resulting in apoptosis, or cell death. By using a proprietary, multi-arm, releasable PEGylation chemistry with irinotecan, Nektar has created a new PEG-conjugate drug with an improved pharmacokinetic profile. This improved profile is expected to enable increased and sustained exposure of the tumor to the active metabolite compared with shorter-acting irinotecan formulations.

In preclinical studies, NKTR-102 exhibited superior pharmacokinetics in a repeated dose study in animal models, with a 6-fold increase in exposure (AUC) and a 4-fold lower peak plasma concentration (C_{max}) of SN38, compared with the equivalent dosing of irinotecan (Figure 1).

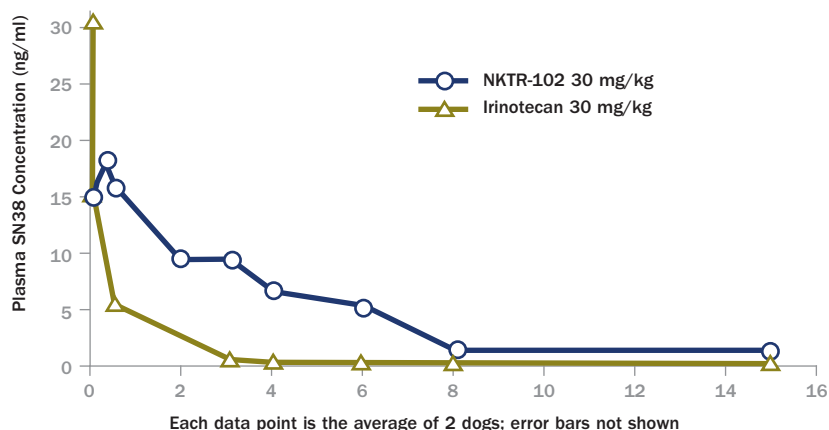


Figure 1: NKTR-102 Achieves Greater and Sustained SN38 Exposure in Animal Model Relative to Irinotecan

A repeated dose study in mice bearing HT29 colorectal tumors showed that NKTR-102 produces a 2-3 log increase in SN-38 exposure in tumors (Figure 2).

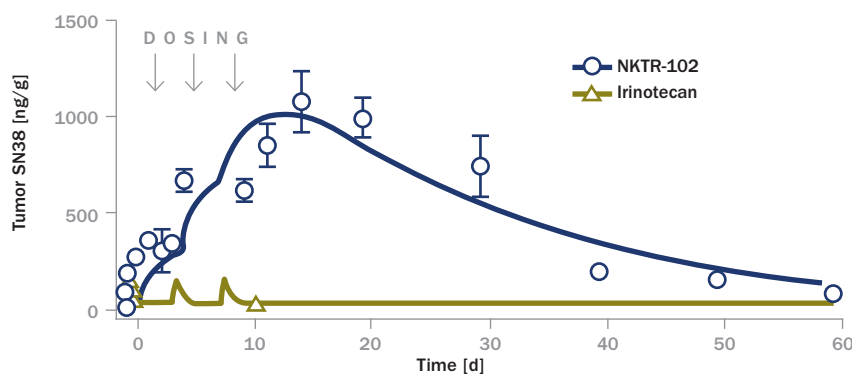


Figure 2: NKTR-102 Produces 2-3 Log Increase in SN-38 Exposure in Colorectal Tumors in Mice

The pharmacokinetic profile of NKTR-102 in humans also shows a higher sustained concentration of SN-38 in plasma compared with a simulated dose of irinotecan (Figure 3).

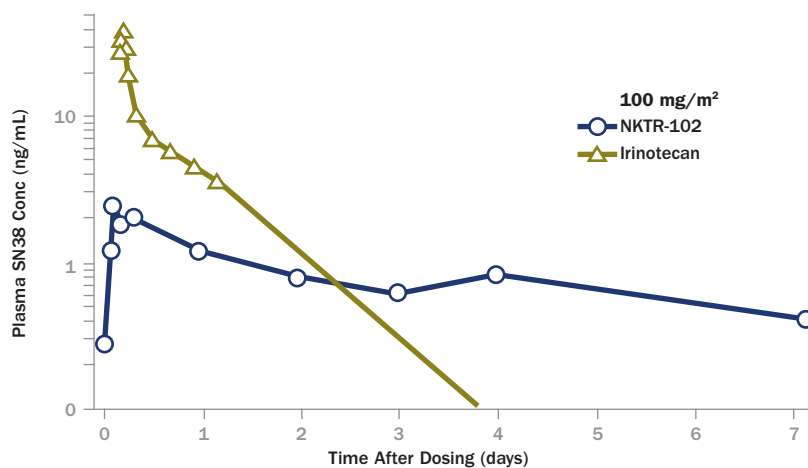


Figure 3: Pharmacokinetic Profile of a Single Dose NKTR-102 compared to Simulated Irinotecan Dose in a Cancer Patient

Nektar Advanced Polymer Conjugate Technology

Nektar is developing novel oncolytics with enhanced properties by using custom polymer conjugate chemistry and a pro-drug design that has a proprietary multi-branched, releaseable architecture. Our novel technology approach can be used to enhance the properties of therapeutic agents by increasing drug circulation time, improving pharmacokinetics, decreasing immunogenicity and dosing frequency, increasing bioavailability and improving drug solubility and stability. Nektar technology has been successfully used in eight approved partnered products over the last fourteen years which include UCB's Cimzia®, Roche's PEGASYS® for hepatitis C and Amgen's Neulasta® for neutropenia.

