A phase II study of etirinotecan pegol (NKTR-102) in patients with refractory brain metastases and advanced lung cancer or metastatic breast cancer (MBC)

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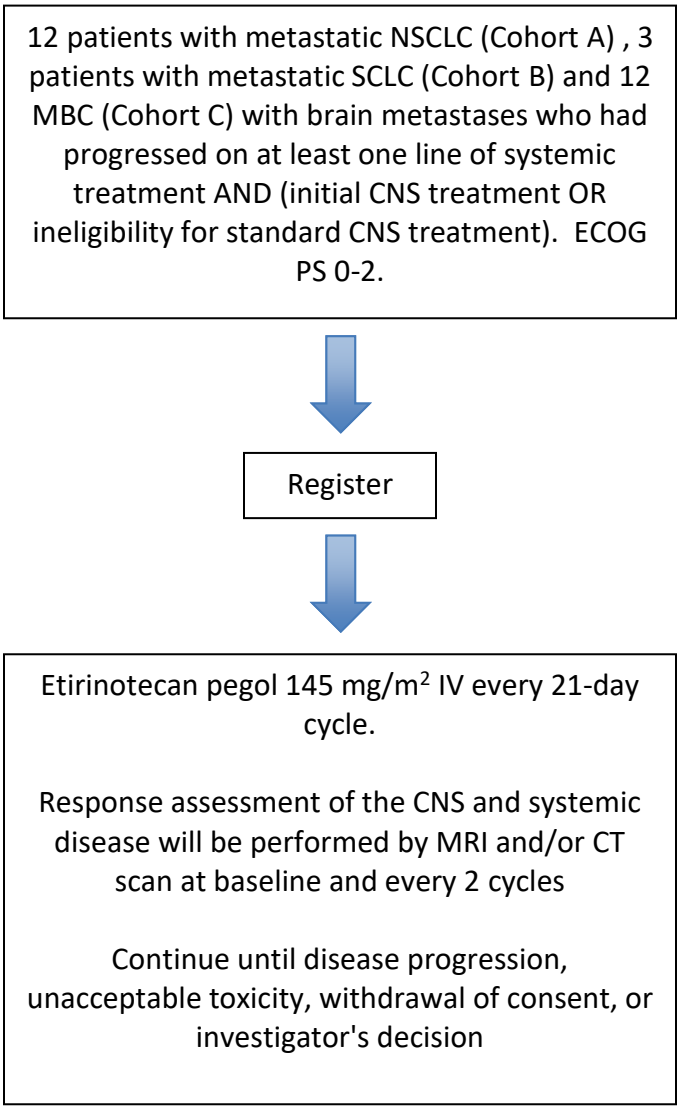
PROTOCOL SYNOPSIS

TITLE	A phase II study of etirinotecan pegol (NKTR-102) in patients with advanced lung cancer or metastatic breast cancer (MBC) and refractory brain metastases
STUDY PHASE	II
INDICATION	Metastatic non-small cell lung cancer, or small cell lung cancer, or breast cancer with brain metastases progressing after at least one systemic therapy AND one CNS treatment OR not eligible for standard CNS treatment
INVESTIGATIONAL PRODUCT OR PROCEDURE	Etirinotecan pegol (NKTR-102)
PRIMARY OBJECTIVE	For cohort A, to determine the CNS disease control rate (number of patients with stable disease or partial response or complete response / total number of treated patients) at 12 weeks following treatment with etirinotecan pegol in patients with advanced NSCLC with refractory brain metastases For cohort C, to determine the CNS disease control rate (number of patients with stable disease or partial response or complete response / total number of treated patients) at 12 weeks following treatment with etirinotecan pegol in patients with locally recurrent or MBC and refractory brain metastases
SECONDARY OBJECTIVES	Cohort A and Cohort C: • To measure the overall disease control rate and response rate for patients receiving study therapy • To measure the systemic (non-CNS) disease control rate and response rate for patients receiving study therapy • To observe the progression-free survival of the study population • To observe the overall survival of the study population Cohort B: • To observe CNS and systemic disease control in SCLC

	Cohorts A ,B and C: • To determine the safety profile of etirinotecan pegol (NKTR-102)
TREATMENT SUMMARY	All patients will receive etirinotecan pegol (NKTR-102) 145 mg/m^2 IV as monotherapy once every 21-day cycle. Response assessment of the CNS and systemic disease will be performed by MRI and/or CT scan at baseline and every 2 cycles. Patients will receive therapy until disease progression, unacceptable toxicity, withdrawal of consent, or investigator's decision.
SAMPLE SIZE	Cohort A: 12 NSCLC patients Cohort B: 3 SCLC patients Cohort C: 12 patients with MBC to the brain
STATISTICAL CONSIDERATIONS	This is a single-stage phase II design with CNS disease control rate at 12 weeks as the primary endpoint. In cohort A, 12 patients with NSCLC will be enrolled. In Cohort C 12 patients with MBC will be enrolled In Cohort A or Cohort C, if 3 or more patients have controlled disease in either cohort (SD, PR, or CR) in the CNS at 12 weeks, we will be able to reject the null hypothesis that the disease control rate is not larger than 5%, assuming a one-sided significance level of 5%. The sample size and cutoff provide 81% power with an effective alpha level of 2% (one-sided). This calculation is based on binomial probabilities, assuming an alternative of 33% The study will also include an exploratory, observational group of up to 3 patients with SCLC (Cohort B).

SCHEMA


12 patients with metastatic NSCLC (Cohort A) , 3 patients with metastatic SCLC (Cohort B) and 12 MBC (Cohort C) with brain metastases who had progressed on at least one line of systemic treatment AND (initial CNS treatment OR ineligibility for standard CNS treatment). ECOG PS 0-2.
Register
Etirinotecan pegol 145 mg/m2 IV every 21-day cycle.
Response assessment of the CNS and systemic disease will be performed by MRI and/or CT scan at baseline and every 2 cycles
Continue until disease progression, unacceptable toxicity, withdrawal of consent, or investigator's decision

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Include additional abbreviations as needed. Remove any unnecessary abbreviations.

ADL	Activities of daily living
AE	Adverse event
BID	Twice daily
BSA	Body surface area
CBC	Complete blood count
CI	Confidence interval
CMAX	Maximum concentration of drug
CNS	Central nervous system
CRF	Case report/Record form
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
GI	Gastrointestinal
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HPF	High-power field
HTN	Hypertensions
IRB	Institutional Review Board
IV	Intravenous
LLN	Lower limit of normal
NSCLC	Non-small cell lung cancer
OS	Overall survival
PLT	Platelet
PD	Progressive diseased
PFS	Progression free survival
PR	Partial response
QD	Once daily
RECIST	Response evaluation criteria in solid tumors
RR	Response rate
SAE	Serious adverse event
SCLC	Small cell lung cancer
SD	Stable disease
TKI	Tyrosine kinase inhibitor
TTP	Time to progression
ULN	Upper limit of normal
UNK	Unknown
WBC	White blood cell
WHO	World Health Organization

1 OBJECTIVES

1.1 Primary Objective

For cohort A and Cohort C, to determine the CNS disease control rate (number of patients with stable disease or partial response or complete response / total number of treated patients) at 12 weeks following treatment with etirinotecan pegol in patients with advanced NSCLC or with MBC with refractory brain metastases

1.2 Secondary Objectives

Cohorts A and C:

- To measure the overall disease control rate and response rate for patients receiving study therapy
- To measure the systemic (non-CNS) disease control rate and response rate for patients receiving study therapy
- To observe the progression-free survival of the study population
- To observe the overall survival of the study population

Cohort B:

- To observe CNS and systemic disease control in SCLC

Cohorts A, B and C:

- To determine the safety profile of etirinotecan pegol (NKTR-102)

2 BACKGROUND

2.1 Lung and breast cancers

Lung cancer

Lung cancer is the leading cause of cancer-related deaths in the United States, with estimated 159,000 deaths in 2013(Siegel, Naishadham et al. 2013), and worldwide, with 1.3 million deaths per year.(Jemal, Bray et al. 2011) Lung cancer frequently metastasizes to the brain, resulting in an extremely poor prognosis with few effective therapies.(Sorensen, Hansen et al. 1988)

In non-small cell lung cancer, newly diagnosed brain metastases are often treated with radiation therapy and/or surgery. Concurrent chemoradiation for CNS disease is not supported by adequate evidence. There is no standard of care treatment chemotherapy for relapsed or progressing CNS disease, though pemetrexed chemotherapy or erlotinib targeted therapy can work in selected patient groups for limited periods of time. In a series of 39 patients with NSCLC and brain metastases who received pemetrexed as a second-line or further-line treatment, 15 patients (38%) had a partial response in the brain, and 12 patients (31%) had stable disease.(Bearz, Garassino et al. 2010) In a phase II study of erlotinib as second-line therapy in 48 Chinese patients with NSCLC and asymptomatic brain metastases, response (PR or CR) was observed in 67% of patients with known EGFR mutations, 33% with wild-type tumors, and 68% with unknown EGFR mutation status.(Wu, Zhou et al. 2013) Of note, neither pemetrexed nor

erlotinib has been shown to have significant activity in squamous histology, thus further necessitating the need for a better agent that is potentially efficacious for brain metastases of all NSCLC histologies.

In small cell lung cancer, several studies have suggested that brain metastases are as sensitive to chemotherapy, such as cisplatin and etoposide, as extracranial disease at least initially, with response rates ranging from 27% to 85% for previously untreated patients(Lee, Murphy et al. 1989; Twelves, Souhami et al. 1990; Kristjansen, Soelberg Sorensen et al. 1993) and 22% to 50% for previously treated patients.(Kristensen, Kristjansen et al. 1992; Groen, Smit et al. 1993; Postmus, Smit et al. 1995; Kaba, Kyritsis et al. 1997; Grossi, Scolaro et al. 2001; Korfel, Oehm et al. 2002) However, there is also evidence that the response rate for brain metastases is significant lower than that for systemic disease.(Seute, Leffers et al. 2006) While the addition of whole brain radiation can increase the response rate but does not necessarily improve overall survival,(Postmus, Haaxma-Reiche et al. 2000) the use of prophylactic cranial irradiation is indicated for patients with response to chemotherapy and can improve survival,(Slotman, Faivre-Finn et al. 2007) suggesting that treatment of brain metastasis is important. Finally, while topotecan is the only FDA approved therapy for the second line treatment of small cell lung cancer,(von Pawel, Schiller et al. 1999; von Pawel, Gatzemeier et al. 2001; O'Brien, Ciuleanu et al. 2006; Eckardt, von Pawel et al. 2007) many clinicians prefer the use of irinotecan instead with its favorable response and toxicity profile. Therefore, etirinotecan pegol appears ideally suited for both the systemic and CNS treatment of SCLC that is resistant or refractory to platinum.

