



**TITLE: A Phase II Study of Single Agent Topoisomerase-I Inhibitor Polymer Conjugate, Etirinotecan Pegol (NKTR-102), in Patients with Relapsed Small Cell Lung Cancer**

**Roswell Park Cancer Institute**

**Study Number: I 225612**

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**Amendment 7: February 4, 2016**

**Amendment 8: September 23, 2016**

**Amendment 9: January 27, 2017**

**IND Number/Holder: IND 119186**

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**Industry/Other Supporter: Nektar Therapeutics**

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## Network Investigator Signature Page

**Title: A Phase II Study of Single Agent Topoisomerase-I Inhibitor Polymer Conjugate, Etirinotecan Pegol (NKTR-102), in Patients with Relapsed Small Cell Lung Cancer**

### Protocol Approval and Investigator Agreement

I have read and familiarized myself with this protocol and agree to conduct the study as described according to Good Clinical Practices (GCP) and International Conference on Harmonisation (ICH) guidelines.

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Principal Investigator's Signature

Date

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Principal Investigator's Print

Address:

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Phone:

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Fax:

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Email:

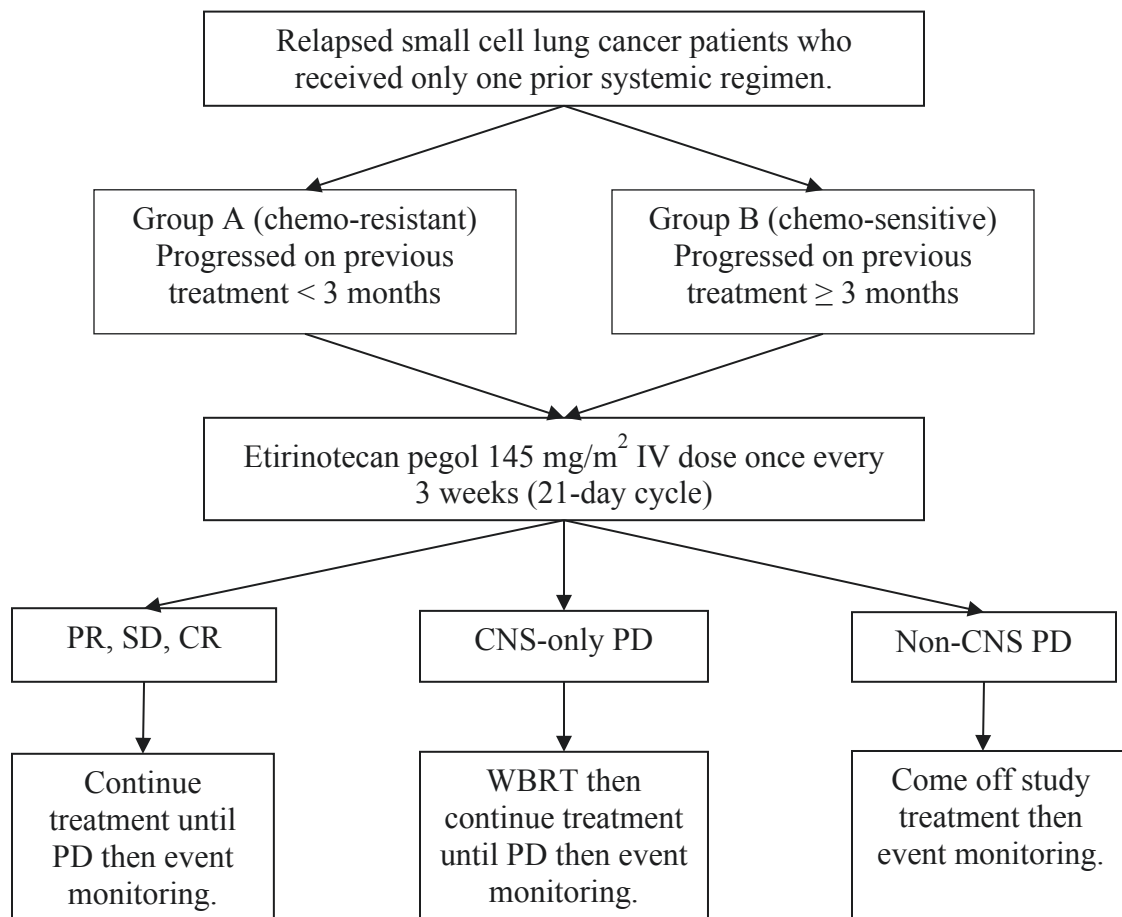
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NOTE: Please see **Appendix A** for Network-specific instructions that will apply to your site.

**SYNOPSIS**

<b>Title / Phase</b>	A Phase II Study of Single Agent Topoisomerase-I Inhibitor Polymer Conjugate, Etirinotecan Pegol (NKTR-102), in Patients with Relapsed Small Cell Lung Cancer
<b>Roswell Park Cancer Institute Study Number</b>	I 225612
<b>Roswell Park Cancer Institute Investigator</b>	Hongbin Chen, MD, PhD
<b>Sponsor</b>	Nektar Therapeutics
<b>Study Drug</b>	Etirinotecan Pegol (NKTR-102)
<b>Objectives</b>	<p><b>Primary Objective:</b></p> <ul style="list-style-type: none"> <li>To evaluate the 18-week progression free survival (PFS) rate of relapsed SCLC patients treated with NKTR-102.</li> </ul> <p><b>Secondary Objectives:</b></p> <ul style="list-style-type: none"> <li>To evaluate the objective response rate.</li> <li>To evaluate the duration of response.</li> <li>To evaluate the overall survival.</li> <li>To evaluate the toxicity of NKTR-102 in this patient population.</li> </ul> <p><b>Correlative Objective:</b></p> <ul style="list-style-type: none"> <li>To explore the correlation between UGT1A1 polymorphisms and NKTR-102 toxicities.</li> </ul>
<b>Study Design</b>	This is a single stage Phase II study of relapsed small cell lung cancer patients who have received only one prior systemic therapy regimen. There will be 2 patient cohorts: those progressing on first-line therapy < 3 months after completion of treatment (Group A: chemo resistant) and those progressing on first-line therapy ≥ 3 months after completion of treatment (Group B: chemo sensitive). Etirinotecan pegol will be administered at 145 mg/m <sup>2</sup> IV once every 3 weeks. Cycles will be repeated every 21 days (± 3 days) until disease progression. Patients who develop metastases in the central nervous system (CNS) as the only site of disease progression could receive therapeutic whole brain radiation therapy (WBRT), or gamma knife radiosurgery and after completion of WBRT continue on NKTR-102. Imaging studies are scheduled to be obtained after every other 21-day cycle.
<b>Target Accrual and Study Duration</b>	This study will accrue a total of 38 patients over approximately 3 years (Group A; 20 patients, Group B; 18 patients). Patients will be on study for approximately 18 – 24 months.
<b>Study Procedures</b>	<p><b>Adverse Events:</b> From time of Cycle 1 Day 1 until 30 days after receiving last dose of study drug.</p> <p><b>Hematology:</b> ≤ 14 days prior to initiation of study drug, Cycle 1 (Day 1 and weekly), and prior to treatment on Day 1 of subsequent cycles, 30-Day Follow-Up.</p> <p><b>Chemistry:</b> ≤ 14 days prior to initiation of study drug, Cycle 1 (Day 1 and weekly), prior to treatment on Day 1 of subsequent cycles, 30-Day Follow-Up.</p> <p><b>Physical Examination (including vital signs, body weight, and height):</b></p>

	<p>≤ 14 days prior to initiation of study drug, Cycle 1 (Day 1 and weekly), and prior to treatment on Day 1 of subsequent cycles, 30-Day Follow-Up.</p> <p><b>Performance Status:</b> ≤ 14 days prior to initiation of study drug, Cycle 1 (Day 1 and weekly), and prior to treatment on Day 1 of subsequent cycles, 30-Day Follow-Up.</p> <p><b>12-Lead ECG:</b> ≤ 14 days prior to initiation of study drug and prior to treatment on Day 1 of Cycle 2 and Cycle 3, if clinically indicated.</p>
Statistical Analysis	<p><b>Efficacy Assessments:</b></p> <ul style="list-style-type: none"> <li>18-week PFS is defined as the proportion of patients whose disease has not progressed at 18 weeks after getting etirinotecan pegol.</li> <li>Tumor response is defined as a complete response (CR) or partial response (PR) by RECIST 1.1 criteria, which will be evaluated by CT-scan every other cycle.</li> <li>OS is defined as the time from enrollment to death from any cause.</li> </ul> <p><b>Safety Assessments:</b></p> <ul style="list-style-type: none"> <li>The maximum grade for each type of adverse events (AEs) will be recorded for each patient based on NCI CTCAE version 4.0, and frequency tables will be reviewed to determine AE and toxicity (unrelated, unlikely, possible, probably, or definitely related to study treatment) patterns in each group.</li> <li>A single-stage design will be used to assess the primary endpoint separately for each. Based on this, the primary endpoint of this trial will be the proportion of patients who are progression-free at 18 weeks.</li> </ul>

**Study Schema**

Roswell Park Cancer Institute Study Number: I 225612

**INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM**

Subject Name: (Network sites use subject initials): \_\_\_\_\_

Medical Record No.: (Network sites use subject ID): \_\_\_\_\_

**Title: A Phase II Study of Single Agent Topoisomerase-I Inhibitor Polymer Conjugate, Etirinotecan Pegol (NKTR-102), in Patients with Relapsed Small Cell Lung Cancer**

INCLUSION CRITERIA				
Yes	No	N/A	All answers must be "YES or "N/A" for patient enrollment.	Date
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1. Written informed consent granted prior to initiation of any study-specific screening procedures, given with the understanding that the patient has the right to withdraw from the study at any time, without prejudice.	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2. 18 years of age or older.	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	3. Histologic or cytologic diagnosis of SCLC. (Note: Patients with mixed histology are not eligible.)	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4. ECOG performance status of 0 or 1 (refer to <b>Appendix B</b> ).	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5. Presence of measurable disease as defined by $\geq 1$ lesion whose longest diameter can be accurately measured as $\geq 20$ mm with conventional techniques or as $\geq 10$ mm with spiral CT.	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6. Previously treated SCLC with only one prior treatment regimen [cyclophosphamide/doxorubicin/vincristine (CAV) alternating with etoposide/cisplatin (EP) is acceptable].	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7. Resolution of all acute toxic effects of prior chemotherapy, radiotherapy, hormonal therapy, or surgery to NCI-CTCAE version 4.0 Grade $\leq 1$ , except for diarrhea (which must be Grade 0 without supportive antidiarrheal medications) and alopecia (any grade).	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8. Adequate hematologic, liver, and renal function, defined as: <ul style="list-style-type: none"> <li>• Platelet count <math>\geq 100 \times 10^9/L</math></li> <li>• Hgb <math>\geq 9</math> gm/dL</li> <li>• Absolute neutrophil count (ANC) <math>\geq 1500/\mu L</math></li> <li>• Serum creatinine <math>\leq 1.5</math> mg/dL or creatinine clearance <math>&gt; 45</math> mL/min. Use either measured or calculated with Cockcroft - Gault formula (<b>Appendix C</b>).</li> <li>• Serum total bilirubin <math>\leq 1.5 \times</math> ULN</li> <li>• Aspartate Transaminase (AST) and alanine transaminase (ALT) <math>\leq 3 \times</math> ULN or <math>\leq 5 \times</math> ULN if caused by liver metastasis</li> </ul>	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9. Women of childbearing potential must have a negative pregnancy test performed within seven days prior to the start of study drug. Male and female subjects of child-bearing potential must agree to use double-barrier contraceptive measures, or avoidance of intercourse during the study and for 6 months after last investigational drug dose received.	

Study participant meets all entry criteria: ☐ Yes ☐ No

Investigator Signature: \_\_\_\_\_ Date: \_\_\_\_\_

Roswell Park Cancer Institute Study Number: I 225612

**INVESTIGATOR STUDY ELIGIBILITY VERIFICATION FORM****Subject Name:** (Network sites use subject initials): \_\_\_\_\_**Medical Record No.:** (Network sites use subject ID): \_\_\_\_\_**Title: A Phase II Study of Single Agent Topoisomerase-I Inhibitor Polymer Conjugate, Etirinotecan Pegol (NKTR-102), in Patients with Relapsed Small Cell Lung Cancer**

EXCLUSION CRITERIA				
Yes	No	N/A	All answers must be "NO" or "N/A" for patient enrollment.	Date
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	1. Previous anti-cancer chemotherapy, immunotherapy or investigational agents < 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to the first day of study defined treatment. Palliative radiation < 2 weeks, biological therapy within 2 weeks, hormonal therapy within 1 week prior to Day 1 Cycle 1.	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	2. Prior treatment with a topoisomerase-I inhibitor (e.g., topotecan, irinotecan).	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	3. Prior malignancy except for non-melanoma skin cancer and carcinoma in situ, unless diagnosed and definitively treated more than 5 years prior to enrollment.	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	4. Substance abuses, medical, psychological or social conditions that may, in the opinion of the Investigator, interfere with the patient's participation in the study or evaluation of the study results.	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5. Known human immunodeficiency virus (HIV) infection due to concerns of potential drug interaction with various antiretroviral agents.	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6. Pregnancy or breast-feeding.	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	7. Concurrent administration or received CYP3A4 inducers or inhibitors within 2 weeks prior to the first day of study drug treatment. Lists including medications and substances known or with the potential to interact with CYP3A4 are provided in <b>Section 7.3.7</b> .	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8. Patients with chronic or acute GI disorders resulting in diarrhea of any severity grade; patients who are using chronic anti-diarrheal supportive care (more than 3 days/week) to control diarrhea in the 28 days prior to study entry.	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9. Major surgery < 4 weeks or minor surgery (e.g., talc pleurodesis, excisional biopsy, etc) < 2 weeks prior to the first day of study defined treatment.	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	10. Have central nervous system (CNS) metastases (unless the patient has completed successful local therapy for CNS metastases and has been off corticosteroids for at least 4 weeks before starting study therapy). Brain imaging is required in symptomatic patients to rule out brain metastases, but is not required in asymptomatic patients.	
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.	



