Nektar Therapeutics

CLINICAL STUDY PROTOCOL

A PHASE 3 OPEN-LABEL, RANDOMIZED, MULTICENTER STUDY OF NKTR-102 VERSUS TREATMENT OF PHYSICIAN'S CHOICE (TPC) IN PATIENTS WITH METASTATIC BREAST CANCER WHO HAVE STABLE BRAIN METASTASES AND HAVE BEEN PREVIOUSLY TREATED WITH AN ANTHRACYCLINE, A TAXANE, AND CAPECITABINE

Protocol Number:	15-102-14
Protocol Date Final:	07 February 2019
Protocol Version:	Amendment 4.1 (Germany)
Supersedes:	Protocol Amendment 4.0 dated 16 April 2018
EudraCT Number:	2016-002453-38
IND Number:	113864
Sponsor:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA
Sponsor's Medical Contact and Study Medical Monitor:	[redacted] Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA

[redacted]

INVESTIGATOR SIGNATURE PAGE

Nektar Therapeutics

TITLE:	A Phase 3 Open-Label, Randomized, Multicenter Study of NKTR-102 versus Treatment of Physician's Choice (TPC) in Patients with Metastatic Breast Cancer Who Have Stable Brain Metastases and Have Been Previously Treated with an Anthracycline, a Taxane, and Capecitabine
PROTOCOL NUMBER:	15-102-14
PHASE OF STUDY:	3
PROTOCOL DATE:	07 February 2019
STUDY SPONSOR:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA

PRINCIPAL INVESTIGATOR COMMITMENT:

I, the undersigned Principal Investigator, submit this statement of commitment as evidence that I understand my responsibilities pursuant to the Code of Federal Regulations (21 CFR § 312) and ICH E6 Good Clinical Practice guidelines, as well as with any and all applicable federal, state and/or local laws and regulations, and agree to conduct the study in accordance with the protocol referenced herein.

_____

Principal Investigator Printed Name

_____ _____

Principal Investigator Signature **Date**

LIST OF STUDY CONTACTS

Study Contact	Name	Contact Information
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

TABLE OF CONTENTS

INVESTIGATOR SIGNATURE PAGE....2
PRINCIPAL INVESTIGATOR COMMITMENT: 2
PROTOCOL APPROVAL PAGE 3
LIST OF STUDY CONTACTS....4
1.0 STUDY SYNOPSIS 15
1.1 Study Schematic....19
1.2 Adaptive Design Study Flow....20
1.3 Schedule of Assessments 21
2.0 INTRODUCTION....24
2.1 Background....24
2.2 BEACON Study Results in Patients with a History of Brain Metastases....26
2.3 NKTR-102 35
2.3.1 NKTR-102 Safety Profile 35
2.3.1.1 Study Drug Discontinuation due to Adverse Events and Physician Decision....37
2.3.2 Safety of NKTR-102 Compared with 7 TPC Agents in the BEACON Study 39
2.3.3 Safety Conclusions....40
2.4 Comparator Drug 41
2.5 Risks/Benefits and Population 42
2.6 Study and Dose Rationale....42
3.0 STUDY OBJECTIVES....44
3.1 Primary Objective 44
3.2 Secondary Objectives....44
3.3 Exploratory Objective....45
4.0 STUDY DESIGN....46
5.0 SELECTION OF STUDY POPULATION 49
5.1 Inclusion Criteria 50
5.2 Exclusion Criteria 53
5.3 Removal of Patients from Study Therapy or Assessments....55
6.0 TREATMENT PLAN....57
6.1 Study Assessments....57

[redacted]

[redacted]