Metastatic breast cancer (MBC)

Despite progressive improvements in disease control rates and improved survival in metastatic breast cancer, brain metastasis remains a devastating complication in the natural history of advanced disease progression and is invariably associated with worsened survival in advanced disease.(Sanna, Franceschelli et al. 2007) Standard therapy includes surgical resection for oligo metastatic disease, whole brain radiation, and stereotactic surgery when feasible. In general, systemic chemotherapy has poor CSF penetration and the brain is considered sanctuary for metastatic disease.(Freilich, Seidman et al. 1995) With the limited current treatment options, new treatment approaches and novel therapeutic agents are needs to enrich our armamentarium in treatment of brain metastasis.

While all subtypes of breast cancer can be complicated by the development of brain metastasis, triple negative and HER2-positive disease carry the highest risk of CNS involvement.(Sanna, Franceschelli et al. 2007)

2.2 Etirinotecan pegol

NKTR-102 (etirinotecan pegol) is a polyethylene glycol (PEG) conjugate prodrug of irinotecan having topoisomerase I inhibitor antitumor activity. Irinotecan is a topoisomerase I inhibitor approved worldwide for the treatment of colorectal cancer (CRC). Irinotecan is indicated as a component of first-line therapy in combination with 5-fluorouracil (5-FU) and leucovorin for patients with metastatic carcinoma of the colon or rectum or as a single agent in patients whose

disease has recurred or progressed following initial fluorouracil-based therapy. Irinotecan has a half-life (T½) of approximately 9 hours in humans and upon repeat dosing demonstrates the saw-tooth pharmacokinetic (PK) profile that typifies a short T½ for both irinotecan and its major active metabolite, 7-ethyl-10-hydroxy-camptothecin (SN38), with a T½ of about 47 hours. NKTR-102 was specifically engineered to provide an extended release of irinotecan thereby providing a more continuous exposure to the active metabolite SN38. By reducing peak concentration and markedly prolonging the T½ of SN38 to about 50 days, it is possible that anti-tumor activity can be enhanced while maintaining a favorable toxicity profile. In addition, the large NKTR-102 molecule does not freely pass out of intact vasculature, which may account for relatively higher concentrations of the compound and the active metabolites in tumor tissues in *in vivo* models, where the local vasculature may be relatively more permeable.

2.2.1 Preclinical data

NKTR-102 doses are expressed as irinotecan equivalents throughout the entire protocol.

Pharmacokinetic, pharmacologic, and toxicologic characteristics of NKTR-102 have been studied in mice, rats, and dogs. Pharmacokinetic studies in mice, rats, and dogs showed that NKTR-102 disposition kinetics are dominated by the polymer moiety. In all species examined, dosing of NKTR-102 resulted in sustained and greater exposure to the active metabolite SN38 than dosing with irinotecan at equivalent doses and schedules. Interspecies differences in the metabolism of NKTR-102 were observed. Rodents achieved higher SN38 exposure than dogs, presumably because of more rapid and extensive cleavage of irinotecan due to higher level of esterases in rodents than in dogs.

The anti-tumor activity of NKTR-102 was evaluated in mouse models of human colorectal (HT29), non-small cell lung (NCI H460), breast (MCF-7), ovarian (A2780), and gastric (NCI-N87) tumors. NKTR-102 was active in all models, with dose-related increases in number of regressions and tumor growth delay. Tumor growth delay was frequently the highest possible value, with evidence of sustained tumor growth suppression for 2 to 10 weeks after administration of the last dose. In contrast, irinotecan resulted in little to no suppression of tumor growth. In an HT29 colorectal tumor model, NKTR-102 was eliminated very slowly from the tumor (T½=17 days) and achieved higher and more sustained tumor exposures to its active metabolites compared with irinotecan. The increased tumor exposure following NKTR-102 correlated with superior and sustained suppression of tumor growth. 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 given with cetuximab in a mouse model of human DLD-1 colorectal tumor, with bevacizumab in a mouse model of human HT29 colorectal tumor, with 5-FU in a model of human HT29 colorectal tumor, and with Doxil® in a model of human A2780 ovarian tumor.

Brain tumor exposure and anti-tumor activity of NKTR-102 was also evaluated in an experimental model of breast cancer brain metastases using brain-seeking MDA-MB-231Br breast cancer cells. Preferential accumulation in brain tumor tissue over plasma was observed with NKTR-102, but not with irinotecan. Vehicle- and irinotecan-treated animals showed a

median survival of 21 days, while 50% of NKTR-102-treated animals were still alive 61 days after treatment initiation, with a censored median survival of 51 days.

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/m2), 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 ≥ 30 mg/kg of NKTR-102.

2.2.2 Clinical pharmacokinetics

The apparent elimination T½ for SN38 after NKTR-102 for Injection administration is approximately 50 days versus approximately 2 days after irinotecan dosing. This greatly increased SN38 T½ from NKTR-102 results in plasma SN38 concentrations that are significantly more prolonged between doses than are possible with irinotecan. After an initial dose of NKTR-102 at the recommended Phase 2 dose of 145 mg/m2, plasma SN38 AUC is approximately the same as with the 350 mg/m2 dose of irinotecan, but maximal concentrations are approximately 10-fold less. Moreover, plasma SN38 concentrations are sustained throughout the q21d dosing interval, compared to lack of SN38 exposure for 70% of the q21d dosing interval after an irinotecan dose of 145 mg/m2. Eighty percent of steady-state for SN38 exposure is typically reached after 4 cycles of therapy on the q21d schedule. Overall, NKTR-102 for Injection administration resulted in prolonged and controlled systemic exposure to SN38. Pharmacokinetics of NKTR-102 and metabolites are predictable and do not require complex dosing adjustments.

2.2.3 Clinical safety

As of 18 October 2013, safety data from 786 patients across all clinical studies (completed and ongoing; single-agent and combination therapy) have been analyzed and included in the Investigator's Brochure, version 10.

Observations across all studies (including safety data from ongoing studies) have been generally consistent with regard to the overall safety profile of etirinotecan pegol. Gastrointestinal toxicity, especially diarrhea, is the most common and clinically significant toxicity occurring with the use etirinotecan pegol. 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 etirinotecan pegol. The incidence of grade 3 diarrhea in the phase 2 study in patients with 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 three patients in the ongoing phase 2 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 etirinotecan pegol 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 etirinotecan pegol for the q21d schedule is 93 days (range 8 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 etirinotecan pegol; however, data from clinical studies evaluating etirinotecan pegol suggest a lower frequency and severity of neutropenia than for irinotecan. Etirinotecan pegol administered at a dose level of 145 mg/m² in a q21d schedule overall across all ongoing phase 2 studies showed an overall incidence of neutropenia of ≤ 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.

2.2.4 Clinical Efficacy

A Phase 1 clinical study of single-agent NKTR-102 is completed and was designed to evaluate the safety, tolerability, and PK of the different treatment schedules of NKTR-102 in patients with refractory solid tumors. The MTD of NKTR-102 was 115 mg/m2 for the wx3 q4wk treatment schedule, and 145 mg/m2 for the q21d and q14d treatment schedules.

Efficacy data observed in this completed Phase 1 study showed that NKTR-102 has an encouraging level of anti-tumor activity (11%) in a broad spectrum of tumors: eight confirmed PRs in patients with triple-negative breast cancer, non-small cell and small cell lung cancers, cervix, colorectal, pancreas, maxillary sinus, and bladder.

A Phase 2a study is also completed and was designed to determine the tolerable dose, safety and efficacy of NKTR-102 in combination with cetuximab in patients with refractory solid tumors. When NKTR-102 for Injection was administered in combination with cetuximab, 100 mg/m2 at q21d was better tolerated than 125 mg/m2 at q21d.

In addition a Phase 2 study of NKTR-102 in patients with MBC evaluating 2 treatment regimens (145 mg/m2 q14d and q21d; n = 70 patients; 35 patients per treatment regimen) showed significant antitumor activity when efficacy data were presented in *The Lancet Oncology*.(Awada, Garcia et al. 2013) The ORR by RECIST version 1.0 was 28.6% with 2 CRs and 18 PRs. The median PFS was 4.7 months and OS was 10.3 months. Clinical activity

appeared to be numerically superior in the 21d schedule, although the trial was not designed to compare the 2 treatment arms.

Two Phase 2 clinical studies are evaluating NKTR-102 in colorectal and ovarian cancers. The Phase 2 study in CRC patients is currently ongoing. In the Phase 2 study of patients with ovarian cancer, efficacy data are presented in the Journal of Clinical Oncology.(Vergote, Garcia et al. 2013) The ORR was 20% (20% for the once-every-14-day schedule and 19% for the once-every-21-day schedule). Median PFS was 4.1 months for every 14 days and 5.3 months for every 21 days. Median OS was 10.0 months for every 14 days and 11.7 months for every 21 days. Efficacy data from this study of patients with ovarian cancer are preliminary, since the data evaluation is currently ongoing. See Section **5.3 of the Investigator's Brochure version 10** for details on antitumor efficacy from Phase 1 and 2 trials investigating NKTR-102.