Roswell Park Cancer Institute Study Number: I 225612

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<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	12. Unwilling or unable to follow protocol requirements.	
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**Study participant meets all entry criteria:**      ☐      **Yes**      ☐      **No**

**Investigator Signature:** \_\_\_\_\_ **Date:** \_\_\_\_\_

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## 1 BACKGROUND

Small-cell lung cancer (SCLC) is one of the most aggressive and lethal cancers in humans. It accounts for 15% - 20% of lung cancer. The standard combination cytotoxic chemotherapy agents have shown antitumor activity with initial responses seen in 70%–90% for both limited-stage disease (LD) and extensive-stage disease (ED) of SCLC.<sup>1-3</sup> Fifty to 60% of patients with LD and 20% - 40% of patients with ED will achieve a clinical complete response (CR) to initial chemotherapy with or without thoracic radiotherapy. Long-term survival is low and most patients eventually develop progressive disease. Overall, the median survival time (MST) for LD and ED is 12 – 15 months and 8 – 10 months, respectively, with 5-year survival of 10% (LD) and 0% - 2% (ED).<sup>4,5</sup> Even among patients who achieve CR, there is a high rate of relapse.<sup>6</sup> In previous studies, 60% of LD patients achieved a CR.<sup>1,3</sup> Seventy percent of these CR patients relapsed within 2 years. Although SCLC is very responsive to initial treatment, most patients relapse with relatively resistant disease. Moreover, among patients who relapse, prognosis remains poor with second-line therapy. Response to subsequent therapy is influenced by the progression-free interval from cessation of initial therapy. Patients who relapse within 3 months are considered to have refractory disease and typically have response rates to second-line therapy that are inferior to patients considered to have ‘sensitive’ disease, generally defined as those who relapse more than 3 months after therapy.<sup>7</sup> The first generation topoisomerase-I inhibitors such as; topotecan and irinotecan are the second line treatment for relapsed SCLC with the response rate (RR) 13% - 47% and progression-free survival (PFS) 2.2 - 3.7 months compared with other single cytotoxic drugs or best supportive care (**Table 1**).<sup>6,8-12</sup> Based on the high relapse rate after CR, leveling off of the therapeutic results, and poor long-term survival, it is clear that new active agents are needed in the treatment of relapsed SCLC.

The anti-tumor activity of topoisomerase-I inhibitor, irinotecan, has been demonstrated in multiple tumor types including SCLC<sup>13-18</sup>, non-small cell lung cancer (NSCLC)<sup>19-21</sup>, gastric adenocarcinoma<sup>22,23</sup>, colorectal cancer<sup>24,25</sup> and ovarian cancer<sup>26-28</sup>. Immediately after dosing, however, standard topoisomerase-I inhibitors reach high peak concentrations and diffuse quickly throughout the body, penetrating and damaging healthy tissue, such as bone marrow, as well as tumor tissue. Subsequent rapid metabolism limits topoisomerase-I exposure in tumor cells, reducing the duration of their effect and resulting in a much lower tumor exposure to the active metabolite that may limit their efficacy. The usage of irinotecan is often hampered by its sub-optimal toxicity profiles and pharmacokinetics. It has a half-life ( $t_{1/2}$ ) of approximately 9 hours in humans, and repeat dosing demonstrates the saw-tooth pharmacokinetic (PK) profile that typifies a short  $t_{1/2}$  for both irinotecan and its major active metabolite, 7-ethyl-10- hydroxy-camptothecin (SN38), with a  $t_{1/2}$  of about 47 hours (**Figure 1**). Additionally, there is no good second-line therapy available. Accordingly, due to the activity observed as front-line therapy and some activity of each of the single agents as second-line therapy, this study will investigate the efficacy of novel generation of topoisomerase-I inhibitor, NKTR-102, against relapsed or refractory small cell lung cancer. Because of the fact that second-line treatment is not curative and these patients have a limited survival, this study will explore NKTR-102 that would be less toxic than irinotecan and would be applicable in the community practice.



**Table 1. Topotecan and Irinotecan in Relapsed Small Cell Lung Cancer**

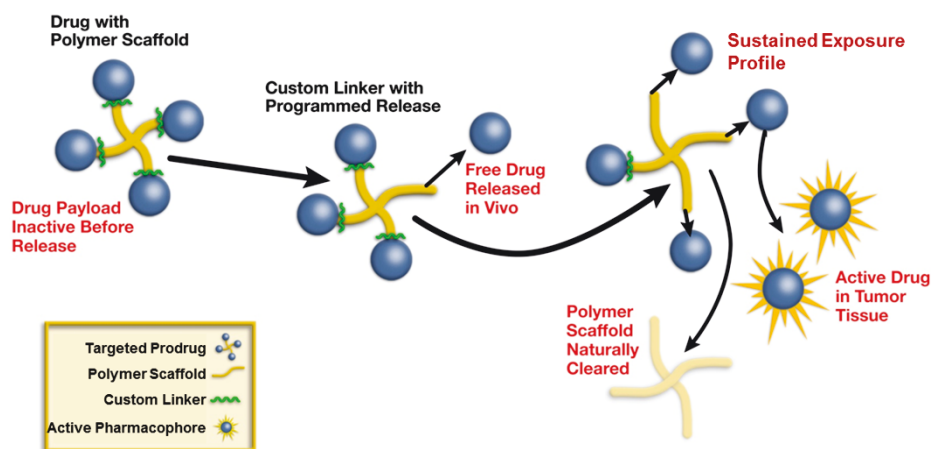
	Phase (N)	Primary endpoint	RR (%)	TTP/PFS (months)	OS (months)
Topotecan IV vs CAV <sup>6</sup>	Phase III (211)	ORR	26 vs 19	3.3 vs 3	6 both arms
Oral topotecan vs BSC <sup>12</sup>	Phase III (141)	OS	7 (topotecan arm)	4 of TTP (topotecan arm)	6 vs 3.5
Topotecan IV vs Oral Topotecan <sup>8</sup>	Phase III (309)	ORR	22 vs 18	3.7 vs 3	3.5 vs 3.3
Amrubicin vs Topotecan <sup>9</sup>	Phase II (60)	ORR	38 vs 13 53 vs 21 (chemosensitive) 17 vs 0 (refractory)	3.5 vs 2.2	NA
Amrubicin vs Topotecan <sup>10</sup>	Phase II (76)	ORR	44 vs 15	4.5 vs 3.3	9.2 vs 7.6
Irinotecan (single arm) <sup>11</sup>	Phase II (16)	ORR	47	NA	6

\*CAV; cyclophosphamide/doxorubicin/vincristine, BSC; best supportive care, NA; not available, ORR; overall response rate, OS; overall survival, PFS; progression-free survival, RR; response rate, TTP; time to progression.

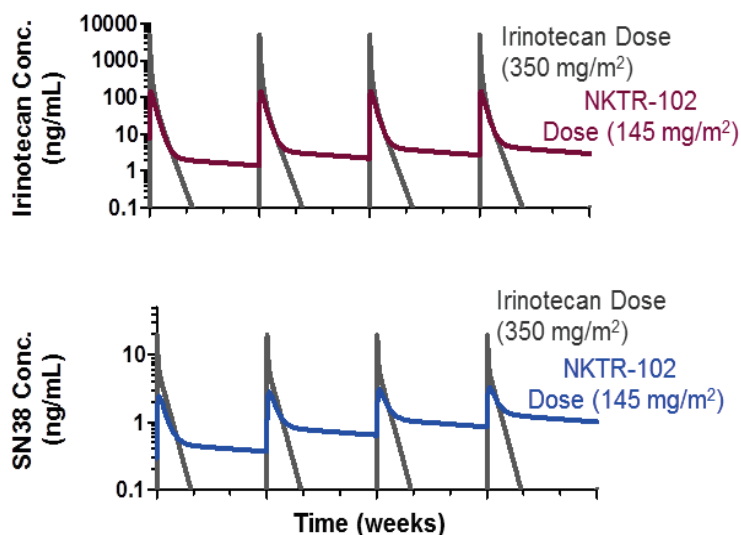
### 1.1 Study Drug: NKTR-102

Etirinotecan pegol (NKTR-102) is a polyethylene glycol (PEG) conjugate of irinotecan. It is a unique and a next generation topoisomerase I-inhibitor designed for prolonged tumor cell exposure using the polymer conjugate technology platform which conjugates cytotoxic small molecules to a uniquely engineered macromolecular polymer core using specialized linkers which provide a continuous concentration of active drug in tumor cells with reduced peak concentrations and minimizing its toxicities (**Figure 1**).

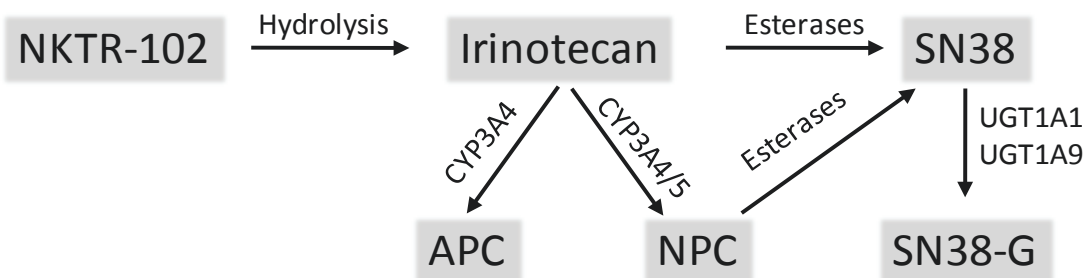
**Figure 1. Targeted Prodrug Enables Sustained Exposure and Continuous Targeting to Tumors**



Unlike first generation topoisomerase-I inhibitors that exhibit a high initial peak concentration and short half-life, NKTR-102's unique pro-drug design results in a lowered initial peak concentration of active topoisomerase-I inhibitor in the blood (**Figure 2**). It provides an extended release of irinotecan thereby providing a more continuous exposure to the active metabolite SN38. By reducing peak concentration and markedly prolonging the  $t_{1/2}$  of SN38 to about 50 days, it is possible that anti-tumor activity can be enhanced while maintaining a favorable toxicity profile. The large NKTR-102 molecule is inactive when administered. Over time, natural processes in the body continuously free active drug that then works to stop tumor cell division through inhibition of topoisomerase-I.

**Figure 2. Concentration and Time Curve of Irinotecan and SN38 After Administration of NKTR-102**

The proposed biotransformation pathway of NKTR-102 is shown in **Figure 3**. After cleavage of irinotecan from the PEG moiety, this pathway is the same as that for irinotecan and SN38.

**Figure 3. Proposed Metabolic Pathway for NKTR-102**

Abbreviations: UGT; uridine diphosphate glucuronosyltransferases, CYP; cytochrome P450, SN38; 7-ethyl-10-hydroxycamptothecin, APC; 7-ethyl-10-[4-N-(5-aminopentanoic acid)-1-piperidino]-carbonyloxycamptothecin, NPC; 7-ethyl-10-[4-amino-1-piperidino]-carbonyloxycamptothecin.

## 1.2 Preclinical Studies

Pharmacokinetic, pharmacologic, and toxicologic characteristics of NKTR-102 have been studied in mice, rats, and dogs. Pharmacokinetic studies in mice, rats, and dogs showed slower plasma clearance (CL) as well as greater and sustained exposure to irinotecan and SN38 following NKTR-102 dosing compared to irinotecan dosing. In mice and rats, the SN38 terminal  $t_{1/2}$  increased by approximately one order of magnitude, and SN38 total exposure, expressed in terms of area under the curve (AUC), increased by more than two orders of magnitude.

Prolonged exposure to irinotecan and SN38 was also observed in dogs, where SN38  $t_{1/2}$  values increased by approximately one order of magnitude and SN38 AUC values increased 2- to 6-fold following NKTR-102 dosing, when compared to equivalent irinotecan dosing.

The anti-tumor activity of NKTR-102 was evaluated in several tumor xenograft studies, and included cell lines from human colorectal (HT29), non-small cell lung (NCI H460), breast (MCF-7), ovarian (A2780), and gastric (NCI-N87) tumors. Significantly longer tumor growth delays were seen with NKTR-102 compared to irinotecan in all tumor xenograft studies. NKTR-102 is hypothesized to be more efficacious than irinotecan due to greater and prolonged topoisomerase-I inhibition resulting from prolonged tumor cell exposure to both irinotecan and SN38. The relative benefit was sustained in combination studies comparing anti-tumor activity of NKTR-102 to irinotecan each given with other therapy. These included NKTR-102 or irinotecan given with cetuximab in a mouse model of human DLD-1 colorectal tumor, NKTR-102 or irinotecan given with bevacizumab in a mouse model of human HT29 colorectal tumor, and NKTR-102 or irinotecan given with 5-FU in a model of human HT29 colorectal tumor.