Anti-Tumor Activity of Single-Agent NKTR-102 Shows Enhanced Tumor Growth Inhibition Compared with Irinotecan

Data from preclinical studies of NKTR-102 have been presented most recently at the 14th European Cancer Conference in September 2007, the AACR-NCI-EORTC conference in October 2007 and the AACR conference in April 2008.

Preclinical studies in an irinotecan-resistant mouse colorectal tumor model showed NKTR-102 inhibited tumor growth by 94% at the highest dose of 90 mg/kg on day 50. There was no significant decrease in tumor growth and no tumor regression from equivalent doses of irinotecan (Figure 4).

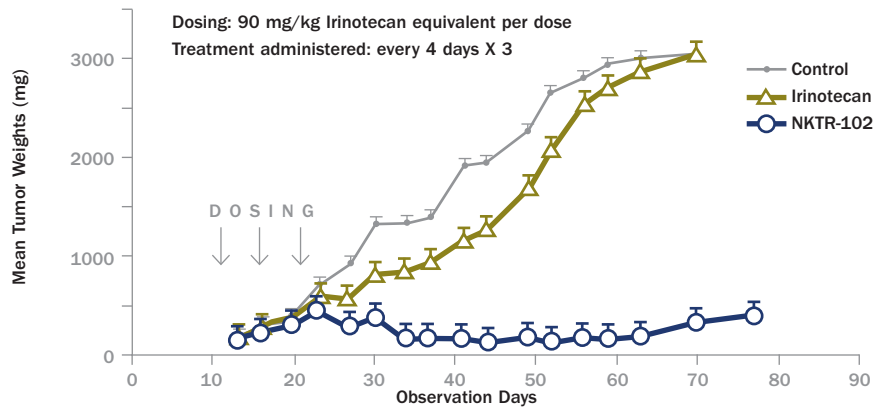


Figure 4: NKTR-102 Inhibits Growth of Irinotecan-Resistant Human Colon Tumor (HT29) in Mouse Xenograft Model

NKTR-102 showed similar anti-tumor activity and inhibited tumor growth by greater than 90% in mouse xenograft models of lung (NCI-H460) and breast (MCF-7) cancers as compared with controls.

NKTR-102 in Combination with Bevacizumab Demonstrates Additive Anti-Tumor Activity in Preclinical Study

Treatment regimens combining irinotecan, other chemotherapeutics and bevacizumab (an antibody against vascular endothelial growth factor [VEGF]) are commonly used in the treatment of colorectal cancer. In preclinical studies, NKTR-102 co-administered with bevacizumab had an additive effect, inhibiting tumor growth by up to 97% in the HT29 mouse xenograft model of colorectal cancer, which was greater than monotherapy with either NKTR-102 or bevacizumab (Figure 5).

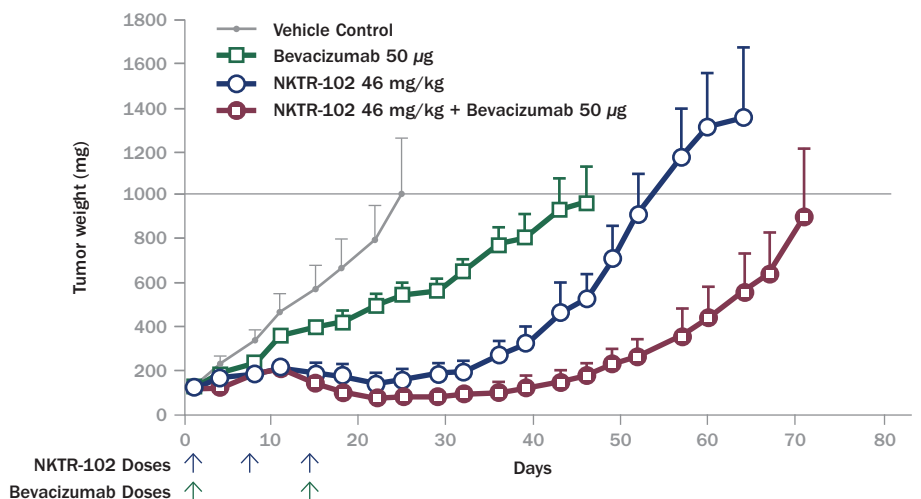


Figure 5: NKTR-102 In Combination with Bevacizumab Exhibits Additive Tumor Growth Inhibition in a Mouse HT29 Colorectal Tumor Model

NKTR-102 at 46 mg/kg, co-administered with bevacizumab, also resulted in eight partial tumor regressions and one complete tumor regression. This compares with no tumor regressions observed with bevacizumab monotherapy, and two partial and one complete regression with NKTR- 102 monotherapy.