The NKTR-102 Phase 3 clinical program (BEACON trial) began enrollment in December 2011 and closed enrollment in August 2013. This study compares NKTR-102 for Injection 145 mg/m2 q21d to TPC in patients with locally recurrent or metastatic breast cancer who were previously treated with an anthracycline, a taxane, and capecitabine therapy. On 17 March 2015, Nektar Therapeutics announced results of the BEACON study, a trial comparing NKTR-102 to Treatment of Physician's Choice ("TPC", any of seven standard of care anticancer drugs) in women with advanced breast cancer. In a topline analysis of 852 patients from the trial, NKTR-102 provided a 2.1 month improvement in median overall survival (OS) over (12.4 months for patients receiving NKTR-102 compared to 10.3 months for patients receiving TPC). The overall comparison of survival did not show a statistically significant result comparing the NKTR-102 group to the TPC group. The incidence of severe toxicities was lower in the NKTR-102 arm (48%) compared to the TPC arm (63%). Common severe toxicities observed with NKTR-102 were diarrhea (9.6%), low white blood cell counts (9.4%) which could lead to infection, low red blood cell counts (4.7%) which could lead to being tired and fatigue (4.5%). Common severe toxicities observed with TPC were low white blood cell counts (30.5%) which could lead to infection, low red blood cell counts (4.7%) which could lead to being tired, and feeling short of breath (4.4%).
Severe nerve pain was seen in 3.7% of patients on TPC versus 0.5% of patients in the NKTR-102 arm.. The full press release can be read on <http://www.nektar.com> www.nektar.com.

This trial was also presented at ASCO 2015 with the abstract verbatim as follows. EP is the first long-acting topoisomerase 1 inhibitor providing sustained levels of SN38. In Phase II, EP demonstrated a 29% ORR following a median of 2 prior regimens for aBC. BEACON study (NCT01492101) randomized (1:1) pts with aBC and progressive disease following A,T and C to EP (145 mg/m2q3w over 90 minutes) or TPC (any of 7 cytotoxics). Methods: Eligible pts had any ER/HER2 and ECOG 0-1; stable brain metastases were allowed. 852 pts enrolled over 20 months and reached target for events in Dec2014. The choice of TPC: eribulin 40%, vinorelbine 23%, gemcitabine 18%, taxane 15%, ixabepilone 4%. Primary efficacy endpoint was overall survival (OS) by 2-sided log-rank test stratified by region, prior eribulin and receptor status; the study had 90% power to detect a target Hazard Ratio (HR) of 0.77. Circulating tumor cells (CTCs) were isolated in ~80% of pts and analyzed for target-specific pharmacodynamic biomarkers. This is the first presentation of these data. Results: EP provided a 2.1 month improvement in median OS over TPC (12.4 vs 10.3 months; HR 0.87, p = 0.08). In a pre-

specified subgroup of 67 pts with brain metastases, EP showed an improvement of 5.2 months in median OS (10.0 vs 4.8 months; HR 0.51, $p < 0.01$); the proportion of pts with brain metastases alive at 12-mo survival was higher with EP (44.4% vs 19.4%). Similarly, in pts with liver metastases (n = 456) median OS improved with EP (10.9 vs 8.3 months; HR 0.73, $p = 0.002$). Grade (G) ≥ 3 AEs were lower with EP (48%) than TPC (63%). Common G ≥ 3 AE with EP: diarrhea (9.6%), neutropenia (9.6%), anemia (4.7%) and fatigue (4.5%); TPC: neutropenia (30.5%), anemia (4.7%) and dyspnea (4.4%). Severe neuropathy: 3.7% of pts (TPC) vs 0.5% (EP). Alopecia was less with EP (10% vs 23%). Data on efficacy in CTC biomarker defined sub-groups (TOP1, TOP2) will be presented. Conclusions: EP provided a clinically meaningful benefit to pts with late-stage aBC, although this did not reach statistical significance. In pts with brain metastases, median OS doubled; improved survival was also seen in other pt subsets. Toxicity with EP was less than with TPC. Clinical trial information: NCT01492101.(Perez, Awada et al. 2015)

For clinicaltrials.gov compliance

Etirinotecan pegol is not approved by the FDA for this indication. Stanford will hold the IND for use of etirinotecan pegol in advanced lung cancer and metastatic breast cancer patients with brain metastases.

2.3 Rationale

Etirinotecan pegol is a topoisomerase I inhibitor that has demonstrated promising results in drug-resistant solid tumors, such as advanced and heavily pre-treated breast and ovarian cancers.(Awada, Garcia et al. 2013; Vergote, Garcia et al. 2013) The active metabolite of etirinotecan pegol is SN-38, a drug known to have activity in solid tumors. Irinotecan, which is converted to SN-38, can only be given every 1-3 weeks based on its toxicity profile. In that time, however, serum levels of irinotecan drop to undetectable. The long-acting delivery mechanism of etirinotecan pegol, however, provides sustained levels of SN-38 throughout treatment cycles with an improved side effects profile. It is also believed that pegylation may allow more drug accumulation in tumors, including brain metastases, creating a higher local concentration of chemotherapy. This makes etirinotecan pegol an attractive agent for study in patients with advanced tumors with brain metastases.

2.4 Study Design

The primary purpose of this protocol is to evaluate the efficacy of etirinotecan pegol as a treatment for advanced NSCLC and SCLC and locally recurrent or MBCwith brain metastases. We will evaluate a single group of 12 patients with NSCLC (Cohort A), 3 patients with SCLC (Cohort B) and 12 patients with metastatic breast cancer (Cohort C) in this single-arm, non-randomized study. This trial is open; neither investigators nor patients will be blinded. It will be powered based on an estimated minimal non-treatment disease control rate of 5%, type I error of 5%, and power of 81%. We will consider achieving a 33% disease control rate a positive signal.

Primary Endpoint:

- For cohort A and C, to determine the CNS disease control rate (number of patients with SD+PR+CR/total number of evaluable patients) at 12 weeks

Secondary Endpoints:

Cohort A and C:

- To measure the overall disease control rate and response rate for patients receiving study therapy
- To measure the systemic (non-CNS) disease control rate and response rate for patients receiving study therapy
- To observe the progression-free survival of the study population
- To observe the overall survival of the study population

Cohort B:

- To observe CNS and/or systemic disease control in SCLC

Cohorts A, B, and C:

- To determine the safety profile of etirinotecan pegol (NKTR-102)

We will recruit 12 eligible patients with NSCLC (Cohort A), 3 eligible patients with SCLC (Cohort B) and 12 patients with MBC to the brain (Cohort C) who enroll on study and receive at least one dose of study therapy. All patients will receive etirinotecan pegol on a 21-day dosing schedule (cycle). Patients will not receive other concurrent chemotherapy. Patients will be followed with a clinical exam every cycle and body CT and brain MRI every 2 cycles for the first 4 cycles, then consistently through the end of treatment. Those who have not progressed will continue to receive etirinotecan pegol until disease progression, unacceptable toxicity, withdrawal of consent, or investigator's decision.

We will monitor for toxicity as defined in the CTCAE version 4. Adverse reactions attributed to etirinotecan pegol will follow dose delay and modifications outlined in section 6.1.

The Stanford Cancer Center data safety monitoring board (DSMB) will be used to review the safety of etirinotecan pegol in the study and to assess interim efficacy data.

2.5 Correlative Studies Background

DNA is continually shed into the circulation by primary or metastatic tumors, and can be isolated in the form of cell-free DNA (cfDNA). Methods to quantitatively identify rare strands of DNA have become much more powerful following the development of next-generation sequencing (NGS), which uses massively parallel PCR-based methodologies to quantitatively measure the prevalence of a population of DNA molecules.

At Stanford, our collaborator Max Diehn has developed a highly sensitive method to sequence tumor DNA in the peripheral blood, termed CAPP-Seq (CAncer Personalized Profiling by Deep Sequencing). CAPP-Seq uses targeted hybrid capture to identify genomic "hotspot" alterations in a region totaling approximately 125 kB, a relatively small fraction of the entire genome.

Designed specifically to identify mutations in non-small cell lung cancer (NSCLC), CAPP-Seq can be applied to peripheral blood plasma as well as paraffin-embedded tumor tissue. By sequencing a limited portion of the entire genome at over 5000-fold depth producing relatively even coverage of the targeted regions, CAPP-Seq identifies at least one mutation in >90% of NSCLC tumors and detects mutant allele frequencies down to 0.025% with a negligible technical background (~0.007%), allowing accurate quantitation of circulating tumor DNA in early and advanced stage tumors. (Figure 2) In contrast, a recently published similar technique has a allelic detection frequency of 2-5% to detect cancer specific mutations and small nucleotide variants (SNVs).(Newman, Bratman et al. 2014)

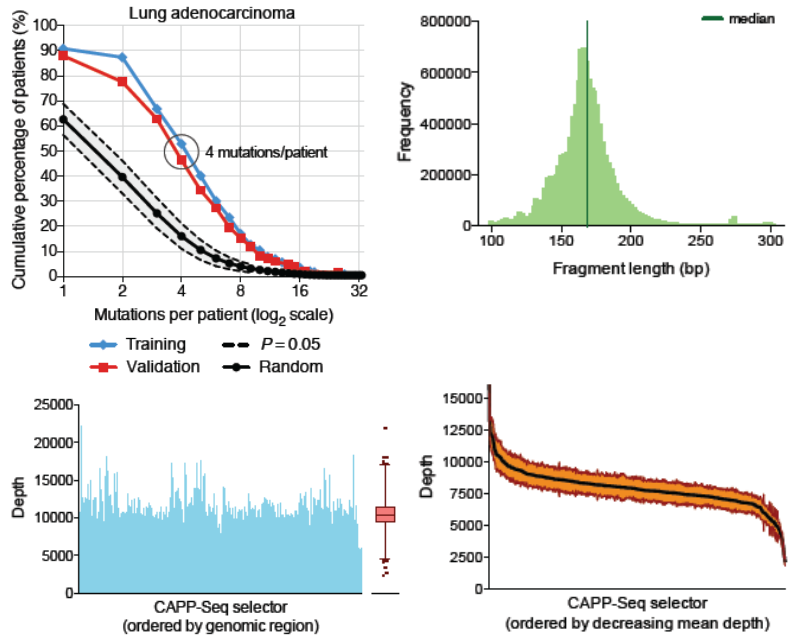


Figure 2: CAPP-Seq in NSCLC, which can identify >1 individual mutations in most tumors, average peripheral blood cfDNA fragment length, and even coverage above 5000-depth of sequencing.