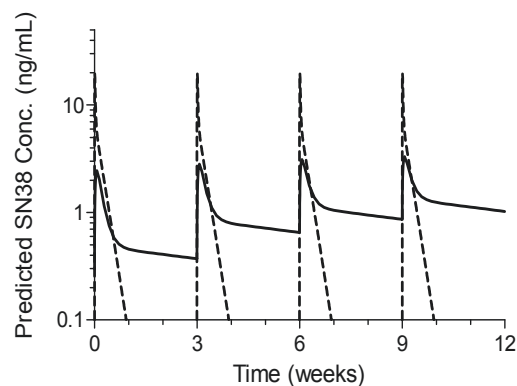
The safety of NKTR-102 was evaluated in both single and repeat-dose toxicity studies in rats and dogs. Toxicity studies included a comparator group of irinotecan-treated animals. In all studies conducted, NKTR-102 was better tolerated than equivalent doses of irinotecan. The maximum tolerated dose (MTD) of NKTR-102 in toxicology studies was 25% to 50% higher for NKTR-102 than irinotecan based on irinotecan equivalent dosing. Direct comparison of NKTR-102 with irinotecan at the same doses in a 4-weekly dose study in dogs showed substantially lower neutropenia and gastrointestinal (GI) effects with NKTR-102. A 3-month toxicity study in the dog has demonstrated that a dose of 30 mg/kg of NKTR-102 (600 mg/m<sup>2</sup>), every two weeks, was tolerated without major overt toxicity; the no observed adverse effect level (NOAEL) was determined to be 6 mg/kg of NKTR-102; the MTD was determined to be  $\geq$  30 mg/kg of NKTR-102.

### **1.3 Clinical Studies**

#### **1.3.1 Clinical Pharmacokinetics**

The  $t_{1/2}$  for SN38 after NKTR-102 administration is approximately 50 days, whereas after irinotecan administration, the SN38  $t_{1/2}$  has been reported as 10 to 47 hours.<sup>29</sup> This greatly increased SN38  $t_{1/2}$  results in plasma SN38 concentrations that are significantly more sustained between doses than are possible with irinotecan. Shown in **Figure 4**, a single 145 mg/m<sup>2</sup> dose of NKTR-102 results in approximately the same SN38 plasma exposure (AUC) as a 350 mg/m<sup>2</sup> dose of irinotecan, but exposure is continuous throughout a 21-day cycle rather than intermittent (there is no measurable SN38 after approximately 1 week with irinotecan), and maximal concentrations are approximately 5- to 10-fold less for NKTR-102 versus irinotecan.<sup>30</sup>

**Figure 4. Predicted Plasma SN38 Concentration-Time Profiles After Administration of 145 mg/m<sup>2</sup> NKTR-102 (solid line) or 350 mg/m<sup>2</sup> Irinotecan (broken line)**



Simulation of SN38 after irinotecan administration is based on [Xie et al., 2002](#).<sup>30</sup> Simulation of SN38 after NKTR-102 administration is based on 06-IN-IR001 derived population parameters for SN38.

Interpatient variability in SN38 clearance (CL) and volume of distribution (V) is similar to that reported for SN38 following irinotecan administration. There has been no obvious correlation of toxicity or SN38 PK parameters with age, race, gender, past or present smoking status, or baseline liver or renal function. Cumulative plasma SN38 AUC is not predictive of the occurrence of NCI-CTCAE Grade 2 or higher diarrhea. Further exploratory analyses, including assessment of toxicity based on uridine diphosphate-glucuronosyl transferase 1A1 (*UGT1A1*) status, are ongoing.

### 1.3.2 Clinical Safety

As of July 2012, a total of 397 patients across all clinical studies (completed and ongoing; single-agent and combination therapy) have received at least 1 administration of NKTR-102. Safety data from 309 patients are included in the Investigator's Brochure, version 8.0. Observations across all studies (including safety data from ongoing studies) have been generally consistent with regard to the overall safety profile of NKTR-102. Gastrointestinal toxicity, especially diarrhea, is the most common and clinically significant toxicity occurring with the use of NKTR-102. Other frequently observed AEs have been nausea, vomiting, fatigue, and dehydration (secondary to diarrhea and/or vomiting). Diarrhea and dehydration were also the most common serious adverse events (SAEs) across all studies evaluating NKTR-102. The incidence of Grade 3 diarrhea in the Phase II study in patients with metastatic breast cancer (MBC) at the recommended dose and schedule equaled 23%, with 11% Grade 3 dehydration and 6% Grade 3 vomiting (there was no Grade 4 diarrhea, dehydration or vomiting). Prolonged severe diarrhea with associated dehydration leading to pre-renal azotemia/kidney failure has been fatal in 3 patients in the ongoing Phase II studies in metastatic colorectal, ovarian, and breast cancers (one each of an ovarian cancer and breast cancer patient on the 14-day schedule; one CRC patient on the 21-day schedule). Early cholinergic toxicities (including diarrhea), commonly associated with irinotecan, has not been observed with the use of NKTR-102 in any of the completed or ongoing clinical studies. Late-onset, severe diarrhea can occur: the median

time-to-onset of Grade 3 diarrhea for NKTR-102 for the q21d schedule is 93 days (range 8 days to 107 days). Early, proactive and aggressive intervention with anti-diarrheal therapy, IV hydration, and maintenance of electrolyte balance was observed to have a significant favorable effect on the clinical course of events, as this may prevent volume depletion, electrolyte imbalances and the development of kidney failure. Myelosuppression, especially neutropenia, can occur in patients receiving NKTR-102; however, data from clinical studies evaluating NKTR-102 suggest a lower frequency and severity of neutropenia than for irinotecan. NKTR-102 administered at a dose level of 145 mg/m<sup>2</sup> in a q21d schedule overall across all ongoing Phase II studies showed an overall incidence of neutropenia of  $\leq 20\%$  (all NCI-CTCAE grades) with 11% reported as NCI-CTCAE Grade 3/4. The onset of neutropenia in the concomitant setting of severe diarrhea and dehydration with fever and infection must be carefully monitored and proactively treated as it can potentially lead to neutropenic sepsis, which may be fatal.

### 1.3.3 Clinical Efficacy

Nektar initiated its NKTR-102 clinical program with the Phase I Study 06-IN-IR001. Study 06-IN-IR001 evaluated three treatment schedules (wx3 q4wk, q21d, and q14d) in patients with refractory solid tumors. In all schedules, NKTR-102 was administered as an IV infusion over 90 minutes. NKTR-102 demonstrated anti-tumor activity in a broad spectrum of tumors (**Table 2**). Eight of the 76 patients enrolled in this study had a confirmed partial response (PR) by RECIST 1.0 (for an ORR of 11%). These responses were seen in lung cancers (SCLC and NSCLC), breast, bladder, cervix, maxillary sinus, pancreas, and colorectal cancers. Two unconfirmed responses were seen in colorectal cancer and ovarian cancer. These findings led to the initiation of a Phase II development program in colorectal cancer and in cancers not normally associated with use of irinotecan in the US, but for which preliminary evidence was seen of anti-tumor activity associated with NKTR-102 (ovarian and breast). On the basis of the results of this study, the recommended Phase II dose was initially identified as 170 mg/m<sup>2</sup> on either a q14d or q21d schedule. The dose was later revised to 145 mg/m<sup>2</sup> q14d or q21d after additional safety data related to diarrhea were received from this Phase I study and from the ongoing Phase II studies.

**Table 2. Phase I Study of NKTR-102**

	Primary Tumor	Confirmed PR	Unconfirmed PR	SD $\geq 90$ days	PR + SD
CRC	17	1	1	5	7 (41%)
NSCLC	15	1	-	3	4 (26%)
SCLC	3	1	-	1	2 (66%)
Cervix	5	1	-	-	1 (20%)
Pancreas	5	1	-	-	1 (20%)

Breast	4	1			1 (25%)
Head & Neck	3	1	-	-	1 (33%)
Bladder	1	1	-	-	1 (100%)
Ovarian	5	-	1	-	1 (20%)

\*CRC; colorectal cancer, NSCLC; non-small cell lung cancer, PR; partial response, SCLC; small cell lung cancer, SD; stable disease.

A Phase II study (Protocol 08-PIR-05) of NKTR-102 in patients with MBC evaluating two treatment regimens (145 mg/m<sup>2</sup> q14d and q21d; n = 70; 35 per treatment regimen) showed significant antitumor activity.<sup>31</sup> The study showed the following activity in the two treatment regimens combined: The ORRs in the total population was 29%, including 2 complete responders and an additional 4 patients who had complete resolution of target lesions. The ORR was maintained in patients with advanced or high-risk disease (ORR equal to 31% in patients who had received prior anthracycline, taxane, capecitabine [ATC]; ORR in patients with triple negative breast cancer [TNBC] was 39%). As of May 2011, median progression free survival (PFS) and overall survival (OS) were 4.6 months and 10.3 months, respectively; the q21d schedule had longer PFS and OS than the q14d regimen (5.3 months versus 3.5 months, and 13.1 months versus 8.8 months, respectively). Based on better tolerability, a trend towards improved OS and PFS, as well as the convenience of a less frequent dosing regimen, the q21d 145 mg/mg<sup>2</sup> treatment schedule of NKTR-102 was selected for the Phase III study.

A Phase II study (Protocol 08-PIR-04) of NKTR-102 in patients with platinum resistant ovarian cancer evaluated two treatment regimens (145 mg/m<sup>2</sup> q14d and q21d; n = 71; 36 and 35 patients per treatment regimen). Overall, NKTR-102 produced a RECIST 1.0 ORR of 23% and Gynecologic Cancer InterGroup (GCIG) response of 38% in the q21d regimen.<sup>32</sup> In those patients whose disease had progressed following both platinum (within 6 months) and liposomal doxorubicin (n = 33), ORR equaled 21%, median PFS equaled 5.4 months and OS equaled 13.9 months.<sup>33</sup> Based on these data, enrollment to the q21d regimen continued for patients with platinum resistant disease whose disease has also progressed following pegylated liposomal doxorubicin. A randomized Phase II study (Protocol 08-PIR-03) comparing single-agent NKTR-102 to single-agent irinotecan in patients with 2<sup>nd</sup>-line metastatic colorectal cancer (whose malignancy is positive for a KRAS mutation) is ongoing.

The Phase IIa study of NKTR-102 in combination with cetuximab (Protocol 07-PIR-02) is completed and the Phase I study of NKTR-102 in combination with 5-fluorouracil/leucovorin (FULPIRI) (Protocol 09-PIR-07) is in progress. See the Investigator's Brochure for additional information on these clinical trials.



## 1.4 Correlative Studies

### 1.4.1 Pharmacogenetics

The genes that have been associated with irinotecan pharmacodynamic and pharmacokinetic pathways include those responsible for activation, inactivation and transport of the drug. These genes include *ABCB1*, *ABCC2*, *ABCG2*, *BCHE*, *CES1*, *CES2*, *CYP3A4*, *CYP3A5*, *SLCO1B1*, *TOPI*, *UGT1A1*, *1A3*, *1A4*, *1A6*, *1A7*, *1A8*, *1A9* and *UGT1A10*. As NKTR-102 is a conjugate of irinotecan, most of the irinotecan pathway genes may interact with it thus resulting in similar phenotypic effects. Hence, several genetic variants associated with the pathways may contribute to the clinical outcome of NKTR-102 therapy.

Some of the well-known genetic variants that have been associated with irinotecan clinical outcomes include the polymorphic repeat in *UGT1A1* promoter region (*UGT1A1*\*28, rs8175347; *UGT1A1*\*93) and the *ABCB1* (1236C > T, 2677G > T/A, 3435C > T), *ABCC2* (-24C > T, 1249G > A, 3972C > T), and *ABCG2* (34G > A, 421C > A) polymorphisms. It is reported that nearly 50% of the variations in neutropenia among individuals could be explained by a combination of genetic polymorphisms and non-genetic covariates, with gene combinations attributing to 28% of the variations, suggesting a polygenetic basis for neutropenia.<sup>32</sup> *UGT1A1*\*28 and \*93 genotypes have been associated with toxicity; *ABCC2* 3972C > T with severe diarrhea in both Korean and European patients while *SLCO1B1*\*5 allele is reported to be associated with increased risk of severe neutropenia in Asians, and the *SLCO1B1*\*1b allele is suggested to be protective of neutropenia.<sup>32-35</sup>

This Phase II study (38 patient samples) will initially focus, in an exploratory manner, on the primary genes which will activate (*CES1*, *CES2*, *CYP3A4*, and *CYP3A5*) and inactivate (*UGT1A1*) NKTR-102. It is hypothesized that germline polymorphic variants in *CES1*, *CES2*, *CYP3A4*, *CYP3A5* and *UGT1A1* may affect toxicity as well as response to NKTR-102 therapy.

**SNP Identification:** We will generate tagSNPs from National Center for Biotechnology Information (NCBI), HapMap and/or the Genome Variation Server databases using the Caucasian SNP information for these 5 genes in addition to using SNPs previously reported in literature. These SNPs will be selected with sufficient frequency that its impact on the clinical outcome at a population level would be meaningful and have some degree of likelihood to alter the function of the gene in a biologically relevant manner. Fifty-three SNPs have been identified for genotyping.

**Genotyping:** The tagSNPs will be genotyped using the MassARRAY Compact system (Sequenom) at RPCI as previously described.<sup>36</sup> Whenever possible, the published methods and primers will be used for polymorphic variants such as *UGT1A1*\*28.