Clinical Data

In a Phase 1 dose-escalation trial, the safety, pharmacokinetics and anti-tumor activity of NKTR-102 monotherapy were evaluated in 57 patients with advanced solid tumors who had failed prior treatments or had no standard treatment available to them. Patients were enrolled in one of three dose schedules and received 90-minute infusions of NKTR-102 (PEGylated irinotecan) as follows: weekly for three weeks with the fourth week off (n=32); q14 days (n=11); or q21 days (n=15). Tumor responses were evaluated according to RECIST (Response Evaluation Criteria in Solid Tumors) criteria.

Of the 57 patients in total from all dose schedules, 14 reported significant anti-tumor activity. Eight patients had confirmed partial responses (greater than 30% tumor regression per RECIST). Of these eight partial responses, all responses ranged from a 40% reduction to as high as a 58% reduction in tumor size. Six patients in the study had minor responses (tumor regression by more than 15% but less than 30% per RECIST, or demonstrated significant cancer biomarker reduction). Responders were seen in a variety of tumor settings, including breast, ovarian, and cervical (Figure 6). Nektar plans to initiate Phase 2 studies to evaluate NKTR-102 in these tumor types in the fourth quarter of 2008.

Tumor	Regimen/Dose	Number of Prior Agents
Breast (triple negative)	Q3 week, 170 mg/m ²	7
Ovarian	Q 2 week, 145 mg/m ²	6
Bladder	Q2 week, 145 mg/m ²	3
Maxillary sinus (neuroendocrine)	Q2 week, 170 mg/m ²	None
Colon cancer	Q2 week, 220 mg/m ² (reduced to 170 mg/m ²)	2
Small cell lung	Weeklyx3q4 weeks, 58 mg/m ²	6
Non small cell lung	Weeklyx3q4week, 145 mg/m ²	3
Cervical	Weeklyx3Q4 week, 173 mg/m ²	3

Note: Partial responses defined as 30% or greater reduction in tumor size

Figure 6: NKTR-102: Phase 1 Clinical Trial Partial Responses Observed in Multiple Tumors

The observed plasma half-life of the active metabolite (SN38) of NKTR-102 was 50 days; this is significantly longer than the observed half-life of 30-50 hours with irinotecan dosing.¹ Increased SN38 levels, the active metabolite of irinotecan responsible for its anti-tumor activity, were also observed with administration of NKTR-102, with exposures up to 4.4-fold higher than predicted with irinotecan at equivalent doses.

Patients enrolled in the NKTR-102 Phase 1 study had failed all prior established treatment regimens. The majority of patients had progressive disease despite three or more previous regimens. All partial responses were observed following the first or second course of treatment, highlighting the value of an oncolytic with an extended half-life and sustained delivery of the active metabolite.

Phase 2 Clinical Development Plan for NKTR-102

NKTR-102 is currently in a Phase 2a study to evaluate NKTR-102 in combination with cetuximab.

Recent data presented at the 2008 American Society of Clinical Oncologists (ASCO) Annual Meeting demonstrated that colorectal cancer (CRC) patients with tumors that have K-Ras oncogene mutations (K-Ras mutant types) do not respond to EGFR-inhibitors, such as cetuximab. It is estimated that up to 45% of colorectal cancer cases have this mutated K-Ras gene. To target this newly-characterized K-Ras mutant patient population, Nektar has initiated a prospective study to evaluate the efficacy of NKTR-102 monotherapy in these patients. The primary endpoint of this randomized trial will be a clinically meaningful improvement in progression-free survival as compared to standard irinotecan monotherapy.

Additional studies are underway in 2009 for NKTR-102 in breast, cervical and ovarian cancer. These trials will be open-label, single-arm studies to evaluate the overall response rate (ORR) of NKTR-102 monotherapy in each tumor setting. The studies implement a minimax design, known as the Simon design, which was first proposed by Dr. Richard Simon of the National Cancer Institute in 1989. The two-stage design is routinely used in the evaluation of oncolytics.

¹Diederik F. S. Kehler et al., Factors Involved in Prolongation of the Terminal Disposition Phase of SN-38: Clinical and Experimental Studies, *Clinical Cancer Research* 2000; 6; 3451–3458.



Nektar Therapeutics is a biopharmaceutical company developing novel therapeutics based on its advanced polymer conjugate chemistry technology platform. Nektar's technology and drug development expertise have enabled nine approved products for partners, which include leading biopharmaceutical companies. Nektar is also developing a robust pipeline of its own high-value therapeutics that addresses unmet medical needs by leveraging and expanding its technology platforms to improve and enable molecules. For more information on Nektar Therapeutics, please visit www.nektar.com.