Here we propose to apply CAPP-Seq to detect tumor signatures longitudinally over time in blood specimens from patients undergoing active treatment for NSCLC. By interrogating hundreds of recurrently mutated genomic regions, CAPP-Seq can identify mutations in the vast majority of individual NSCLCs and can thus be directly applied to a broad patient population. We have deliberately optimized CAPP-Seq for use on plasma samples collected in routinely available EDTA-containing tubes, as opposed to more specialized tubes. Finally, CAPP-Seq is economical at less than $300 per assay currently and will be covered by Stanford research funds, and per sample costs should drop further as sequencing costs continue to fall. This will not be done for Cohort C

3. PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Refer to the Participant Eligibility Checklist in Appendix A.

3.1 Inclusion Criteria

3.1.1 Patients must have histologically proven metastatic **non-small cell lung cancer** (Stage IV disease or recurrent metastatic disease, according to the 7th edition of the lung cancer TNM classification system) (for cohort A),

-or-

Histologically proven metastatic **small cell lung cancer** (extensive stage or recurrent metastatic disease) for cohort B. (Patients with tumors having mixed small cell and non-small cell elements may be enrolled on cohort B.),

-or-

Females with histologically or cytologically confirmed carcinoma of the breast (either the primary or metastatic lesions) for whom single-agent cytotoxic chemotherapy is indicated..

3.1.2 Patients must have previously received at least one line of prior systemic chemotherapy or targeted treatment for metastatic disease OR have received prior adjuvant systemic chemotherapy within prior 6 months. Patients with MBC must have received at least a taxane based regimen. Patients with EGFR and ALK mutations should have failed prior standard tyrosine kinase inhibitor (TKI) therapy. Patients must have completed previous treatment (including other investigational therapy) in greater than or equal to the following times prior to initiation of study treatment:

- Chemotherapy/targeted therapy administered in a daily or weekly schedule must be completed ≥ 2 weeks prior to study treatment;
- Chemotherapy/targeted therapy administered in a 2-weekly schedule must be completed ≥ 3 weeks prior to study treatment;
- Chemotherapy/targeted therapy administered in a 3-weekly or greater schedule must be completed ≥ 4 weeks prior to study treatment.

3.1.3 Patients must have previously received at least one CNS-directed treatment (such as surgery or radiation) OR not be eligible for CNS stereotactic radiosurgery

3.1.4 Patients must have measurable CNS disease, either previously untreated (not counting systemic therapy), or progressed following previous radiation treatment. Lesions that have progressed after prior radiosurgery should not be selected as measurable disease if they are suspected of being radionecrosis. The following measurement criteria are required (not counting tumor edema, as visualized by contrast enhanced MRI with slice thickness of 1.5 mm or smaller, unless prospective permission is obtained from the PI allowing absence of contrast or thicker slices):

- At least one CNS tumor measuring 10 mm or greater in longest diameter,
  -OR-
- At least one CNS tumor measuring 5-9 mm in longest diameter, plus one or two additional CNS tumors measuring 3 mm or greater in longest diameter, for which the sum of the longest diameters of these lesions is equal to or greater than 10 mm. Patient may have additional tumors as well.

3.1.5 Patients must be at least 18 years of age.

3.1.6 Patients must have a life expectancy of 3 months or longer.

3.1.7 Patients must have an ECOG performance status of 0, 1, or 2.

3.1.8 Women of childbearing potential (less than 12 consecutive months since last regular menses, or surgically sterile) must have a negative serum β-hCG pregnancy test and must agree to use hormonal, IUD, or barrier birth control with spermicide to avoid pregnancy during the study. Agreement to participate in this study via the informed consent will indicate subjects commitment to subject avoid pregnancy in self or a partner of childbearing potential for up to 6 months after the last dose of study therapy.

3.1.9 Adequate organ function as evidenced by:

a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L without GCSF support within 7 days

b. Hemoglobin (Hgb) ≥ 9.0 g/dL (90 g/L) without blood transfusion within 7 days

c. Platelet count $\geq 100 \times 10^9$/L without platelet transfusion within 7 days

d. Bilirubin ≤ 1.5 x upper limit of normal (ULN), except for patients with documented history of Gilbert's disease who may have direct bilirubin ≤ 1.5 x upper limit of normal (ULN)

e. Alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ 2.5 X ULN (for patients with liver metastases, ≤ 5 X ULN)

g. Serum creatinine ≤ 1.5 X ULN; or calculated creatinine clearance ≥ 50 mL/min (using Cockcroft-Gault formula); or measured creatinine clearance ≥ 50 mL/min.

3.1.10 Patients must be willing and able to comply with the protocol and provide written informed consent prior to study-specific screening procedures.

3.2 Exclusion Criteria

3.2.1 Previous treatment with a camptothecin derivative (eg,, irinotecan, topotecan, and investigational agents including but not limited to exatecan, rubitecan, gimatecan, karenitecan, SN38 investigational agents, EZN-2208, SN-2310, and AR-67) is not allowed.

3.2.2 Patients may not have a known history of leptomeningeal disease, as diagnosed by positive CSF cytology, unless prospective permission for enrollment is granted from the sponsor and the PI.

3.2.3 Patients may not have had major surgery or radiotherapy (therapeutic and/or palliative) within 14 days prior to initiation of study treatment, including CNS-directed radiation therapy. Minor procedures, such as tumor biopsy, thoracentesis, or intraveneous catheter placement are allowed with no waiting period.

3.2.4 Patients may not have the following co-morbid disease or concurrent illness:

a. Chronic or acute GI disorders resulting in diarrhea of any severity grade. Patients may not use chronic anti-diarrheal supportive care (more than 3 days/week) to control diarrhea in the 28 days prior to first dose of investigational drug (exception: anti-diarrheal medications used to control symptoms from a medication that will be discontinued prior to study are allowed with a 7 day washout before study therapy, for example loperamide for erlotinib-associated diarrhea)

b. Known cirrhosis, defined as Child-Pugh Class A or higher liver disease.

c. Other malignancy undergoing active treatment.

d. Any other severe/uncontrolled inter-current illness or significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation.

3.2.5 Patients may not have a known allergy or hypersensitivity to any of the components of the investigational therapy, including polyethylene glycol (PEG) or topoisomerase inhibitors.

3.2.6 Patients may not be receiving the following medications at the time of first dose of investigational drug:

a. pharmacotherapy for known hepatitis B or C, tuberculosis, or HIV.

b. any of the following enzyme inducing anti-epileptic medications (EIAEDs): phenytoin, carbamazepine, oxcarbazepine, phenobarbital.

c. other chemotherapy, hormonal therapy, immunotherapy, other investigational agents, or biologic agents for the treatment of cancer except for bisphosphonates or denosumab.

3.2.7 Pregnant or nursing patients will be excluded from the study.

3.2.8 Significant unresolved toxicities from previous anticancer therapy that have not resolved, or have not stabilized at a new baseline.

3.3 Informed Consent Process

All participants must be provided a consent form describing the study with sufficient information for participants to make an informed decision regarding their participation. Participants must sign the IRB approved informed consent prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

3.4 Randomization Procedures

Patients in this study will not be randomized.

3.5 Study Timeline

Primary Completion:
The study will reach primary completion 24 months from the time the study opens to accrual.

Study Completion:
The study will reach study completion 36 months from the time the study opens to accrual.

4. TREATMENT PLAN

Screening, study visits, and end of treatment visit will be conducted as outlined on the Study Calendar (Section 9).

Study drug will be administered every cycle (21 days) using the dose in section 5.1, below.

Post-treatment Follow-Up
Unless a patient has specifically withdrawn consent to be followed for survival, he or she will be contacted by phone or clinic visit approximately every 12 weeks following the End of Treatment visit, or as directed by the Sponsor, to collect data regarding survival status. In addition, unless consent was withdrawn for contact during survival follow-up period, patients will be asked about subsequent anti-cancer therapy and progression if not determined during study treatment. Follow-up will continue until death, withdrawal by patient, lost to follow up, or study termination by Sponsor.

For any toxicity the investigator attributes to study drug, the investigator will assess the patient to determine whether the toxicity has resolved or worsened. Interval of assessment must be based on the clinical significance of the toxicity; patients should be more frequently assessed for grade 3 or higher toxicities. Information on whether the toxicity has resolved or worsened must be entered into the eCRF.

4.1 General Concomitant Medication and Supportive Care Guidelines

The treatments listed below are permitted while on study:

- Bone agents such as bisphosphonates and denosumab for prevention of skeletal related events
- Palliative and supportive care for disease-related symptoms
- Limited exposure/duration radiation therapy to treat pain is permitted. Radiation therapy use must be recorded in the eCRF.
- Steroids for edema/symptom management will be considered palliative and supportive care and doses will be recorded in the eCRF.
- Standard therapies for concurrent medical conditions, including antiemetic prophylaxis and early interventional antidiarrheal therapy.
- Premedication with an antihistamine and/or a corticosteroid is allowed in subsequent cycles following occurrence of a self-limiting CTCAE v4.0 grade 1-2 allergic/hypersensitivity reaction to a prior infusion.

- Nutritional supplements (including "nutriceuticals") are permitted as long as the agent is not considered "investigational" in the country. Their use should be recorded in the eCRF.
- Palliative radiotherapy to the CNS or other body sites is permitted with permission from the overall study PI. Generally study treatment should not be given within 7 days before or after radiotherapy.

The treatments listed below are prohibited while on study. For treatments prohibited on study, alternative medical intervention should be considered. If a prohibited treatment is required, study treatment must be discontinued but the patient should continue to be followed for study outcomes.

- Other investigational agents.
- Any concurrent chemotherapy, hormonal therapy, immunotherapy, or other systemic therapy for cancer.
- Investigators must monitor patients for use of potent cytochrome P450 3A4 (CYP3A4) inducers or inhibitors, as they may induce or inhibit irinotecan or SN38 metabolism. Some of these agents are OTC medications, eg, St John's Wort. Patients must provide a complete list of all concomitant medications as part of the screening process.