## 1.5 Risks Associated with NKTR-102

A majority of NKTR-102 related treatment-emergent adverse events (TEAEs) occurred in the system organ class (SOC) of GI disorders with diarrhea experienced most commonly by 85.5% of patients, followed closely by nausea (77.6%), fatigue (51.3%), and vomiting (48.7%). Other clinically significant NKTR-102-related TEAEs with an incidence rate > 10% included anorexia, dehydration, alopecia, electrolyte disturbances like hypokalemia and hypomagnesemia,



abdominal pain, anemia, and blurred vision, in decreasing order of frequency. Prolonged severe diarrhea with dehydration leading to pre-renal azotemia and subsequent acute renal insufficiency has been fatal in three patients in the ongoing Phase II studies in metastatic colorectal, ovarian, and breast cancers (one patient in each study). To date, early onset cholinergic diarrhea (as seen with irinotecan) has not been observed in any patient who received NKTR-102. Given the extended  $t_{1/2}$  of SN38 derived from NKTR-102 (approximately 50 days), late onset diarrhea may occur and can be life-threatening if treatment is delayed. Early, proactive, and aggressive intervention with anti-diarrheal therapy, IV hydration, and maintenance of electrolyte balance is essential to prevent volume depletion, electrolyte imbalances, and the development of kidney failure.

Myelosuppression, especially neutropenia, can occur in patients receiving NKTR-102. Neutropenia in the setting of dehydration and unresolving GI toxicities may lead to the development of life-threatening or fatal sepsis. To date across all clinical studies, three patients have died within 30 days from last dose of NKTR-102 due to potentially drug-related neutropenic sepsis or complications of neutropenic sepsis, such as septic shock.

Prior to retreatment, patients must meet minimal requirements with respect to hematopoietic function especially neutrophil count with an ANC of  $\geq 1.5 \times 10^9/L$ . Except for diarrhea (complete resolution of diarrhea to Grade 0 should be present for at least seven days without the need for anti-diarrheal medications and/or supportive care prior to retreatment with NKTR-102), all Grade 3 or higher toxicities must resolve to baseline or Grade 1 severity prior to retreatment. Supportive care may be implemented in order to ameliorate diarrhea, nausea, vomiting, anorexia, or myelosuppression. Dose reductions must also be implemented for patients who experience recurrent or specific severe toxicities as defined by the dose modification guidelines included in each protocol.

Hypersensitivity or mild allergic reactions characterized by itching, flushing, dizziness, muscle twitching, and/or temporary speech impairment have been observed in some patients. In most cases, symptoms were mild in severity and management with antihistamines and/or steroids led to successful resolution of these events. In many patients, NKTR-102 rechallenge has been successful in subsequent cycles of therapy following premedication with antihistamines and/or corticosteroids.

## **2 RATIONALE**

Small-cell lung cancer (SCLC) is one of the most aggressive and lethal cancers in humans. Although standard combination cytotoxic chemotherapy agents have shown antitumor activity with initial responses seen in 70% - 90% for both limited and extensive stages of SCLC, long-term survival is low and most patients eventually develop progressive disease within the first 2 years. Moreover, among patients who relapse, prognosis remains poor with second-line therapy (**Table 1**).

Etirinotecan pegol (NKTR-102) is a targeted, long-acting topoisomerase-I inhibitor designed to provide continuous exposure to SN38 (7-ethyl-10-hydroxycamptothecin), while reducing excessively high irinotecan and SN38 plasma concentrations associated with toxicities upon administration of irinotecan. Preclinical and clinical studies have shown that the half-life of

active drug generated from NKTR-102 is greatly extended to 50 days and that active drug remains in circulation throughout the entire chemotherapy cycle, providing sustained exposure to active metabolite of irinotecan (SN38). We propose to investigate the efficacy of NKTR-102 against relapsed or refractory small cell lung cancer.

### **3 OBJECTIVES**

#### **3.1 Primary Objective**

The primary objective of this study is to evaluate the 18-week progression free survival (PFS) rate of relapsed SCLC patients treated with NKTR-102.

#### **3.2 Secondary Objectives**

- To evaluate the objective response rate.
- To evaluate the duration of response.
- To evaluate the overall survival.
- To evaluate the toxicity of NKTR-102 in this patient population.

#### **3.3 Correlative Objective**

- To explore the correlation between UGT1A1 polymorphisms and NKTR-102 toxicities.

### **4 METHODOLOGY**

#### **4.1 Study Design**

This is a single stage Phase II study of relapsed small cell lung cancer patients who have received only one prior systemic therapy regimen. There will be 2 patient cohorts: those progressing on first-line therapy < 3 months after completion of treatment (Group A: chemo resistant) and those progressing on first-line therapy  $\geq$  3 months after completion of treatment (Group B: chemo sensitive). Eirinotecan pegol will be administered at 145 mg/m<sup>2</sup> IV once every 3 weeks. Cycles will be repeated every 21 days ( $\pm$  3 days) until disease progression. Patients who develop metastases in the central nervous system (CNS) as the only site of disease progression could receive therapeutic whole brain radiation therapy (WBRT), or gamma knife radiosurgery and after completion of WBRT continue on NKTR-102. Imaging studies are scheduled to be obtained after every other 21-day cycle.

#### **4.2 Target Accrual and Study Duration**

A maximum of 38 subjects (20 patients from Group A and 18 patients from Group B) at multiple sites, including RPCI will be enrolled. Accrual is expected to take up to 4 years. Patients will be on study for approximately 18 – 24 months.

## 5 SUBJECT SELECTION

### 5.1 Inclusion criteria

Each prospective subject must meet ALL of the following inclusion criteria in order to be eligible for this study (except where noted):

1. Written informed consent granted prior to initiation of any study-specific screening procedures, given with the understanding that the patient has the right to withdraw from the study at any time, without prejudice.
2. 18 years of age or older.
3. Histologic or cytologic diagnosis of SCLC. (Note: Patients with mixed histology are not eligible.)
4. ECOG performance status of 0 or 1 (refer to **Appendix B**).
5. Presence of measurable disease as defined in with  $\geq 1$  lesion whose longest diameter can be accurately measured as  $\geq 20$  mm with conventional techniques or as  $\geq 10$  mm with spiral CT.
6. Previously treated SCLC with only one prior treatment regimen [cyclophosphamide/doxorubicin/vincristine (CAV) alternating with etoposide/cisplatin (EP) is acceptable].
7. Resolution of all acute toxic effects of prior chemotherapy, radiotherapy, hormonal therapy, or surgery to NCI-CTCAE version 4.0 Grade  $\leq 1$ , except for diarrhea (which must be grade 0 without supportive antidiarrheal medications) and alopecia (any grade).
8. Adequate hematologic, liver, and renal function, defined as:
  - Platelet count  $\geq 100 \times 10^9/L$
  - Hgb  $\geq 9$  gm/dL
  - Absolute neutrophil count (ANC)  $\geq 1500/\mu L$
  - Serum creatinine  $\leq 1.5$  mg/dL or creatinine clearance  $> 45$  mL/min. Use either measured or calculated with Cockcroft -Gault formula (**Appendix C**)
  - Serum total bilirubin  $\leq 1.5 \times$  ULN
  - Aspartate Transaminase (AST) and alanine transaminase (ALT)  $\leq 3 \times$  ULN or  $\leq 5 \times$  ULN if caused by liver metastasis
9. Women of childbearing potential must have a negative pregnancy test performed within seven days prior to the start of study drug. Male and female subjects of child-bearing potential must agree to use double-barrier contraceptive measures, or avoidance of intercourse during the study and for 6 months after last investigational drug dose received

## 5.2 Exclusion criteria

Potential subjects who meet ANY of the following exclusion criteria are not eligible for enrollment into this study:

1. Previous anti-cancer chemotherapy, immunotherapy or investigational agents < 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to the first day of study defined treatment. Palliative radiation < 2 weeks, biological therapy within 2 weeks, hormonal therapy within 1 week prior to Day 1 Cycle 1.
2. Prior treatment with a topoisomerase-I inhibitor (e.g., topotecan, irinotecan).
3. Prior malignancy except for non-melanoma skin cancer and carcinoma in situ, unless diagnosed and definitively treated more than 5 years prior to enrollment.
4. Substance abuses, medical, psychological or social conditions that may, in the opinion of the Investigator, interfere with the patient's participation in the study or evaluation of the study results.
5. Known human immunodeficiency virus (HIV) infection due to concerns of potential drug interaction with various antiretroviral agents.
6. Pregnancy or breast-feeding.
7. Concurrent administration or received CYP3A4 inducers or inhibitors within 2 weeks prior to the first day of study drug treatment. Lists including medications and substances known or with the potential to interact with CYP3A4 are provided in **Section 7.3.7**.
8. Patients with chronic or acute GI disorders resulting in diarrhea of any severity grade; patients who are using chronic anti-diarrheal supportive care (more than 3 days/week) to control diarrhea in the 28 days prior to study entry.
9. Major surgery < 4 weeks or minor surgery (e.g. talc pleurodesis, excisional biopsy, etc) < 2 weeks prior to the first day of study defined treatment.
10. Have central nervous system (CNS) metastases (unless the patient has completed successful local therapy for CNS metastases and has been off corticosteroids for at least 4 weeks before starting study therapy). Brain imaging is required in symptomatic patients to rule out brain metastases, but is not required in asymptomatic patients.
11. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
12. Unwilling or unable to follow protocol requirements.

## 5.3 Inclusion of Women and Minorities

This study will be available to all eligible subjects, regardless of race, gender, or ethnic origin. There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment

effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

#### **5.4 Subject Withdrawal**

It is the right and the duty of the investigator or co-investigator to stop treatment in any case in which emerging effects are of unacceptable risk to the individual subject. In addition, the investigator or co-investigator is to stop treatment of any subject with unmanageable factors that may interfere significantly with the trial procedures and/or the interpretation of results.

A subject must be discontinued from treatment for any of the following reasons:

- The subject or legal representative (such as, a parent or legal guardian) withdraws consent.
- Disease progression.
- The development of unacceptable toxicity for which symptomatic treatment and/or dose reduction are not considered sufficient.
- The development of an intercurrent condition precluding further administration of the treatment.
- The investigator believes it is no longer in the best interest of the subject to receive treatment on the study.
- Pregnancy of the subject.
- Failure to comply with requirements of the study.
- Administrative reasons (e.g., termination of the study by the Principal Investigator).

### **6 INVESTIGATIONAL PRODUCT**

NKTR-102 will be provided by Nektar Therapeutics.

#### **6.1 Active Substance and Source**

The investigational drug product (NKTR-102 for Injection) is formulated as a sterile lyophilized powder of NKTR-102 in lactate buffer at pH 3.5, intended for dilution with commercially available 5% dextrose injection (w/w%; D5W) or 0.9% sodium chloride for injection before IV infusion. The pH of the formulation is in the range of 3.2 to 4.2, and NKTR-102 for Injection storage condition is 2°C to 8°C (with a shelf-life of 36 months).

NKTR-102 (drug substance) is light sensitive. The lyophilized drug product (NKTR-102 for Injection) will be supplied in 25 mL Type 1 amber colored glass vials packaged in cartons. Each carton will contain 10 vials of NKTR-102. Each vial contains lyophilized NKTR-102 equivalent to 100 mg of irinotecan. Each vial and carton will be labeled to comply with local regulations.

## 6.2 Drug Shipment

NKTR-102 will be shipped to participating sites. Each site will document the date of receipt and condition of the shipment. Drug shipment records will be retained by the investigational pharmacist or designee.

## 6.3 Reconstitution and Handling

The NKTR-102 for injection vial is for single use only. Allow vial(s) to reach room temperature (approximately 30 minutes).

Using pharmacy standard operating procedure, withdraw 20 mL of D5W from a 250 mL D5W infusion bag using sterile needle and syringe and inject into each vial of lyophilized study drug required for a given dose. The final concentration in the vial is now 5 mg/mL. **Note: Normal Saline (0.9% w/w) may also be used as diluent for reconstitution. It is not necessary to remove overfill.**

Gently invert vial for 1-5 minutes until study drug has fully dissolved. Visually inspect vial contents for particulate matter and repeat inspection when study drug is withdrawn from vial into syringe. If any particulate matter is seen, return the syringe contents to the vial and invert several more times.

If the study drug does not fully dissolve and particulates or small matter is identified in the reconstituted NKTR-102, it is recommended that the reconstituted drug in question NOT be used. Please document in the investigational drug accountability log and prepare a new dose for the patient. Please also quarantine the drug in question and contact Nektar with the following additional information:

- i. Details on how the NKTR-102 was reconstituted
- ii. What diluents were used and in what volume(s)?
- iii. How long was the drug product reconstituted for?

**Due to the high viscosity, the study drug solution in the syringe may contain trapped bubbles. This is normal.**

Inject the required volume of reconstituted study drug back into the 250 mL infusion bag. The final concentration of NKTR-102 in a 250 mL D5W or Normal Saline infusion bag must be within a range of 0.2 to 1.6 mg/mL and 0.16 to 1.6 mg/mL respectively.

Inspect the 250 mL infusion bag for particulates prior to infusion. If the particulates do not clear with gentle inversion, discard the bag, document in the investigational drug accountability log and inform Nektar.

The reconstituted drug may be stored protected from direct ambient lighting at room temperature (15°C to 30°C) for up to 6 hours prior to start of infusion. Other drugs must not be added to the infusion solution.



#### **6.4 Storage and Stability**

The Investigator or designate is responsible to store and dispense the investigational product and will ensure that study drug is securely maintained in a locked, limited-access facility, as specified by Nektar Therapeutics and in accordance with the applicable regulatory requirements.