For a list of these agents, see:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#4

4.2 Criteria for Removal from Study

Patients may choose to discontinue the trial at any time, for any reason, and without prejudice to further treatment. A patient who withdraws consent from study participation will be asked to state the level of withdrawal:

1. Withdrawal from treatment only; in this case follow up and survival data will continue as planned.

2. Withdrawal from contact during the post-treatment period (allowing no collection of off-study data, such as subsequent anti-cancer therapy, progression if not determined during study treatment, and survival)

In the event of withdrawal of consent, the study staff and/or investigator must make every effort to ascertain the level of consent withdrawn. The type of consent withdrawal must be noted in source documents and eCRF.

Patients will stop study drug therapy for any of the following reasons. These patients will be followed up for efficacy outcomes until the end of the study. They must be followed for safety until resolution or permanent sequelae of all toxicities attributable to the study drug:

- Any unacceptable toxicity
- The patient withdraws consent for treatment

- Investigator's decision, eg, clinical deterioration or not in the patient's best interests to continue in the study
- Pregnancy
- The patient is lost to follow-up
- Death
- Consistent and significant non-compliance of the patient with protocol-mandated procedures
- The study is terminated by the investigator or Nektar. If the study is terminated by Nektar, patients who are receiving clinical benefit from their participation in this study (defined as SD or an objective response without unacceptable toxicity) will continue to receive etirinotecan pegol from Nektar.

Patients may continue on study therapy with permission of the overall study PI in the following situations:

- Patients with progression of disease as determined by the investigator should generally discontinue study therapy. However, if the patient is having clinical benefit (for example response or stable disease in the CNS or systemically, with mild progression in the other compartment) patients may be considered to continue on therapy post-progression. The patient should have permission from the overall study PI to receive post-progression therapy before the second post progression dose is given (i.e. they can receive one post progression dose without prospective permission)

- For patients who require > 28 days delay (starting from the time the next dose was supposed to be administered), the post-study treatment period would begin, including follow-up for survival, 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 and they should have permission from the overall study PI before resuming treatment

If a patient withdraws from study treatment, the investigator must promptly notify the Stanford Medical Monitor and will make every effort to complete the End-of-Treatment visit. Every effort must be made to ascertain if patients will permit follow-up for survival.

Before a patient is considered "lost to follow-up", study personnel must contact the patient at least twice by phone and once by mail with documented receipt. Study personnel may use public records to check for mortality for any patients considered "lost to follow-up," if permitted by applicable laws or regulations.

4.3 Alternatives

Patients may withdraw from the study at any time without prejudice to their further care. Patients with progressing advanced lung cancer or MBC and brain metastases may be offered a variety of alternate treatment options. They may also be offered palliative and supportive care services.

5. INVESTIGATIONAL AGENT/DEVICE/PROCEDURE INFORMATION

5.1 Etirinotecan pegol

The drug substance etirinotecan pegol (topoisomerase I inhibitor polymer conjugate) is a conjugate that was engineered by attaching a PEG polymer to irinotecan molecules that are released following *in vivo* cleavage of a biodegradable linker. Table 5 provides the nomenclature information for etirinotecan pegol.

Table 5: Nomenclature

Compound Number/Name	NKTR-102/etirinotecan pegol
Manufacturer	Nektar Therapeutics
Chemical classification	Topoisomerase 1 inhibitor

The investigational drug product (NKTR-102 for Injection) is formulated as a sterile lyophilized powder of etirinotecan pegol in lactate buffer at pH 3.5, intended for dilution with commercially available 5% Dextrose Injection, USP (w/w%; D5W) or 0.9% Sodium Chloride for Injection, USP, before IV infusion. The pH of the formulation is in the range of 3.2 to 4.2, and etirinotecan pegol for injection storage condition is 2°C - 8°C (with a shelf-life of at least 48 months).

Etirinotecan pegol (drug substance) is light-sensitive. The vial provides sufficient protection for the drug product. The diluted drug product does not require light precautions. The lyophilized drug product (NKTR-102 for Injection) will be supplied in 25 mL type 1 amber colored glass vials packaged in cartons. Each vial contains lyophilized etirinotecan pegol equivalent to 100 mg of irinotecan. Each vial and carton will be labeled to comply with local guidelines.

Body surface area (BSA) will be determined before the start of each cycle using the Mosteller formula, based on baseline height and most recent weight.

Dose:
Each patient's etirinotecan pegol dose will be determined by multiplying most recent BSA times the starting dose of 145 mg/m^2, with BSA capped at 2.4 m^2.

NKTR-102 for Injection will be administered as an IV infusion over 90 minutes (± 15 minutes). Pre-medications should not be administered prior to the initial infusion, but if a patient reports symptoms (such as nausea and/or vomiting), prophylactic use of anti-emetics may be attempted.

Etirinotecan pegol will be initiated and maintained at a dose of 145 mg/m^2 every 21 days unless dose delay or modifications are required per guidelines specified in the protocol until progression or unacceptable toxicity develops.

5.2 Availability

Nektar Therapeutics will provide the study drug.

An initial supply of NKTR-102 for Injection vials will be shipped refrigerated (2 to 8 degrees C) to the site pharmacy upon completion of the site activation process. Re-supply will occur via manual shipment request to Nektar Drug Supply & Distribution. Based on expanded stability

data, the temperature monitors used for etirinotecan pegol for Injection shipments have been programmed to alarm when the transit temperature falls outside -25°C to 25°C.

5.3 Agent Ordering

Drug Supply & Distribution
Nektar Therapeutics
455 Mission Bay Blvd South
[redacted]

Re-supply will occur via direct contact with the supplier, Nektar Therapeutics. Upon individual patient enrollment, Nektar will supply up to 2 months of drug product for dosing for enrolled patients.

5.4 Agent Accountability

NKTR-102 for Injection vials will be stored as per instructions provided in the pharmacy manual in a secured site with restricted access. Study drug accountability will be recorded by the site pharmacist. The pharmacist or designee will:

- Maintain records of product delivery, inventory, destruction, and returns
- Maintain temperature monitoring
- Maintain up-to-date accountability of the study drug in the trial accountability log
- Document the use or disposition of study product by each patient
- Return or destroy unused study product as per Nektar's instructions and approval

6. DOSE MODIFICATIONS

6.1 Re-treatment Criteria

Prior to initiation of subsequent cycles, patients must meet requirements with respect to hematopoietic function:

Hgb $\geq$ 8.0 g/dL
ANC $\geq$ 1.5 x 10^9/L
platelets $\geq$ 75 x 10^9/L.

Diarrhea must be fully resolved to CTCAE grade 0 for at least 7 days without supportive antidiarrheal measures prior to re-treatment.

Any treatment-related non-hematologic toxicities must have resolved to baseline or CTCAE grade 1 except for non-clinically significant toxicities, such as electrolyte abnormalities in the absence of diarrhea.

Supportive care may be implemented in order to ameliorate diarrhea, nausea, vomiting, anorexia, or myelosuppression.

Dose reductions may also be implemented for patients who experience recurrent or specific severe toxicities. See table 6.1.

6.2 Treatment Delay due to Drug Related Toxicity

All AEs will be assessed according to CTCAE version 4.0. In the event of multiple toxicities, dose delays and modifications should occur in accordance with the worst toxicity observed. If the patient fails to meet the criteria for re-treatment (section 6.1 above), treatment may be delayed, followed by an additional evaluation to determine feasibility of re-treatment. Initiation of subsequent doses may be delayed for a maximum of 28 days to allow recovery from any toxicity to permit re-treatment (with the delay calculated from the scheduled date of the next infusion). Patients whose treatment delays are ≥14 days but ≤28 days due to a drug-related toxicity should initiate their *next* treatment cycle with a dose reduction (see Sections 6.2 + 6.3). For example: if a patient receives therapy on March 1, the next cycle should be initiated on March 22); the patient would receive a dose reduction if the dose is delayed such that it occurs between April 5 - 18. Patients who require > 28 days delay due to unresolved toxicity must be withdrawn from treatment (the post-study treatment period would begin, including follow-up for survival), 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.

6.3 Dose Modifications for Drug Related Toxicity

Dose escalation for etirinotecan pegol is not permitted. Patients who undergo dose reduction of etirinotecan pegol due to observed toxicity may not be re-escalated to the previous dose level upon resolution of the toxicity.

Etirinotecan pegol dose modifications (reductions or delays) must be recorded for each patient in the appropriate section of the eCRF.

Dose levels:
Etirinotecan pegol doses for an individual patient may be reduced to:

Dose level -1: 120 mg/m^2

Dose level -2: 95 mg/m^2

Only two dose reductions are permitted. Patients will be off study if toxicity requires a dose reduction beyond the 2 dose reduction steps. Dose reductions and holds should generally follow the recommendations below, but dose reduction or dose holds can be for lower grade or other toxicities, or dose reductions or holds can be omitted, at investigator discretion if believed to be in the best interest of the patient.

- DURING A CYCLE: Table 6.1/Column 2 describes the recommended guidelines for management and supportive care during a cycle of therapy.
- INITIATION OF A SUBSEQUENT CYCLE: Table 6.1/Column 3 describes the recommended dose modifications for Day 1 in subsequent cycles of therapy. All dose

modifications in a new cycle should be based on the worst toxicity observed in the previous cycle and are relative to the Day 1 dose of the previous cycle.