Drug product NKTR-102 for injection and reconstituted infusion solution can be handled in normal room lighting, but should be protected from extensive exposure to light. It is not necessary to cover the IV bag and administration set with sheathing or aluminum foil.

All study drug supplies must be kept in a locked limited access room within the carton they are packaged and refrigerated at 2°C to 8°C, as specified on the drug label.

#### **6.5 Handling and Disposal**

The Investigator or designee will be responsible for dispensing and accounting for all investigational drug provided by Nektar Therapeutics exercising accepted medical and pharmaceutical practices. Study drugs must be handled as cytotoxic agents and appropriate precautions taken per the institution's environmentally safe handling procedures. All investigational drugs will be dispensed in accordance with the Investigator's prescription or written order.

All products dispensed will be recorded on a product accountability record. Records of product lot numbers and dates received will be entered on a product accountability form. This record will be reviewed by the Sponsor's staff or representative during periodic monitoring visits. It is the Investigator's responsibility to ensure that an accurate record of investigational drug issued and returned is maintained.

Used vials (excess drug), expired product, and unused vials will be destroyed according to standard practices at the site after properly accounting for the dispensing. Partially used vials of study drug will not be re-used for other subjects.

### **7 TREATMENT PLAN**

#### **7.1 Dosage and Administration**

NKTR-102 will be administered 145 mg/m<sup>2</sup> IV dose over a 90-minute period once every 3 weeks. Cycles will be repeated every 21 days ( $\pm$  3 days). The patient's actual weight at baseline (Day 1 of Cycle 1) will be used. It is not necessary to correct dosing based on ideal body weight. If the patient's weight changes by  $> 10\%$  during the course of the study, the body surface area and drug doses should be recalculated.

Treatment will be administered in an outpatient basis. Reported adverse events (AEs) and potential risks are described in Investigator's Brochure. Appropriate dose modifications are described in **Section 7.2**. No other investigational or commercial drugs or therapies other than those described below may be administered with the intent to treat the subject.

## 7.2 Dose Modification Due to Toxicity

All AEs should be assessed according to the NCI-CTCAE version 4.0. In the event of multiple toxicities, dose delays and modifications should occur in accordance with the worst toxicity observed. NKTR-102 dose modifications (reductions or delays) must be recorded for each patient in the appropriate section of the electronic case report form (eCRF).

### 7.2.1 Retreatment Criteria

To ensure safe use of NKTR-102, subjects must meet requirements with respect to hematopoietic function (Hgb  $\geq$  8.0 g/dL; ANC  $\geq$   $1.5 \times 10^9$ /L; platelets  $\geq$   $75 \times 10^9$ /L) prior to initiation of subsequent cycles. Diarrhea must be fully resolved to Grade 0 for at least 7 days without supportive antidiarrheal measures prior to retreatment. Any non-hematologic toxicities must have resolved to baseline or Grade 1 except for alopecia. Supportive care may be implemented in order to ameliorate diarrhea, nausea, vomiting, or myelosuppression. Dose reductions may also be implemented for subjects who experience recurrent or specific severe toxicities.

### 7.2.2 Treatment Delay

If the patient fails to meet the criteria for re-treatment, treatment may be delayed, followed by an additional evaluation to determine feasibility of retreatment. Initiation of subsequent doses may be delayed for a maximum of 28 days to allow recovery from any toxicity to permit retreatment. Subjects whose treatment delays are  $\geq$  14 days but  $\leq$  28 days due to a drug-related toxicity must initiate their next treatment cycle with a dose reduction. Subjects who require  $>$  28 days delay due to unresolved toxicity must be withdrawn from treatment, unless, in the Investigator's opinion, continuing in the study is of benefit for the patient. In this case, the reason of continuation must be documented.

### 7.2.3 Dose Reductions

NKTR-102 doses for an individual patient may be reduced 25 mg/m<sup>2</sup> based on conditions listed in the **Table 3** below. Only 2 dose reductions are permitted. Subjects should be discontinued from the study treatment if toxicity requires a dose reduction beyond the 2 dose reduction steps. Dose re-escalation for NKTR-102 is not permitted.

**Table 3. Dose Modifications Based on Toxicities**

Toxicity NCI CTCAE Grade	During a Cycle: Recommended Guidelines for Management and Supportive Care	Day 1 of New Cycle: Dose Modifications Based on Worst Toxicity in Prior Cycle
<b>Thrombocytopenia / Anemia / Neutropenia / Febrile Neutropenia</b>		
<b>Grade 1 or Grade 2</b>	-	Maintain dose level



<b>Grade 3</b>	<p><u>Platelets</u>: consider platelet transfusion if active bleeding.</p> <p><u>ANC</u>: consider growth factor support in accordance with local guidelines.</p> <p><u>Hgb</u>: erythropoietin-stimulating agents or transfusion as appropriate.</p> <p>If present on a treatment day, hold therapy for a week or until toxicity resolves to Hgb <math>\geq 8</math> g/dL or 80 g/L; ANC <math>\geq 1.5 \times 10^9/L</math>; platelets <math>\geq 75 \times 10^9/L</math>, with a maximum of 28 days.</p>	<p>↓ 1 dose level after 1<sup>st</sup> occurrence.</p> <p>↓ 1 dose level after 2<sup>nd</sup> occurrence.</p> <p>Discontinue patient after 3<sup>rd</sup> occurrence.</p>
<b>Grade 4</b>	<p><u>Platelets</u>: consider platelet transfusion if platelets <math>&lt; 20K</math> or with active bleeding.</p> <p><u>ANC</u>: consider growth factor support in accordance with local guidelines.</p> <p>Antibiotic (Fluoroquinolones) should be initiated even in the absence of fever or diarrhea.</p> <p><u>Hgb</u>: consider erythropoietin-stimulating agents or transfusion as appropriate.</p> <p>If present on a treatment day, hold therapy for a week or until toxicity resolves to Hgb <math>\geq 8</math> g/dL or 80 g/L; ANC <math>\geq 1.5 \times 10^9/L</math>; platelets <math>\geq 75 \times 10^9/L</math>, with a maximum of 28 days.</p>	<p>↓ 1 dose level after 1<sup>st</sup> occurrence.</p> <p>↓ 1 dose level after 2<sup>nd</sup> occurrence.</p> <p>Discontinue patient after 3<sup>rd</sup> occurrence.</p>
<b>Febrile Neutropenia</b>	<p>Subjects should be hospitalized immediately for IV antibiotic therapy if they develop neutropenic fever or sepsis (e.g., growth factor support; antibiotics); consider hospital admission.</p>	<p>↓ 1 dose level after 1<sup>st</sup> occurrence.</p> <p>↓ 1 dose level after 2<sup>nd</sup> occurrence.</p> <p>Discontinue patient after 3<sup>rd</sup> occurrence.</p>

<b>Diarrhea Any Grade</b>	<p>Institute supportive care upon first loose stool. (Unless contraindicated, use loperamide). Monitor bowel function; if diarrhea continues with 1<sup>st</sup> supportive care agent, consider switching to a 2<sup>nd</sup> agent or add a 2<sup>nd</sup> agent (unless contraindicated, use diphenoxylate/atropine).</p> <p>Monitor for dehydration, electrolyte abnormalities; correct if present.</p> <p>Administer antibiotic therapy (oral fluoroquinolones) if the patient develops ileus, fevers or Grade 3/4 neutropenia.</p> <p>Subjects should be immediately hospitalized for IV antibiotics therapy if they have evidence of colitis or ileus even in the absence of neutropenia or fever.</p> <p>If worsening diarrhea, octreotide may be attempted.</p> <p>Monitor bowel function for continued need of supportive care.</p> <p>Stop supportive care after the patient is 48 hour without diarrhea.</p>	<p>Confirm with the patient that diarrhea is no longer present for <math>\geq 7</math> days without having received supportive care prior to retreatment.</p> <p>Treatment may be delayed up to 28 days; after this, contact Medical Monitor.</p>
<b>Grade 1</b>	If still present within 7 days prior to treatment hold therapy until diarrhea is no longer present for $\geq 7$ days without having received supportive care.	Maintain dose level; consider prophylactic anti-diarrheal supportive care
<b>Grade 2</b>	If still present within 7 days prior to treatment hold therapy until diarrhea is no longer present for $\geq 7$ days without having received supportive care.	<p>↓ 1 dose level after 1st occurrence.</p> <p>↓ 1 dose level after 2nd occurrence.</p> <p>Discontinue patient after 3rd occurrence.</p>
<b>Grade 3/4</b>	If still present within 7 days prior to treatment hold therapy until diarrhea is no longer present for $\geq 7$ days without having received supportive care.	<p>↓ 2 dose level after 1st occurrence.</p> <p>Provided that adequate supportive care has been given to the patient, discontinue patient after 2nd occurrence. If the patient has not received adequate supportive care, retreatment may be attempted for a 2<sup>nd</sup> episode of Grade 3 diarrhea (re-instruct patient on supportive care).</p> <p>Patients must be discontinued for a 2<sup>nd</sup> episode of Grade 4 diarrhea.</p>

<b>Dehydration</b>		
<b>Grade 1 or Grade 2</b>	Consider anti-emetic and/or anti-diarrheal therapy. If Grade 2 present on a treatment day, hold therapy for a week or until toxicity resolves to baseline or Grade $\leq$ 1, with a maximum of 28 days.	Consider prophylactic anti-emetic therapy. Maintain dose level.
<b>Grade 3</b>	Use anti-emetic and/or anti-diarrheal therapy. If present on a treatment day, hold therapy for a week or until toxicity resolves to baseline or Grade $\leq$ 1, with a maximum of 28 days.	Consider prophylactic anti-emetic therapy. ↓ 1 dose level after 1st occurrence; ↓ 1 dose level after 2nd occurrence Discontinue patient after 3rd occurrence
<b>Grade 4</b>	Use anti-emetic therapy and IV fluids. Consider hospital admission. If present on a treatment day, hold therapy for a week or until toxicity resolves to baseline or Grade $\leq$ 1, with a maximum of 28 days.	Use prophylactic anti-emetic therapy. ↓ 2 dose level after 1st occurrence. Discontinue patient after 2nd occurrence.
<b>Nausea / Vomiting / Abdominal Pain</b>		
<b>Grade 1 or Grade 2</b>	Consider anti-emetic therapy. If Grade 2 present on a treatment day, hold therapy for a week or until toxicity resolves to baseline or Grade $\leq$ 1, with a maximum of 28 days.	Consider prophylactic anti-emetic therapy. Maintain dose level.
<b>Grade 3 or Grade 4</b>	Use anti-emetic therapy. Consider administration of IV fluids. If present on a treatment day, hold therapy for a week or until toxicity resolves to baseline or Grade $\leq$ 1, with a maximum of 28 days.	After 1st occurrence use prophylactic anti-emetic therapy and maintain dose level ↓ 1 dose level after 2nd occurrence Discontinue patient after 3rd occurrence
<b>Other Drug-Related Non-Hematologic Toxicities (Except Fatigue/Asthenia and Alopecia)</b>		
<b>Grade 1 or Grade 2</b>	Consider supportive care as appropriate. If Grade 2 present on a treatment day, hold therapy for a week or until toxicity resolves to baseline or Grade $\leq$ 1, with a maximum of 28 days.	Maintain dose level (for Grade 2 toxicity, the Investigator may use discretion to ↓ 1 dose level after 1 <sup>st</sup> occurrence depending on the nature of the toxicity).
<b>Grade 3 or Grade 4</b>	Use supportive care as appropriate. If present on a treatment day, hold therapy for a week or until toxicity resolves to baseline or Grade $\leq$ 1, with a maximum of 28 days.	↓ 1 dose level after 1 <sup>st</sup> occurrence; supportive care as appropriate. ↓ 1 dose level after 2 <sup>nd</sup> occurrence. Discontinue patient after 3 <sup>rd</sup> occurrence.

### **7.3 Concomitant Medication and Supportive Care**

#### **7.3.1 Anti-Emetic Therapy**

Prophylactic anti-emetics will be allowed according to standard practices.

Based on investigator discretion, an investigator may prescribe prophylactic antiemetics prior to the first dose of the study drugs. The patient must be carefully monitored throughout the study period, and given adequate fluid and electrolyte replacement to prevent dehydration and electrolyte imbalance. Dexamethasone, ondansetron, lorazepam or prochlorperazine can be given at the discretion of the treating physician.

#### **7.3.2 Anti-Diarrheal Therapy**

Severe diarrhea can occur without any evidence of significant GI toxicity observed in preceding courses of treatment with NKTR-102. Exposure to SN38, the active metabolite of NKTR-102, is a function of dose, schedule, and each patient's capacity to metabolize and eliminate NKTR-102 and SN38. Given the extended  $t_{1/2}$  of SN38 derived from NKTR-102 (approximately 50 days), late onset diarrhea may occur and can be life threatening if treatment is not delayed. Early proactive and aggressive intervention with anti-diarrheal therapy, IV hydration, and maintenance of electrolyte balance is essential to prevent volume depletion, electrolyte imbalances, and the development of kidney failure.

Prophylactic antidiarrheal medications should not be used, as they can confound the evaluation of recovery to Grade 0 and monitoring of diarrhea associated with NKTR-102. Use of antidiarrheal medications for the treatment of diarrhea or loose stool is mandatory.

Guidelines for the treatment of diarrhea include:

1. Each patient must be instructed to immediately begin taking loperamide at the very first episode of poorly formed or loose stools or the earliest onset of bowel movements that are more frequent than normally expected for the patient.
2. One dosage regimen for loperamide used in clinical trials consisted of the following: 4 mg at the first onset of diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. Loperamide is not recommended to be used for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus. During the night, the patient may take 4 mg of loperamide every 4 hours.
3. The use of concomitant drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients must be advised to contact their physician to discuss any laxative use.
4. Patients must be instructed to contact their physician or nurse if any of the following occur: diarrhea for the first time during study drug treatment; black or bloody stools; symptoms of dehydration such as excessive thirst, dry lips and mouth, lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; inability to get diarrhea under control within 24 hours; or fever or evidence of infection.

5. Patients who are dehydrated must promptly receive adequate IV fluids, electrolytes to combat electrolyte imbalance if present and antibiotics in case of fever. Serial complete and differential blood counts must be done for early identification of the concomitant occurrence of neutropenia.

### **7.3.3 Platelet Transfusion**

Patients may receive transfusions (platelets or blood products) at the Investigator's discretion. If platelet count  $< 20,000/\text{mm}^3$ , 1 unit single-donor apheresis platelet transfusion may be given. A post-transfusion platelet count should be collected at 15 minutes post-transfusion to demonstrate increment.

### **7.3.4 Growth Factor Use**

Prophylactic use of growth factor support is not permitted, however use of growth factor support in a setting of neutropenia is permitted. Use of growth factor support must follow American Society Clinical Oncology (ASCO), ESMO guidelines or standard of care at the local institution. If a patient required growth factor support during a previous cycle, a patient may be administered prophylactic growth factor support during a subsequent cycle at the investigator's discretion.

### **7.3.5 Other Antineoplastic Therapy**

The administration of other antineoplastic therapy (e.g., chemotherapy, hormone therapy, immunotherapy, targeted therapy, monoclonal antibodies and radiation therapy) is not permitted. Patients requiring radiation therapy after the start of the study are considered as having progression of disease and must discontinue study treatment.

### **7.3.6 Bisphosphonates and Denosumab**

Patients may continue or start Bisphosphonates and Denosumab if required during the study.

### **7.3.7 Medications NOT ALLOWED During Study (*P450 inhibitors/inducers*)**

Because there is a potential for interaction of drug with other concomitantly administered drugs through the cytochrome P450 system, the electronic case report form (eCRF) must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Investigator should be alerted if the subject is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

In vitro drug interaction studies of NKTR-102 with cytochrome P450 3A4 enzyme (CYP3A4) have not been done. However, drug interactions have been documented between CYP3A4 enzymes and irinotecan and are listed in the Camptosar® USPI August 2010. Please refer to the Camptosar® package insert for further information.

**St. John's Wort:** St. John's Wort is an inducer of CYP3A4 enzymes. Exposure to the active metabolite SN-38 is reduced in patients receiving concomitant St. John's Wort. St. John's Wort should be discontinued at least 2 weeks prior to the first cycle of irinotecan, and St. John's Wort is contraindicated during irinotecan therapy.

***Anticonvulsants:*** Exposure to irinotecan and its active metabolite SN-38 is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin, phenobarbital or carbamazepine. The appropriate starting dose for patients taking these anticonvulsants has not been formally defined. The following drugs are also CYP3A4 inducers: rifampin, rifabutin. For patients requiring anticonvulsant treatment, consideration should be given to substituting non-enzyme inducing anticonvulsants at least 2 weeks prior to initiation of NKTR-102 therapy. Dexamethasone does not appear to alter the pharmacokinetics of irinotecan.

***Ketoconazole:*** Ketoconazole is a strong inhibitor of CYP3A4 enzymes. Patients receiving concomitant ketoconazole have increased exposure to irinotecan and its active metabolite SN-38. Patients should discontinue ketoconazole at least 1 week prior to starting irinotecan therapy and ketoconazole is contraindicated during irinotecan therapy.

***Neuromuscular blocking agents:*** Interaction between irinotecan and neuromuscular blocking agents cannot be ruled out. Irinotecan has anticholinesterase activity, which may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarizing drugs may be antagonized.

***Atazanavir sulfate:*** Coadministration of atazanavir sulfate, a CYP3A4 and UGT1A1 inhibitor has the potential to increase systemic exposure to SN-38, the active metabolite of irinotecan.

The Principal Investigator should be contacted with any questions related to concomitant medications (from 4 weeks prior to the first dose of NKTR-102 through 4 weeks after the last dose of NKTR-102).

#### **7.4 Duration of Treatment**

Subjects may remain on study treatment in the absence of disease progression, unacceptable toxicity, and withdrawal from study or study termination. Patients who develop metastases in the central nervous system (CNS) as the only site of disease progression could receive therapeutic whole brain radiation therapy (WBRT), or gamma knife radiosurgery and after completion of WBRT continue on NKTR-102. Imaging studies are scheduled to be obtained after every other 21-day cycle.

#### **7.5 Treatment Discontinuation**

Upon treatment discontinuation all end of treatment evaluations and tests will be conducted. All subjects who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the subject's medical records and the appropriate eCRF.

Reasons for treatment discontinuation should be classified as follows:

- Death
- Progressive disease
- Treatment-related toxicity

- Toxicity unrelated to treatment
- Noncompliance
- Investigator judgment
  - The Investigator may withdraw a subject if, in his/her judgment, it is in the subject's best interest to do so.
- Subject voluntary withdrawal
  - A subject may withdraw from the study at any time, for any reason. If a subject discontinues treatment, an attempt should be made to obtain information regarding the reason for withdrawal.

Subjects who are unavailable for follow-up evaluations should be classified as lost to follow-up for 1 of the following reasons:

- Lost to follow-up: For a subject to be considered lost to follow-up, the investigator must make 2 attempts to re-establish contact with the subject. The attempts to re-establish subject contact must be documented (e.g., certified letter).
- Death: Date and cause of death will be recorded for those subjects who die within 30 days after last dose of study drug (telephone contact is acceptable).

## **7.6 Compliance**

On Day 1 of each treatment cycle, study-treatment administration will be documented on the eCRF. Any deviations from the protocol-specified study drug administration will be documented, including the date and reason for each dosing noncompliance.

## **7.7 Subject Randomization and Registration**

This is a non-randomized study. Patients will be categorized into two groups depending on their prior response to treatment. Group A (chemoresistant group) includes patients progressing < 3 months after first-line therapy and Group B (chemosensitive group) includes patients progressing  $\geq$  3 months after first-line therapy.

## **7.8 Baseline Evaluations**

The following will be performed  $\leq$  14 days prior to initiation study drug:

- Informed consent: Must be completed prior to receiving any study-related procedures.
- Medical history (Full history)
- Physical examination, including vital signs, body weight, and height
- ECOG performance status
- Adverse events evaluation



- Tumor assessment by CT/PET or CT scan should be performed within 28 days prior to initiation of study drug
- CT scan/MRI brain (brain imaging is required in symptomatic patients to rule out brain metastases, but not required in asymptomatic patients)
- Pregnancy test (urine or serum) in females of childbearing potential. Must be done  $\leq 7$  days prior to initiation of study drug.
- Coagulation (INR, PTT)
- Hematology (4 hour fasting) (i.e., complete blood count (CBC) with automated differentials or the physician discretion; WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, %neutrophils, absolute neutrophils, %lymphocytes, absolute lymphocytes, %monocytes, absolute monocytes, %eosinophils, absolute eosinophils, %basophils, absolute basophils, %Large Unspecified Cells (LUC), %lymphocyte total, absolute lymphocyte total, platelet confirmation, and differential confirmation)
- Chemistry (4 hour fasting) (i.e., complete metabolic panel (CMP): chloride, CO<sub>2</sub>, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap
- 12-Lead ECG. The patient will be asked to lie down and rest for about 10 minutes before this procedure.

### **7.9 Evaluations Performed on Cycle 1 Day 1**

- Medical history (Updated from previous clinical visit)
- Physical examination, including vital signs and body weight
- ECOG performance status
- Adverse events evaluation
- Hematology (4 hour fasting) (i.e., complete blood count (CBC) with automated differentials or the physician discretion; WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, %neutrophils, absolute neutrophils, %lymphocytes, absolute lymphocytes, %monocytes, absolute monocytes, %eosinophils, absolute eosinophils, %basophils, absolute basophils, %Large Unspecified Cells (LUC), %lymphocyte total, absolute lymphocyte total, platelet confirmation, and differential confirmation)
- Chemistry (4 hour fasting) (i.e., complete metabolic panel (CMP): chloride, CO<sub>2</sub>, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap
- Pharmacogenetic blood sample



**7.10 Evaluations Performed Weekly for Cycle 1**

- Medical history (Updated from previous clinical visit)
- Physical examination, including vital signs and body weight
- ECOG performance status
- Adverse events evaluation
- Hematology (4 hour fasting) (i.e., complete blood count (CBC) with automated differentials or the physician discretion; WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, %neutrophils, absolute neutrophils, %lymphocytes, absolute lymphocytes, %monocytes, absolute monocytes, %eosinophils, absolute eosinophils, %basophils, absolute basophils, % Large Unspecified Cells (LUC), %lymphocyte total, absolute lymphocyte total, platelet confirmation, and differential confirmation)
- Chemistry (4 hour fasting) (i.e., complete metabolic panel (CMP): chloride, CO<sub>2</sub>, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap)

**7.11 Evaluations Performed Prior to Treatment on Day 1 of Subsequent Cycles**

- Medical history (Updated from previous clinical visit)
- Physical examination, including vital signs and body weight
- ECOG performance status
- Adverse events evaluation
- Hematology (4 hour fasting) (i.e., complete blood count (CBC) with automated differentials or the physician discretion; WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, %neutrophils, absolute neutrophils, %lymphocytes, absolute lymphocytes, %monocytes, absolute monocytes, %eosinophils, absolute eosinophils, %basophils, absolute basophils, %Large Unspecified Cells (LUC), %lymphocyte total, absolute lymphocyte total, platelet confirmation, and differential confirmation)
- Chemistry (4 hour fasting) (i.e., complete metabolic panel (CMP): chloride, CO<sub>2</sub>, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap)
- 12-Lead ECG (prior to Cycle 2 and Cycle 3, if clinically indicated). The patient will be asked to lie down and rest for about 10 minutes before this procedure.
- Radiological assessments (same method as baseline) to be performed every other cycle after completing Cycle 2. Confirmation of objective tumor responses should be performed consistent with RECIST 1.1.

**7.12 Evaluations Performed at 30 Day Follow-Up**

- Medical history (Updated from previous clinical visit)
- Physical examination, including vital signs and body weight
- ECOG performance status
- Adverse events evaluation
- Hematology (4 hour fasting) (i.e., complete blood count (CBC) with automated differentials or the physician discretion; WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, %neutrophils, absolute neutrophils, %lymphocytes, absolute lymphocytes, %monocytes, absolute monocytes, %eosinophils, absolute eosinophils, %basophils, absolute basophils, %Large Unspecified Cells (LUC), %lymphocyte total, absolute lymphocyte total, platelet confirmation, and differential confirmation)
- Chemistry (4 hour fasting) (i.e., complete metabolic panel (CMP): chloride, CO<sub>2</sub>, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap

**7.13 Survival Follow-up**

- Patients will also be followed for survival every 3 months following the 30 day follow-up visit. Survival follow-up assessments may be collected via telephone.

**7.14 Schedule of Procedures and Observations**

The schedule of procedures and observations for this study is summarized in **Table 4** below.

**Table 4. Schedule of Procedures and Observations**

Tests and Procedures	Screening (≤ 14 Days Prior to Initiation of Study Drug)	Cycle 1		Prior to treatment on Day 1 of Subsequent Cycles (± 3 days)	30 Day Follow- Up (± 7 days)	Survival Follow- Up
		Day 1	Weekly <sup>1</sup> (± 2 days)			
Informed Consent	X					
Medical History	X <sup>2</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	
Physical Exam, (including vital signs, body weight, height) <sup>4</sup>	X	X	X	X	X	
ECOG Performance Status	X	X	X	X	X	
Adverse Event Evaluation	X	X <sup>5</sup>	X	X	X	
Tumor Assessment	X <sup>6</sup>			X <sup>7</sup>		
CT Scan/MRI Brain	X <sup>8</sup>					

Tests and Procedures	Screening (≤ 14 Days Prior to Initiation of Study Drug)	Cycle 1		Prior to treatment on Day 1 of Subsequent Cycles (± 3 days)	30 Day Follow- Up (± 7 days)	Survival Follow- Up
		Day 1	Weekly <sup>1</sup> (± 2 days)			
Pregnancy Test (urine or serum)	X <sup>9</sup>					
Coagulation (INR, PTT)	X					
Hematology (4 hour fasting) <sup>10</sup>	X	X	X	X	X	
Chemistry (4 hour fasting) <sup>11</sup>	X	X	X	X	X	
Pharmacogenetic Blood Sample		X <sup>12</sup>				
12-Lead ECG <sup>13</sup>	X			X <sup>14</sup>		
Survival Follow-Up						X <sup>15</sup>

- 1 Patients will be evaluated weekly during Cycle 1 only. Complete physical examination is not mandatory but will be performed as needed at the discretion of the treating physician.
- 2 Full medical history.
- 3 Updated medical history from previous clinical visit.
- 4 Height collected at baseline only.
- 5 Reassess the patient for adverse events just prior to administration of the first dose of study drug on Day 1 Cycle 1. (Reassess adverse events on Day 1 of subsequent cycles and modify dose if necessary according to the dose modification **Table 3**, if clinically indicated, for Grade 2 or higher adverse events).
- 6 Imaging studies such as chest x-ray, CT scans, PET-CT, and MRIs can be performed ≤ 28 days prior to initiation of study drug. Use same imaging throughout the study. Assessment by physical exam should be done ≤ 14 days prior to initiation of study drug. If using PET-CT, use the CT portion to obtain measurements.
- 7 Tumor assessment must be performed at least every other cycle after completing Cycle 2. Tumor assessment may be performed ± 3 days prior to treatment on Day 1 of subsequent cycles. Tumor assessment should be performed at any time during the treatment cycle that disease progression is clinically suspected so that patient can go off treatment and receive other therapy. If PET-CT was used at baseline, CT only may be used for subsequent cycles.
- 8 Brain imaging is required in symptomatic patients to rule out brain metastases, but is not required in asymptomatic patients.
- 9 Women of childbearing potential only. Must be done ≤ 7 days prior to initiation of study drug.
- 10 Hematology (i.e., complete blood count (CBC) with automated differentials or the physician discretion; WBC, RBC, HGB, HCT, platelet, MCV, MCH, MCHC, %neutrophils, absolute neutrophils, %lymphocytes, absolute lymphocytes, %monocytes, absolute monocytes, %eosinophils, absolute eosinophils, %basophils, absolute basophils, %Large Unspecified Cells (LUC), %lymphocyte total, absolute lymphocyte total, platelet confirmation, and differential confirmation).
- 11 Chemistry (i.e., complete metabolic panel (CMP): chloride, CO<sub>2</sub>, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap).
- 12 Pharmacogenetic blood sample collection will be obtained at Day 1 of Cycle 1.
- 13 The patient will be asked to lie down and rest for about 10 minutes before this procedure.
- 14 Prior to Cycle 2 and Cycle 3, if clinically indicated.
- 15 Survival follow-up assessments may be collected via telephone.