Table 6.1

Toxicity NCI CTCAE Grade	**During a Cycle**	**Dose Modifications for Day 1 of New Cycle Based on Worst Toxicity in Prior Cycle**
Thrombocytopenia / Anemia / Neutropenia / Febrile Neutropenia		
Grade 1 or 2	-	Maintain dose level
Grade 3	Platelets: consider platelet transfusion if active bleeding. ANC: consider growth factor support in accordance with local guidelines. Hgb: erythropoietin-stimulating agents or transfusion as appropriate. If present on a treatment day, hold therapy for a week or until toxicity resolves to grade ≤ 1, with a maximum of 3 weeks.	↓ 1 dose level after 1st occurrence ↓ 1 dose level after 2nd occurrence Discontinue patient after 3rd occurrence
Grade 4 (ANC < 500 x 10^6/L or plt < 25 x 10^9/L or Hgb < 6.5 g/dL)	Platelets: consider platelet transfusion if plt ≤ 10 x 10^9/L or with active bleeding. ANC: consider growth factor support in accordance with local guidelines. Antibiotic, eg, fluoroquinalones, should be considered even in the absence of fever or diarrhea. Hgb: consider erythropoietin-stimulating agents or transfusion as appropriate. If present on a treatment day, hold therapy for a week or until toxicity resolves to grade ≤ 1, with a maximum of 3 weeks.	↓ 1 dose level after 1st occurrence ↓ 1 dose level after 2nd occurrence Discontinue patient after 3rd occurrence
Febrile neutropenia	Patients should be hospitalized immediately for IV antibiotic therapy if they develop neutropenic fever or sepsis.	↓ 1 dose level after1st occurrence ↓ 1 dose level after 2nd occurrence Discontinue patient after 3rd occurrence

Diarrhea		
Any grade	Institute supportive care upon first loose stool [unless contraindicated, use loperamide]. Monitor bowel function; if diarrhea continues with 1st supportive care agent, consider switching to a 2nd agent or add a 2nd agent (unless contraindicated, use diphenoxylate-atropine). Monitor for dehydration, electrolyte abnormalities; correct if present. Administer antibiotic therapy (oral fluoroquinalones) if the patient develops ileus, fever or grade 3/4 neutropenia. Patients should be immediately hospitalized for IV antibiotics therapy if they have evidence of colitis or ileus even in the absence of neutropenia or fever. If worsening diarrhea, octreotide may be attempted. Monitor bowel function for continued need for supportive care. Stop supportive care after the patient is 48 hrs without diarrhea.	Confirm with the patient that diarrhea is no longer present for $\geq$ 7 days without having received supportive care prior to re-treatment. Treatment may be delayed up to 28 days; after this, contact Medical Monitor.
Grade 1		Maintain dose level; consider prophylactic anti-diarrheal supportive care
Grade 2		$\downarrow$ 1 dose level after 2nd occurrence; recommend prophylactic anti-diarrheal supportive care (see section 6.4) After 3rd occurrence; retreatment may be attempted provided that adequate supportive care has been given to the patient (re-instruct patient on the supportive care). (See Section 6.4)

Grade 3		↓ 1 dose level after 1st occurrence; recommend prophylactic anti-diarrheal supportive care (see Section 6.4 ↓ 1 dose level after 2nd occurrence; recommend prophylactic anti-diarrheal supportive care (see Section 6.4) After 3rd occurrence: retreatment may be attempted at 95 mg/m^2 provided that adequate supportive care has been given to the patient (re-instruct patient on supportive care).
Grade 4		↓2 dose level after 1st occurrence; recommend prophylactic anti-diarrheal supportive care (see Section 6.4) Retreatment may be attempted after 2nd recurrence provided that adequate supportive care has been given to the patient (instruct the patient on supportive care)
Dehydration		
Grade 1: Increased oral fluids indicated; dry mucous membranes; diminished skin turgor Grade 2: IV fluids indicated <24 hrs	Consider anti-emetic or anti-diarrheal supportive care	Maintain dose level; consider prophylactic anti-emetic or anti-diarrheal supportive care
Grade 3: IV fluids or hospitalization	Use anti-emetic supportive care	↓ 1 dose level after 1st occurrence; consider prophylactic anti-emetic or anti-diarrheal supportive care ↓ 1 dose level after 2nd occurrence Discontinue patient after 3rd occurrence
Grade 4: Life-threatening consequences; urgent intervention indicated	Use anti-emetic supportive care and IV fluids. Consider hospital admission.	↓2 dose level after 1st occurrence; use prophylactic anti-emetic or anti-diarrheal supportive care Discontinue patient after 2nd occurrence

Nausea / Vomiting / Abdominal Pain		
Grade 1 or 2	Consider anti-emetic supportive care.	Maintain dose level; consider prophylactic anti-emetic supportive care
Grade 3 or 4	Use anti-emetic supportive care. Consider administration of IV fluids.	↓ 1 dose levelafter1st occurrence; use prophylactic anti-emetic supportive care ↓ 1 dose levelafter2nd occurrence Discontinue patient after 3rd occurrence
Other drug-related non-hematologic toxicities (except fatigue/asthenia, alopecia, and non clinically significant electrolyte abnormalities)		
Grade 1 or 2	Consider supportive care as appropriate	Maintain dose level (for grade 2 toxicity, the investigator may use discretion to ↓ 1 dose level after 1st occurrence depending on the nature of the toxicity).
Grade 3 or 4	Use supportive care as indicated	↓ 1 dose levelafter1st occurrence; supportive care as appropriate. ↓ 1 dose levelafter2nd occurrence Discontinue patient after 3rd occurrence

6.4 Antidiarrheal Therapy

Patients receiving to NKTR-102 may experience diarrhea. Diarrhea must be treated promptly with loperamide. It is recommended that patients have loperamide from Cycle 1 Day 1 and throughout the study for their use at home.

Patients with diarrhea must be carefully monitored, given adequate fluid and electrolyte replacement if they become dehydrated, and given antibiotic support if they develop ileus, fever, or severe neutropenia.

Early onset diarrhea (occurring during or shortly after infusion of study drug) has occasionally been seen with NKTR-102 as a cholinergic manifestation. It is usually transient and is only infrequently severe. It may be accompanied by symptoms of blurred vision, blepharospasm, miosis, lacrimation, muscle twitching, and/or intestinal hyperperistalsis that can cause abdominal cramping. If necessary, early diarrhea and other cholinergic symptoms may be ameliorated by administration of atropine (0.25 to 1 mg subcutaneous or IV). However, few patients required atropine in the BEACON study, and the nature of the cholinergic toxicities usually does not warrant the prophylactic use of atropine.

Late onset diarrhea (occurring more than 24 hours after the infusion) can be life-threatening, because it may be prolonged and may lead to dehydration, hypotension, and renal failure. In the BEACON study, 9.6% of patients reported Grade 3 diarrhea. Among those patients, the median

time to onset of Grade 2 diarrhea was 40 days, and the median onset for Grade 3 diarrhea was 43 days. In addition, the median time to resolution of Grade ≤ 2 diarrhea was 1.5 days and the median time to resolution of Grade 3 diarrhea was 6 days. There were no incidents of Grade 4 diarrhea.

Patients must be assessed prior to dosing to ascertain whether they have had diarrhea since the last dose of NKTR-102, whether they are currently receiving anti-diarrheal supportive care, and what was the date of the last episode of diarrhea/loose stool. A patient must be without symptoms of diarrhea and without anti-diarrheal supportive care for at least 7 days prior to the next dose of NKTR-102.

Diarrhea Prophylaxis

In the absence of constipation, the physician may recommend to initiate prophylactic use of loperamide starting with Cycle 2 to mitigate the risk for late onset diarrhea. The recommended loperamide dosage regimen is 2 mg every 24 hours (q24h) starting after the Cycle 2 dose and continuing for 7 days. The 7-day prophylactic regimen is repeated with each subsequent cycle starting after the dose until Cycle 6. In the absence of constipation, the recommended loperamide regimen is 2 mg every 8 to 12 hours (q8-12h) starting after the Cycle 6 dose and continuing for 7 days. The 7-day prophylactic regimen is repeated after the dose in each subsequent cycle.

Diarrhea Treatment

Each patient will be instructed to begin loperamide for diarrhea at the first episode of poorly-formed or loose stool, or at the earliest onset of bowel movements that are more frequent than normally expected for the patient.

The recommended dosage regimen for loperamide is 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. This dosage regimen exceeds the usual dosage recommendations for loperamide; it is not recommended to be used at this high dosage for more than 48 consecutive hours, due to the risk of paralytic ileus. During the night, the patient may take 4 mg of loperamide every 4 hours.

The use of drugs with laxative properties should be avoided due to the potential for exacerbation of diarrhea. Patients should contact their physician to discuss any laxative use.

Patients must be instructed to contact their physician or nurse if any of the following occur: diarrhea at any time during study drug treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; inability to control diarrhea within 24 hours; fever or evidence of infection.

Investigators should contact the Medical Monitor to review diarrheal supportive care instructions for patients whose diarrhea has been documented to be due to a cause other than NKTR-102 (eg, positive stool test for *C. difficile*).

6.5 Antiemetic Therapy

If a patient experiences nausea and/or vomiting, the patient may be given prophylactic antiemetic treatment prior to the next dose of etirinotecan pegol. The patient must be carefully monitored throughout the study period and given adequate fluid and electrolyte replacement to prevent dehydration and electrolyte imbalance.

6.6 Use of Growth Factor Support and Transfusions

Upon etirinotecan pegol administration, patients may experience neutropenia, though its severity appears to be less than seen with Camptosar® (irinotecan) administration. It may be accompanied by gastrointestinal toxicities, such as diarrhea, vomiting, nausea, constipation and abdominal pain/cramping.

Patients who do not meet retreatment criteria for ANC should return to clinic within 1-7 days for reassessment. If the patient continues not to meet retreatment criteria for ANC, the patient should return to clinic at weekly intervals for reassessment. Patients must demonstrate an ANC $\geq 1.5 \times 10^9$/L prior to re-treatment with etirinotecan pegol.

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 Stanford.

Patients may receive transfusions (platelets or blood products) at the investigator's discretion. A patient who has a re-treatment value of Hgb $\leq$ 8.0 g/dL or platelets $\leq 75 \times 10^9$/L may receive a transfusion; however, patients must meet retreatment criteria prior to retreatment.

7. ADVERSE EVENTS AND REPORTING PROCEDURES

7.1 Potential Adverse Events

Observations across all studies (including safety data from ongoing studies presented below as of 18 October 2013, which are preliminary) have been generally consistent with regard to the safety profile of NKTR-102. Gastrointestinal toxicity, especially diarrhea, continues to be the most common and clinically significant toxicity occurring with the use of NKTR-102. Other frequently observed AEs include nausea, fatigue, vomiting, abdominal pain, decreased appetite, constipation, and dehydration. Dehydration has usually been secondary to GI toxicities such as diarrhea and/or vomiting.