## **7.15 Pharmacogenetics**

### **7.15.1 Blood Sample Collection and Processing**

Peripheral blood will be collected from enrolled patients at C1 D1 into (1) 10 mL EDTA lavender top tube. Genomic DNA will be extracted from the blood samples, using the QIAamp DNA isolation kit from Qiagen (Valencia, CA) and following the manufacturer's instructions.

### **7.15.2 Sample Handling and Shipment**

Whole blood samples collected at RPCI will be sent on ice for processing the same day of collection.

Whole blood samples collected at participating sites will be frozen and stored at -70° until batched shipped monthly Monday - Thursday. Do not ship specimens on Fridays or on day before a holiday. Packaging should be clearly labelled as follows with e-mail notification:

Roswell Park Cancer Institute  
Grace Cancer Drug Center (GCDC) Room 151  
Attn: Mateusz Opyrchal – I 225612  
Elm & Carlton Streets  
Buffalo, New York 14263  
716-845-4695  
[Mateusz.Opyrchal@RoswellPark.org](mailto:Mateusz.Opyrchal@RoswellPark.org)

## **8 EFFICACY EVALUATIONS**

### **8.1 Objective Tumor Response**

All protocol-defined imaging studies must be performed at the investigative site or sponsor-approved facility using protocol-defined parameters. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. RECIST 1.1 will be used to assess objective tumor response.

### **8.2 Target Lesions**

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, will be identified as target lesions and recorded and measured at baseline. Target lesions will be selected on the basis of their size. Lesions with the longest diameter (short axis for lymph nodes) and are  $\geq 10$  mm (CT and MRI),  $\geq 15$  mm lymph nodes,  $> 20$  mm CXR and are for accurate repetitive measurements (either by imaging techniques or clinically) will be chosen. A sum of the longest diameter (short axis for lymph nodes) of all target lesions will be calculated and reported as the baseline sum diameters. This will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

- **Complete Response (CR):** Disappearance of all target lesions. Any lymph nodes must have a reduction in short axis to  $< 10$  mm. Changes in tumor measurements must be confirmed by repeat studies performed no less than 6 weeks after the criteria for response are first met.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. Changes in tumor measurements must be confirmed by repeat studies performed no less than 6 weeks after the criteria for response are first met.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as references the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameter while on study. Subjects having a documented response with no confirmation of the response will be listed with stable disease.

### 8.3 Non-Target Lesions

All other small lesions (longest diameter  $< 10$  mm or lymph nodes  $\geq 10$  mm to  $< 15$  mm short axis) and non-measurable lesions (i.e., leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, blastic bone lesions, or abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by imaging) should be identified as non-target lesions and indicated as present in the source documents at baseline. The general location will also be documented on the images drawing a regularly-shaped Region of Interest. Measurements of the non-target lesions will not be performed, but the presence or absence of each should be noted throughout follow-up and evaluation.

- **Complete Response:** Disappearance of all non-target lesions and normalization of tumor marker level, if applicable. All lymph nodes must be non-pathological in size ( $< 10$  mm short axis).
- **Non-Complete Response/Non-Progressive Disease:** Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the upper limits of normal.
- **Progressive Disease:** Appearance of 1 or more new lesions or the unequivocal progression of existing non-target lesions. Although a clear progression of non-target lesions is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed at a later time.

### 8.4 Evaluation of Response

Time point response assessments will be performed every other cycle (timed to coincide with the end of a cycle) with a confirmatory assessment (required for non-randomized trials) no less than

4 weeks after a PR or CR is deemed. To determine time point response, refer to **Table 5** and **Table 6**.

**Table 5. Time Point Response Criteria (+/- non-target disease)**

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

**Table 6. Time Point Response Criteria (non-target disease only)**

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD <sup>1</sup>
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

1 Non-CR/non-PD is preferred over SD for non-target disease since SD is used as endpoint for assessment of efficacy in trials so to assign this category when no lesions can be measured is not advised.

The best overall response is the best response recorded from the start of study treatment until progression or death or discontinuation for any reason (the end of treatment taking into account any requirement for confirmation). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria and will be determined by combining the subject's status of target lesions, non-target lesions, and new lesions.

- **Symptomatic Deterioration:** Subjects with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time, and not related to study treatment or other medical conditions should be reported as progressive disease due to "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment due to symptomatic deterioration. Symptomatic deterioration that may lead to discontinuation of treatment include, but is not limited to, symptoms such as:

- Weight loss > 10% of body weight.



- Worsening of disease-related symptoms (e.g., worsening dyspnea, increasing pain/increasing requirement for narcotic analgesics).
- Decline in performance status of  $> 1$  level on ECOG scale.

### 8.5 Confirmation Measurement

The main goal of confirmation of objective response in clinical trials is to avoid overestimating the response rate observed. This aspect of response evaluation is particularly important in nonrandomized trials where response is the primary endpoint. In this setting, to be assigned a status of partial response or complete response, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than 6 – 8 weeks).

### 8.6 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- **Clinical Lesions:** Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and  $\geq 10$  mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- **Chest x-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond

the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- **PET-CT:** At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.
- **Ultrasound:** Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
- **Endoscopy, Laparoscopy:** The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- **Tumor Markers:** Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
- **Cytology, Histology:** These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

- **FDG-PET:** While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG PET imaging can be identified according to the following algorithm:
- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.



- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

## **9 SAFETY EVALUATION**

### **9.1 Adverse Events**

#### **9.1.1 Definition**

An adverse event or adverse experience (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite').

An AE is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan in other study-related documents.

##### **9.1.1.1 Diagnosis Versus Signs and Symptoms**

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

### **9.1.1.2 Adverse Events Occurring Secondary to Other Events**

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

### **9.1.1.3 Abnormal Laboratory Values**

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7 mEq/L should be recorded as “hyperkalemia”

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

### **9.1.1.4 Preexisting Medical Conditions (Baseline Signs and Symptoms)**

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

## **9.1.2 Grading and Relationship to Drug**

The descriptions and grading scales found in the CTEP Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 4 of the CTCAE is identified and located at: [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). AEs not covered by specific terminology listed should be reported with common medical terminology, and documented according to the grading scales provided in the CTCAE Version 4.

The relationship of event to study drug will be documented by the Investigator as follows:

- **Unrelated:** The event is clearly related to other factors such as the patient's clinical state, other therapeutic interventions or concomitant drugs administered to the patient.
- **Unlikely:** The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the patient's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible:** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the patient's clinical state, other therapeutic interventions or concomitant drugs.
- **Probable:** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the patient's clinical state, therapeutic interventions or concomitant drugs.
- **Definite:** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the patient's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

### 9.1.3 Reporting Adverse Events

**Table 7. Guidelines for Routine Adverse Event Reporting for Phase II Studies (Regardless of Expectedness)**

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated			X	X
Unlikely			X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

- Routine AEs occurring between the start date of intervention until 30 days after the last intervention or until the event has resolved, the study patient is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

## 9.2 Serious Adverse Events

### 9.2.1 Definition

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in **ANY** of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a patient or patient, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does **NOT** include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours).
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

### 9.2.2 Reporting Serious Adverse Events

All new SAEs occurring from the date the patient signs the study consent until 30 days after the last intervention or a new treatment is started, whichever comes first, will be reported. The RPCI SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 30 day follow up period that the investigator determines to be possibly, probably or definitely related to the study intervention should be reported.

SAEs identified as an Unanticipated Problem by the Investigator must be reported. Please refer to [Section 9.5.2](#) for details on reporting Unanticipated Problems.

### 9.3 Investigator Reporting: Notifying Nektar Therapeutics

Nektar is to be notified within 24 hours of first knowledge of the investigator of all life-threatening adverse events and life-threatening suspected adverse reactions, serious adverse events and serious suspected adverse reactions and unexpected adverse events and unexpected suspected adverse reactions whether or not considered related to study treatment. To report such events, an FDA MEDWATCH form (whether initial or follow-up) must be completed by the investigator and transmitted to Nektar by fax. In addition, once each calendar quarter, the investigator must also provide a list of all adverse events observed during the study to Nektar. Network sites will notify Nektar directly (see **Appendix A**).

Nektar Drug Safety Department

Primary Fax: 1-85-482-7233

Backup Fax: 1-415-482-5410

In case of fax difficulties or questions regarding reporting SAEs please contact:

Email: [Pharmacovigilance@nektar.com](mailto:Pharmacovigilance@nektar.com)

General Telephone: 415-482-2300

Nektar Medical Contact

Mary Tagliaferri, M.D.

Nektar Therapeutics

455 Mission Bay Boulevard South  
San Francisco, California 94158 USA

Office Phone: 415-482-5416

Cell Phone: 415-480-9100

#### 9.3.1 E-Mail: [mtagliaferri@nektar.com](mailto:mtagliaferri@nektar.com) Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study patient is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

### 9.4 Unanticipated Problems

#### 9.4.1 Definition

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
  - The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of subject privacy or confidentiality of data.
  - The characteristics of the patient population being studied.

- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed **Serious** per **Section 9.2**.

#### **9.4.2 Reporting Unanticipated Problems**

Unanticipated problem reporting will begin at the time of participant consent. The Unanticipated Problem Form will be submitted to the CRS Compliance Office within 1 business day of becoming aware of the Unanticipated Problem.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS Compliance with an updated Unanticipated Problem Form. The site Investigator or designated research personnel will report all unanticipated problems, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**.

Network sites please see **Appendix A** for reporting instructions.

#### **9.5 FDA Reporting**

When RPCI is the IND holder the following describes the FDA reporting requirements by timeline for AEs and new safety findings that meet the criteria outlined below:

##### **Within 7 Calendar Days**

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Fatal or life-threatening.

##### **Within 15 Calendar Days**

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Serious but not fatal or life-threatening.

Or, meets **ANY** of the following criteria:

- A previous adverse event that is not initially deemed reportable but is later found to fit the criteria for reporting (report within 15 days from when event was deemed reportable).
- Any findings from other studies, including epidemiological studies, pooled analysis of multiple studies, or other clinical studies conducted with the study drug that suggest a significant risk in humans exposed to the drug.
- Any findings from animal or in vitro testing that suggest a significant risk for human patients including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.
- Any clinically important increase in the rate of occurrence of a serious, related or possibly related adverse event over that listed in the protocol or investigator brochure.

Sponsors are also required to identify in IND safety reports, all previous reports concerning similar adverse events and to analyze the significance of the current event in the light of the previous reports.

### **Reporting Process**

The principal investigator or designee will complete and submit a FDA Form 3500A Medwatch for any event that meets the above criteria. Forms will be submitted to the CRS Compliance Office email to: [CRSCompliance@RoswellPark.org](mailto:CRSCompliance@RoswellPark.org).

## **10 DATA AND SAFETY MONITORING**

This study will be reviewed at the scheduled RPCI data and safety monitoring committee meetings and the minutes are forwarded to the IRB for review.

## **11 STATISTICAL METHODOLOGY**

### **11.1 Sample Size Determination and Analysis**

In a Phase II and Phase III study of single agent topotecan or single agent irinotecan as shown in **Table 1** in recurrent SCLC, the median time to progression of the arms were 2.2 - 4 months.<sup>6,8-12</sup> Based on this, the primary endpoint of this trial will be the proportion of patients who are progression-free at 18 weeks. Progression-free survival was chosen as the primary endpoint, rather than response rate, as this is appropriate clinical endpoint for cytotoxic agents such as NKTR-102 and for SCLC. A single-stage design will be used to assess the primary endpoint for each patient group. A treatment success was defined as a patient who was progression-free at 18 weeks. To evaluate Group A, the largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 5%, and the smallest that would warrant further subsequent studies is 25%. Twenty evaluable patients will be entered on this study. If 2 or fewer successes are observed, this regimen will be considered ineffective in this patient population. If 3 or more successes are observed, this will be considered evidence that this treatment may be recommended for further testing in subsequent studies. Assuming that the



number of successes is binomially distributed, this design controls the Type I Error to be  $< 10\%$  and has 90% power to detect 25% 18-week PFS rate. To evaluate Group B, the largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 10%, and the smallest that would warrant further subsequent studies is 35%. Eighteen evaluable patients will be entered on this study. If 3 or fewer successes are observed, this regimen will be considered ineffective in this patient population. If 4 or more successes are observed, this will be considered evidence that this treatment may be recommended for further testing in subsequent studies. Assuming that the number of successes is binomially distributed, this design controls the Type I Error to be  $< 10\%$  and has 90% power to detect 25% 18-week PFS rate. Patients who come off study (e.g., due to toxicity) and start an off-protocol therapy prior to 18 weeks will be considered failures at that point.

The evaluable population is defined as patients who meet eligibility requirements and receive any protocol treatment. Unevaluable patients will be replaced.

Progression-free survival is defined as the time from registration to the date of first documented disease progression or death. Survival time is defined as the time from registration to death due to any cause. Patients who loss-to-follow-up or alive at time of analysis will be censored at the last contact of known alive. The distribution of time to disease progression and survival time will be estimated in each group using the method of Kaplan–Meier. Probability of PFS at 18 weeks and 24 week and probability of survival at 3, 6, and 9 months will be estimated. All eligible and treated patients will be included in the analysis of the primary endpoint.

All adverse events, regardless of attribution, will be summarized (overall and by group).<sup>34</sup>

## **11.2 Randomization**

This is a nonrandomized study. No randomization scheme will be generated. Subjects will be assigned to each group based on their relapsed time.

## **11.3 Demographics and Baseline Characteristics**

Descriptive statistics (as appropriate: n, percent, mean, median, min and max) will be used to summarize demographic and baseline characteristics.

## **11.4 Efficacy Analysis**

Objective tumor response will be tabulated overall (and by dose level if appropriate). Best Response is defined to be the best objective status recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. The RECIST 1.1 criteria will be used for solid tumor evaluation and patients will be re-evaluated every other cycle. Responses will be summarized by simple descriptive summary statistics delineating complete and partial responses as well as stable and progressive disease in the cohorts (overall and by tumor group).



### 11.5 Safety Analysis

As per NCI CTCAE v 4.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. Non-hematologic toxicities will be evaluated via the ordinal CTC standard toxicity grading. Hematologic toxicity measures of thrombocytopenia, neutropenia, and leukopenia will be assessed using continuous variables as the outcome measures (primarily nadir) as well as categorization via CTC standard toxicity grading. Overall toxicity incidence as well as toxicity profiles by dose level, patient and tumor site will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses.

### 11.6 Adverse Event

The number and severity of all adverse events (overall, by regimen, and by dose level if appropriate) will be tabulated and summarized. The Grade 3+ adverse events will also be described and summarized in a similar fashion. This will provide an indication of the level of tolerance for this treatment combination in this patient group.

## 12 CORRELATIVE DATA ANALYSIS

Correlation between correlative study (pharmacogenetic analysis) and other outcome measures like toxicity and response will be carried out in an exploratory manner as described below.

### 12.1 Pharmacogenetic Analysis

The genes that have been associated with irinotecan pharmacodynamic and pharmacokinetic pathways include those responsible for activation, inactivation and transport of the drug. These genes include *ABCB1*, *ABCC2*, *ABCG2*, *BCHE*, *CES1*, *CES2*, *CYP3A4*, *CYP3A5*, *SLCO1B1*, *TOPI*, *UGT1A1*, *1A3,1A4,1A6*, *1A7,1A8*, *1A9* and *UGT1A10*. As NKTR-102 is a conjugate of irinotecan, most of the irinotecan pathway genes may interact with it thus resulting in similar phenotypic effects. Hence, several genetic variants associated with the pathways may contribute to the clinical outcome of NKTR-102 therapy. Some of the well-known genetic variants that have been associated with irinotecan clinical outcomes include the polymorphic repeat in *UGT1A1* promoter region (*UGT1A1*\*28, rs8175347; *UGT1A1*\*93) and the *ABCB1* (1236C > T, 2677G > T/A, 3435C > T), *ABCC2* (-24C > T, 1249G > A, 3972C > T), and *ABCG2* (34G > A, 421C > A) polymorphisms. It is reported that nearly 50% of the variations in neutropenia among individuals could be explained by a combination of genetic polymorphisms and non-genetic covariates, with gene combinations attributing to 28% of the variations, suggesting a polygenic basis for neutropenia.<sup>32</sup> *UGT1A1*\*28 and \*93 genotypes have been associated with toxicity; *ABCC2* 3972C > T with severe diarrhea in both Korean and European patients while *SLCO1B1*\*5 allele is reported to be associated with increased risk of severe neutropenia in Asians, and the *SLCO1B1*\*1b allele is suggested to be protective of neutropenia.<sup>32-35</sup>

This Phase I study will initially focus, in an exploratory manner, on the primary genes which will activate (*CES1*, *CES2*, *CYP3A4*, *CYP3A5*) and inactivate (*UGT1A1*) NKTR-102. It is hypothesized that germline polymorphic variants in *CES1*, *CES2*, *CYP3A4*, *CYP3A5* and *UGT1A1* may affect toxicity as well as response to NKTR-102 therapy.

SNP Identification: We will generate tagSNPs from National Center for Biotechnology Information (NCBI), HapMap and/or the Genome Variation Server databases using the Caucasian SNP information for these 5 genes in addition to using SNPs previously reported in literature. These SNPs will be selected with sufficient frequency that its impact on the clinical outcome at a population level would be meaningful and have some degree of likelihood to alter the function of the gene in a biologically relevant manner. Fifty-three SNPs have been identified for genotyping.

Genotyping: The tagSNPs will be genotyped using the MassARRAY Compact system (Sequenom) at RPCI as previously described.<sup>36</sup> Whenever possible, published methods and primers will be used for polymorphic variants such as *UGT1A1*\*28.

## **13 ETHICAL AND REGULATORY STANDARDS**

### **13.1 Ethical Principles**

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each subject (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the subject is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the subject log and subject records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining subject authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the subject is treated, in accordance with the Declaration of Helsinki, Good Clinical Practice, and according to the guidelines in this protocol, including attached appendices.

### **13.2 Informed Consent**

The Investigator is responsible for obtaining written consent from each subject or the subject's legally authorized representative in accordance with ICH-GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the subject according to ICH-GCP, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The subject should also be made aware that by

signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

The Investigator shall provide a copy of the information sheet and of the signed consent form to the subject and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the subject file. At any stage, the subject may withdraw from the study and such a decision will not affect any further treatment options.

## **14 STUDY RESPONSIBILITIES**

### **14.1 Data Collection**

Data entry into the database is to be completed in a timely fashion (approximately within 28 days) after the subject's clinic visit. If an AE is considered serious it is captured on both the Adverse Event page and the Serious Adverse Event Form, which is handled in an expedited fashion.

Data management activities will be performed using EXPeRT. EXPeRT is a suite of software tools that enables the collection, cleaning and viewing of clinical trial data. CRS data management will design the study-specific database and facilitate its development by the EXPeRT Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database will be put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs. EXPeRT is compliant with all relevant technical aspects of relevant GCP guidelines.

- The system can generate accurate copies of stored data and audit trail information in human readable form.
- System access is limited to authorized individuals through the controlled assignment of unique ID and password combinations.
- The system is designed to periodically force users to change their passwords and verifies that user ID and password combinations remain unique.
- The system automatically generates a permanent time-stamped audit trail of all user interactions.

When data entry is complete, data management will review the data and will query any missing, incomplete, or invalid data points for resolution by the Clinical Research Coordinator and Investigator. Once all queries have been resolved, the data can be released to the statistician for analysis.

### **14.2 Maintenance of Study Documents**

Essential documents should be retained per RPCI's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with RPCI. It is the responsibility of RPCI to inform the Investigator/ institution as to when these documents no longer need to be

retained. If, for any reason, the Investigator desires to no longer maintain the study records, they may be transferred to another institution, another investigator, or to RPCI upon written agreement between the Investigator and RPCI.

## **15 ADMINISTRATIVE RULES**

### **15.1 Revisions to the Protocol**

RPCI may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

### **15.2 Termination of the Study**

It is agreed that, for reasonable cause, either the Investigators or the Sponsor, RPCI may terminate this study, provided a written notice is submitted within the time period provided for in the Research Support Agreement. In addition, RPCI may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of subjects enrolled in the study.

### **15.3 Confidentiality**

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

## 16 APPENDICES

### Appendix A. Instructions for Network Sites

#### 1. CONTACT INFORMATION

All questions related to the protocol or study implementation should be directed to:

Roswell Park Cancer Institute  
CRS Network Office  
ASB K 102B  
Buffalo, New York 14263

**Telephone:**

Monday - Friday; 7:30 AM to 4:00 PM EST  
716-845-3870

After hours, weekends, and holidays request the RPCI Investigator  
716-845-2300

**Fax:** 716-845-8743

#### 2. INFORMED CONSENT

- Informed consent must be obtained by the **site Investigator** from any subjects wishing to participate, **prior to any procedures or change in treatment**.
- An informed consent template is provided by RPCI and can be amended to reflect institutional requirements.
- All consent changes **must** be reviewed by RPCI Network Office prior to submission to the site IRB.
- The informed consent must be IRB approved.
- Always check that the most up to date version of the IRB approved consent is being used.

#### 3. SUBJECT REGISTRATION

The subject completes the **Gender, Race, and Ethnicity Form** and this is placed in the study binder.

**RPCI does not grant exceptions to eligibility criteria.**

##### **Phase 2 Protocol Registration Instructions**

The **Subject Screening and Enrollment Log** must be faxed or emailed to the RPCI Network Office within 24 hours of the date the subject is consented. Once the Investigator has reviewed eligibility, complete the **Eligibility Verification Form** and **fax** to the RPCI Network Monitor at 716-845-8743 or email to [CRSNetworkMonitors@RoswellPark.org](mailto:CRSNetworkMonitors@RoswellPark.org).

#### 4. **STUDY DEVIATIONS**

- If a deviation has occurred to eliminate hazard, this must be reported to the RPCI Network, site IRB and any other regulatory authority involved in the trial.
- ANY study deviation will be recorded on the **Study Deviation Log**.
- Subjects inadvertently enrolled with significant deviation(s) from the study-specified criteria will be removed from the study.
- Notify the RPCI Network Office of any early subject withdrawal and appropriately document the discontinuation and the reason why.

#### 5. **STUDY DOCUMENTATION**

- Study documents must be filled out completely and correctly. Ditto marks are not allowed.
- If an entry has been documented in error put a single line through the entry and initial and date the change. The RPCI Network Monitor must be able to read what has been deleted.
  - Do **NOT** use white-out, magic marker, scratch-outs.
  - Do **NOT** erase entries.
- Use only black ink for documentation on the accountability form and any other study forms.

#### 6. **DRUG ACCOUNTABILITY**

Drug accountability must be strictly maintained.

- Responsibility rests solely with the Investigator but can be delegated as appropriate (e.g., to pharmacy personnel).
- A drug accountability record form (DARF) will record quantities of study drug received, dispensed to subjects and wasted, lot number, date dispensed, subject ID number and initials, quantity returned, balance remaining, manufacturer, expiration date, and the initials of the person dispensing the medication.
- Study drug supply will only be used in accordance with the IRB approved study.
- Drug accountability forms are protocol and agent specific, they are study source documents and will be used to verify compliance with the study.
- An inventory count must be performed with each transaction. Any discrepancies shall be documented and explained.
- Drug accountability forms must be stored with study related documents.
- Each medication provided for this study and each dosage form and strength must have its own DARF.
- Dispensing the wrong study supply is considered a **medication error**.
  - **NEVER** replace investigational agents with commercial product.
  - Do **NOT** “transfer”, “borrow” or “replace” supplies between studies.

## **7. SERIOUS ADVERSE EVENT REPORTING**

The site Investigator or designated research personnel will report all SAEs, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**. The site will notify the RPCI Network Monitor within 1 business day of being made aware of the SAE. A preliminary written report must follow within 24 hours (1 business day) of the first notification using the following forms:

- RPCI SAE report form
- MedWatch 3500A
- Notify Nektar Therapeutics. A complete follow-up report must be sent to the RPCI Network Monitor within 10 working days.

## **8. UNANTICIPATED PROBLEM REPORTING**

An unanticipated problem (UP) is any incident, experience, or outcome that meets **all** of the criteria in **Section 9.4**.

For all adverse events occurring that are unanticipated and related or possibly related to the research drug, biologic or intervention, the participating physician or delegated research staff from each site will notify **their local IRB in accordance with their local institutional guidelines**. The site must also notify the RPCI Network Monitor within 24 hours of being made aware of the Unanticipated Problem by completing the **IRB Unanticipated Problem Report Form** and faxing or emailing it to the RPCI Network Monitor.

**Appendix B. ECOG Performance Status Scores**

Description	Status
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5



**Appendix C. Cockcroft-Gault Calculation for Creatinine Clearance**

$$CrCL = \frac{[(140 - \text{Age}) * \text{Body Mass (in kg)}]}{[72 * \text{Serum Creatinine (in mg/dL)}]}$$

If the patient is female, multiply the above by 0.85.

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