Diarrhea and dehydration (secondary to diarrhea) were also the most common serious adverse events (SAEs) reported across all studies evaluating NKTR-102 (occurring at a frequency of 9.4% and 4.1%, respectively). 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 2 studies in metastatic colorectal, ovarian, and breast cancers (one patient in each study). Although early onset cholinergic diarrhea is reported with the use of irinotecan and patients can receive atropine as a premedication to prevent this, atropine as a premedication is not recommended prior to NKTR-102 for Injection administration, as this toxicity has been only rarely reported in patients who received NKTR-102.

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 T½ 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 X 109/L. Please refer to each specific protocol for retreatment requirements for other hematological toxicities.

Except for diarrhea (which must completely resolve prior to retreatment), 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. Refer to Section 6.6 for more detailed guidance regarding management of NKTR-102 related hematological toxicities especially neutropenia.
Hypersensitivity or mild allergic reactions characterized by itching, swollen tongue, flushing, dizziness, muscle twitching, and/or temporary speech impairment have been observed in some patients. In those patients who experienced muscle twitching, the majority of cases occurred on the day of infusion and were self-limited in nature. 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.

7.1.1 Adverse Event Definition and Assessment

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, at any dose, not necessarily related to the treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can also arise from any use of the drug and from any route of

administration, formulation, or dose. This definition includes intercurrent illnesses or injuries, and exacerbation of preexisting conditions. Clinical laboratory abnormalities will only be reported as AEs if they are deemed clinically significant by the Investigator and/or are associated with signs and symptoms, require intervention or treatment, or require follow-up.

For patients receiving NKTR-102 for Injection, an unexpected AE is one of a type not consistent in nature or severity with information in the current Investigator's Brochure for etirinotecan pegol.

An AE does not include:

- A medical or surgical procedure, eg, surgery, endoscopy, tooth extraction, or transfusion; an AE is the underlying condition that leads to the procedure
- Pre-existing diseases or conditions present or detected before start of study medication administration and which do not worsen or increase in severity or frequency after the administration of study medication
- Situations where an untoward medical occurrence has not occurred, eg, hospitalization for elective surgery for a condition that has not worsened on study, social and/or convenience admissions to grant families a respite in caring for a patient
- Overdose of either study medication or concomitant medication without any signs or symptoms unless the patient is hospitalized for observation

7.1.2 Serious Adverse Event Definition

An adverse event will be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death.
Life threatening:	The AE's placed the patient at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	AE that required or prolonged inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before enrollment in the treatment plan or routine check-ups are not SAE's by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization.
Disabling/incapacitating	AE resulted in substantial and permanent disruption of the patient's ability to carry out normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a patient exposed to the treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria, but could have jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed above.

7.1.3 Adverse Event Attribution

The investigator will evaluate the relationship of each AE to study treatment using the following criteria:

Fatal:	AE resulted in death.
Unrelated:	Another cause of the AE is more plausible, a temporal sequence cannot be established with the onset of the AE and administration of the treatment, or a causal relationship is considered biologically implausible.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of treatment, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when treatment is one of several biologically plausible AE causes.
Definitely Related:	The AE is clearly related to use of the treatment.

7.2 Adverse Event Reporting

Adverse events will be graded according to CTCAE v4.0. Both Serious and Non-Serious Adverse Events will be clearly noted in source documentation and listed on study specific Case Report Forms (CRFs). The Protocol Director or designee will assess each Adverse Event (AE) to determine whether it is unexpected according to the Investigator's Brochure, and related to the investigation. All Serious Adverse Events (SAEs) will be tracked until resolution, or until 30 days after the last dose of the study treatment.

SAEs CTCAE grade 3 and above, and all subsequent follow-up reports, will be reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study specific CRF regardless of the event's relatedness to the investigation. Following review by the DSMC, events meeting the IRB definition of "unanticipated problem" will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences.

It is the investigator's responsibility to report adverse events to the FDA promptly under the terms of the Protocol and in compliance with applicable law. To insure that Nektar is aware of relevant safety data, reports 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" (as such terms are defined in 21 CFR 312.32) (whether initial or follow-up) shall be faxed, within twenty-four (24) hours of first knowledge of the investigator, to the following (or to such other fax number of which Nektar shall notify Stanford and the investigator in writing), with a confirmation copy sent by overnight courier (such as Federal Express) to the address provided below (or to such other address of which Nektar shall notify Stanford and the investigator in writing):

Nektar Global Medical Safety Surveillance

with a copy by express courier addressed to:

Nektar Drug Safety
Nektar Therapeutics
[redacted]

8. CORRELATIVE/SPECIAL STUDIES

We will collect samples for correlative analysis of circulating free tumor DNA on individual patients in all cohorts as outlined above in the correlative studies background. Up to three 10-mL tubes containing sodium-EDTA will be drawn periodically as indicated in the study calendar, below.

Within 2 hours of draw, they should be taken to the laboratory of Max Diehn by the study coordinator, or delegate, for centrifugation to separate blood cells from plasma, and freezing into aliquots at -80 degrees C

They will be processed at the end of the study and the total amount of tumor-related circulating tumor DNA will be assessed as a potential surrogate for response to treatment.

9. STUDY CALENDAR

Study procedures	**Screen-ing** [a]	**Cycle 1** [a]	**Mid-cycle for all cycles**	**Cycle 2** [a]	**Cycle 3+** [a]	**Treatment Discont-inuation Visit** [a]	**Every 3 months until Patient Expires**
	Day -21 to -1	**Day 1**	**Day 2-21**	**Day 22 (week 3)**	**Day 43 (week 6)**		**(+/- 14 days)**
Administration of etirinotecan pegol (90-minute infusion)		X		X	X		
Informed Consent	X						
Verify Eligibility Criteria	X						
Medical History	X	X		X	X	X	
Physical Exam	X	X		X	X	X	
Weight/Height/BSA [f]	X	X		X	X	X	
Vital Signs	X	X		X	X	X	
Labs (CBC with differential and CMP) [b]	X	X		X	X	X	
Serum Pregnancy Test [c]	X					X	
Urinalysis	X						
Coagulation Tests (PT, INR, PTT)	X						
ECOG Performance Score	X	X		X	X	X	
Brain MRI Scan[d]	X				X		
Body CT Scan[d]	X				X		
Assessment of AEs (contact by phone, secure device, or in person)			X			X	
Concomitant Medications	X	X		X	X	X	
Correlative blood[e]		X		X	X	X	
Assessment of Survival							X

[a] Screening assessments must be within 21 days of registration, and study therapy should start within 3 days of patient registration. On treatment visit window is -3/ +7 days. Clinic visit and/or laboratory assessments may be done up to 72 hours before infusion treatment. Off treatment visit should be approximately 30 days after final drug infusion (+/- 14 days), but may be conducted by telephone if infeasible for patient to come to clinic. If patient remains in active screening, informed consent does not need to be repeated if more than 21 days from day 1.
[b] Comprehensive metabolic panel (CMP): Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, potassium, total protein, SGOT[AST], SGPT[ALT], sodium)
[c] Serum pregnancy test for women of childbearing potential.
[d] Brain MRI and body CT should be performed within 8 days prior to visit on week 6 and week 12 on study, even if cycle therapy is delayed for toxicity. Thereafter imaging ideally should be done every 6 weeks (2 cycles) prior to treatment visits, but interval of scans may be increased to every 9- 12 weeks (3-4 cycles) at investigator discretion. Brain MRI should include contrast (unless contraindicated) and slice thickness should be 1.5 mm or thinner (unless permission is given from PI). Body CT should include a CT thorax with IV contrast (unless contraindicated) plus any other areas of known disease that are being measured. **CT thorax window is 28 days from day 1 but MRI is 21 days.**
[e] Cohorts A and B only: Up to Three 10-mL purple top sodium-EDTA tubes pre-treatment (cycle 1), cycle 2, cycle 3, cycle 5, then at imaging visits until disease progression.
[f] Height is only required at baseline

10. MEASUREMENTS

Primary Outcome Measure

The primary outcome measure is CNS disease control rate at 12 weeks for cohort A

- **Title:** CNS disease control rate (number of patients with SD+PR+CR/total number of evaluable patients) at 12 weeks assessed by modified response criteria (Section 10.1)
- **Time Frame**: At 12 weeks
- **Safety Issue**: No, this is not a safety endpoint

Secondary Outcome Measures

For cohort A and C:

- **Title:** Overall disease control rate and response rate for patients receiving study therapy
- **Time Frame**: At 12 weeks
- **Safety Issue**: No, this is not a safety endpoint

- **Title:** Systemic (non-CNS) disease control rate and response rate for patients receiving study therapy
- **Time Frame**: At 12 weeks
- **Safety Issue**: No, this is not a safety endpoint

- **Title:** Progression-free survival of the study population

- **Time Frame**: From date of first dose of etirinotecan pegol to date of disease progression
- **Safety Issue**: No, this is not a safety endpoint

- **Title:** Overall survival of the study population
- **Time Frame**: From date of pathologic diagnosis to date of death
- **Safety Issue**: No, this is not a safety endpoint

For cohort B:

- **Title:** Observation of CNS and/or systemic disease control in SCLC
- **Time Frame**: At 12 weeks
- **Safety Issue**: No, this is not a safety endpoint.

For cohorts A, B and C:

- **Title:** Safety profile of etirinotecan pegol (NKTR-102) in patients with advanced lung cancer with refractory brain metastases
- **Time Frame**: From date of first dose of etirinotecan pegol to date of death
- **Safety Issue**: Yes, observational endpoint. Drug has been tested in other cancer populations.

10.1 Primary and Secondary Outcome measures

10.1.1 Relevant Subset

Cohorts A , B and C will be analyzed separately.

10.1.2 Tumor Measurements and Response Criteria

Anti-Tumor Effect

Imaging will be obtained at baseline throughout treatment for both systemic disease and CNS disease.

10.1.2.1 Measurement of Systemic Disease:

Systemic tumor responses will be assessed by Response Evaluation Criteria in Solid Tumors Guideline (RECIST v1.1)(Eisenhauer, Therasse et al. 2009) For convenience, these criteria are outlined below.

Measurable:

- Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - Body organ lesions: 10 mm by CT, MRI or PET scan (slice thickness no greater than 5 mm)
  - 10 mm caliper measurement by clinical exam (lesions which cannot be

accurately measured with calipers should be recorded as non-measurable)
    - 20 mm by chest X-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm in short axis when assessed by CT, MRI or PET scan (slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable:

- All other lesions, including small lesions (longest diameter < 10mm--except for pathological lymph nodes with ≥ 10 to < 15mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging

Measurement of lesions:

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start

Method of assessment:

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 should always be done rather than 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 and ≥ 10mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.
- Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less.
- Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.
- Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.
- Tumor markers: Tumor markers alone cannot be used to assess objective tumor

response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

- Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol.

Tumor Response Evaluation

Baseline documentation of 'target' and 'non-target' lesions

- When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.
- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Systemic Response Criteria

Complete Response (CR) requires ALL of the following:

- Disappearance of all target and non-target lesions
- All pathological lymph nodes, whether target or non-target, must have reduction in short axis to < 10 mm.
- No new lesion

Partial Response (PR) requires ALL of the following:

- At least 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
- No unequivocal progression of existing non-target lesions
- No new lesion

Progression of Disease (PD) requires ANY of the following:

- At least 20% increase in the sum of diameters of target lesions, taking as reference 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.
- Unequivocal progression of existing non-target lesions
- Appearance of one or more new lesions

Stable Disease (SD) requires ALL of the following:

- Not CR

- Not PR
- Not PD

10.1.2.2 Measurement of CNS Disease:

CNS tumor responses will be assessed by the specific criteria outlined below.

Must be measured by MRI with contrast (unless contrast is contraindicated and lesions are clearly delineated) with a slice thickness of 1.5 mm or thinner (unless permission is given from the PI for another slice thickness to be acceptable – in general the size of the measurable lesion should be at least two times the slice thickness with 0 mm skip).

Measurable disease will be defined as:

- At least one CNS tumor measuring 10 mm or greater in longest diameter,

-OR-

- At least one CNS tumor measuring 5-9 mm in longest diameter, plus one or two additional CNS tumors measuring 3 mm or greater in longest diameter, for which the sum of the longest diameters of all lesions is equal to or greater than 10 mm.

These lesions should be previously untreated (not counting systemic therapy), or progressed following previous radiation treatment. Lesions that have progressed after prior radiation or radiosurgery should not be selected if they are suspected of being radionecrosis.

Non-measurable disease will be defined as:

- Brain lesions smaller than those above.
- Edema, midline shift, or other secondary process
- In general, tumor around a cyst or surgical cavity should be considered non-measurable unless there is a nodular component at least 5 mm in longest diameter.
- Lesions that cannot be reproducibly measured
- Bony skull metastases
- Dural metastases (these may be measurable as systemic disease)
- Cystic-only lesions
- Leptomeningeal disease

Baseline documentation of Target and Non-Target Lesions in the CNS:

For CNS target lesions, each lesion should be measured in mm. Lesions should be classified as measurable or non-measurable (as above) and up to 5 most reproducibly measurable lesions selected as target lesions. If lesions not previously treated with local therapies are present, these are preferred for selection as target lesions. A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of longest diameters (sum LD). All other CNS lesions should be identified as non-target lesions and should also be recorded at baseline. They may be recorded as a group. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or ‘unequivocal progression’. Documentation of how each lesion or group of lesions was previously treated is recommended (stereotactic radiosurgery (SRS), whole brain

radiotherapy (WBRT), surgical resection, etc)

CNS Response Criteria:

Evaluation of Target Lesions:
Complete Response (CR) requires ALL of the following:

- Disappearance of all CNS target lesions, sustained for at least 4 weeks
- No new lesion
- Patient must be off corticosteroids or on physiologic replacement doses only
- Stable or improved clinically.

Partial Response (PR) requires ALL of the following:

- At least 30% decrease, compared with baseline, in the sum LD of CNStarget enhancing lesions, sustained for at least 4 weeks. Note that any lesion <10 mm in LD should be regarded as unchanged from baseline unless there is at least a 3 mm change in the measured LD.
- No new lesion
- Stable to decreased corticosteroid dose
- Stable or improved clinically

Progression of Disease (PD) requires ANY of the following:

- At least 20% increase in the sum of the longest diameters of all target enhancing lesions (compared with baseline if no decrease) on stable or increasing doses of corticosteroids. Note that any lesion <10 mm in LD should be regarded as unchanged from baseline unless there is at least a 3 mm change in the measured LD.
- A significant increase in T2/FLAIR nonenhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to comorbid events
- Appearance of one or more new lesions
- Unequivocal progression of nonmeasurable/nontarget lesions
- Definite clinical deterioration not attributable to other causes apart from the tumor, or to decrease in corticosteroid dose.

Stable Disease (SD) requires ALL of the following:
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD while on study
Evaluation of Non-Target Lesions:
Complete Response (CR) requires ALL of the following:

- disappearance of all enhancing CNS non-target lesions
- No new CNS lesions

Non-CR/Non-PD:

- Persistence of one or more non-target CNS lesion(s) No new lesion

Progression of Disease (PD) requires ANY of the following:

- Unequivocal progression of existing enhancing non-target CNS lesions
- Unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions

Stable Disease (SD) requires ALL of the following:
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD while on study

10.1.3 Overall Response Criteria

The least favorable response from the CNS and systemic measurements will be chosen as the overall response score if they are unequal (from favorable to unfavorable CR > PR > SD > PD), if one site is non-evaluable (NE) then the response score from the other site may be used rather than scoring overall response NE.

Failure to return for evaluation as a result of deteriorating condition may be considered clinical overall progression.

11. REGULATORY CONSIDERATIONS

11.1 Institutional Review of Protocol

The protocol, the proposed informed consent and all forms of participant information related to the study (eg, advertisements used to recruit participants) will be reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators.

11.2 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders, case report forms, eligibility checklists, and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

11.3 Data Management Plan

The Protocol Director, or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case

Report Forms (CRFs) will document treatment outcomes for data analysis. Case report forms will be developed using the OnCore database system and will be maintained by study personnel. The database will be secured with passwords, only accessible to the research team.

12. STATISTICAL CONSIDERATIONS

12.1 Statistical Design

This is a single-stage phase II design with CNS disease control rate at 12 weeks as the primary endpoint. For cohort A and C, 12 patients will be enrolled. If 3 or more patients with either NSCLC or MBC have controlled disease (SD, PR, or CR) in the CNS at 12 weeks, we will be able to reject the null hypothesis that the disease control rate is not larger than 5%, assuming a one-sided significance level of 5%. The sample size and cutoff provide 81% power with an effective alpha level of 2% (one-sided). This calculation is based on binomial probabilities, assuming an alternative of 33%.

For cohort B, up to 3 patients with SCLC will be enrolled. They will be observed for CNS and systemic disease response as an exploratory group.

12.1.1 Randomization

There is no randomization for this single-arm phase II study.

12.2 Interim analyses

There is no stopping rule and no interim analysis.

12.3 Descriptive Statistics and Exploratory Data Analysis

Not applicable

12.4 Primary Analysis

12.4.1 Analysis Population

All participants will be included in data analysis in an intention-to-treat manner.
The safety population: All patients who are randomized and receive at least one dose (or partial dose) of study drug etirinotecan pegol. Safety analyses will be conducted based on this population.

12.4.2. Analysis Plan

The data will be analyzed at least 6 months following the achievement of the primary endpoint (CNS disease control) of the last patient enrolled into this study.

Disease control rate is defined as the number of patients with CNS SD+PR+CR divided by the total number of evaluable patients. The proportion, its 95% confidence interval using the Exact method, and p-value of rejection the null hypothesis (5%) will be summarized.

Patient demographic and clinical characteristics will be described using the appropriate summary

statistics (proportions, means, ranges, etc.)

12.5 Secondary Analysis

12.5.1 Analysis Population

The outcomes will be measured on all enrolled patients in an intention-to-treat manner. Additionally, we may evaluate selected outcomes on the subset of enrolled patients that receive any dose or partial dose of study treatment, and also the Efficacy Evaluable patients (those that receive at least 1 cycle of therapy and have relevant imaging performed at or subsequent to the 6 week timepoint.)

The safety population: All patients who are randomized and receive at least one dose (or partial dose) of study drug etirinotecan pegol. Safety analyses will be conducted based on this population.

12.5.2 Analysis Plan

Time to event data (progression-free survival, overall survival) will be described using Kaplan-Meier estimates. The PFS probability at 12 weeks will be estimated with an 80% power and 95% confidence intervals (80% in accord with the planned alpha level, 95% for comparability with other studies, confidence intervals based on the Grenwood formula for the variance of a survival probability).

Toxicity will be tabulated by organ system and grade.

12.6 Sample Size

12.6.1 Accrual estimates

We estimate that we will enroll 6 eligible and evaluable NSCLC patients, 6 eligible and evaluable patients with locally recurrent or MBC) and 1 or 2 SCLC patients per 12-month period, for a total of 12 NSCLC patients and 3 SCLC patients over 24 months. In addition, there are few trials within northern California competing for accrual in the population of patients with advanced lung cancer or advanced breast cancer with brain metastases.

12.6.2 Sample size justification

The null hypothesis: etirinotecan pegol will have no effect on the disease control rate at 12 weeks for patients with advanced lung cancer with brain metastases.

The alternate hypothesis: etirinotecan pegol will have a significant effect on the disease control rate at 12 weeks for patients with advanced lung cancer with brain metastases.

This study has 81% power to reject a 5% disease control rate at 12 weeks with an effective alpha level of 2% (one-sided) if the true disease control rate is 33% or more.

12.6.3 Effect size justification

This is a single arm, non-randomized, phase II trial of etirinotecan pegol in patients with advanced lung cancer with brain metastases. The disease control rate of 33% is estimated based

on prior studies involving etirinotecan pegol in other cancers. The null hypothesis reflects the opinion that a disease control rate of 5% is not of clinical interest.

12.7 Criteria for future studies

A statistically significant result as described above would be a minimal criterion. An observed disease control rate of 33% would be very encouraging and would motivate proceeding to a larger, phase III trial.

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APPENDICES

APPENDIX A**: Participant Eligibility Checklist**

The Participant Eligibility Checklist will be created directly from the eligibility section of the protocol to avoid discrepancies between the protocol sections, as is standard research practice at Stanford University.