6.2 Physical Examinations, Vital Signs, and BSA....57
6.3 Clinical Laboratory Assessments....58
6.4 Tumor Assessments....58
6.5 Health Related Quality of Life Assessments and Pharmacoeconomics....60
6.6 Survival Follow-Up....60
6.7 Group A: NKTR-102 Treatment Guidelines....61
6.7.1 Treatment Criteria for NKTR-102....61
6.7.2 Dose Modifications due to Treatment-Related Toxicity....61
6.7.3 Antidiarrheal Therapy....66
6.7.3.1 Diarrhea Prophylaxis....67
6.7.3.2 Diarrhea Treatment....68
6.7.4 Antiemetic Therapy....68
6.7.5 Use of Growth Factor Support and Transfusions....69
6.7.6 Hypersensitivity....69
6.8 Group B: Treatment of Physician's Choice (TPC)....70
6.8.1 Dose Modifications due to Toxicity....70
6.8.2 Supportive Care....70
6.9 Concomitant Treatments....70
6.9.1 Permitted Concomitant Treatments....70
6.9.2 Prohibited Concomitant Treatments....71
7.0 INVESTIGATIONAL PRODUCT(S)/STUDY DRUGS....73
7.1 Group A: NKTR-102 (etirinotecan pegol)....73
7.1.1 NKTR-102 Dosage and Administration....74
7.2 Group B: Treatment of Physician's Choice (TPC)....74
8.0 PHARMACOKINETIC, PHARMACOGENOMIC, BIOMARKER, AND EFFICACY MEASUREMENTS....75
8.1 PK Measurements (NKTR-102 Group Only)....75
8.2 Pharmacogenomic Measurements (NKTR-102 Group Only)....75
8.3 Blood Biomarker Measurements....75
8.4 PEG-antibody Measurements in Blood (NKTR-102 Group A Only)....76
8.5 Efficacy Assessments....76
8.6 Tumor Response Evaluation per RECIST....76
8.6.1 Measurements of Response....76

8.6.1.1 Measurable Disease 76
8.6.1.2 Non-Measurable Disease 77
8.6.2 Specifications by Methods of Measurements 77
8.6.2.1 Baseline Documentation of 'Target' and 'Non-Target' Lesions ...78
8.6.3 Evaluation of Target Lesions 79
8.6.4 Evaluation of Non-Target Lesions 79
8.6.5 Evaluation of Best Overall Response per RECIST 80
8.7 Response Assessment Criteria for Brain Metastases per RANO-BM Criteria 81
8.7.1 Measurements of CNS Response (RANO-BM) 81
8.7.1.1 Measurable Disease (RANO-BM) 81
8.7.1.2 Non-Measurable Disease (RANO-BM) 81
8.7.2 Specification of Methods of Measurements 81
8.7.3 Baseline Documentation of Target/Non-Target Lesions (RANO-BM) 82
8.7.4 Evaluation of CNS Target Lesions (RANO-BM) 82
8.7.5 Evaluation of Non-Target CNS Lesions (RANO-BM) 83
8.7.6 CNS Response Criteria for CNS Lesions Proposed by RANO-BM 84
9.0 ASSESSMENT OF SAFETY OR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS 85
9.1 AE Definition and Assessment 85
9.2 Monitoring AEs 86
9.3 Grading of AEs 86
9.4 Causality Relationship of AEs 87
9.5 AE Reporting and Follow-up 88
9.6 Adverse Events of Special Interest (AESI) 88
9.7 Serious AE Definition 89
9.8 Serious AE Reporting 90
9.9 Serious AE Follow-up 90
9.10 Disease Progression – Not Reportable as an AE 91
9.11 Pregnancy 91
9.12 Expedited Reporting of SAEs 92
10.0 STATISTICAL METHODOLOGY 94
10.1 General Considerations 94
10.2 Determination of Sample Size 94

[redacted]

10.3 Interim and Final Analyses 95
10.4 Analysis Populations....95
10.5 Demographic and Baseline Disease Characteristics 96
10.6 Treatment Compliance....96
10.7 Efficacy Analyses 96
10.7.1 Primary Endpoint - Overall Survival 96
10.7.2 Secondary Endpoints....97
10.7.2.1 Progression-Free Survival (Outside the CNS)....97
10.7.2.2 Progression-Free Survival in Brain Metastasis....97
10.7.2.3 Progression-Free Survival (Overall)....98
10.7.2.4 Objective Response Rate 98
10.7.2.5 Clinical Benefit Rate....98
10.7.2.6 Duration of Response....99
10.7.2.7 WBRT 99
10.7.2.8 HRQoL....99
10.7.2.9 Magnitude of Clinical Benefit 99
10.8 Pharmacokinetics and Correlative Studies....100
10.9 Safety Analyses....100
10.9.1 Adverse Events and Deaths....100
10.9.2 Extent of Exposure....101
10.9.3 PEG-antibody Analysis....101
10.9.4 Additional Safety Analyses....101
10.9.5 Laboratory Assessments....101
10.10 Missing Data 101
10.11 Method of Randomization 101
11.0 STUDY OR STUDY SITE TERMINATION....103
12.0 QUALITY CONTROL AND QUALITY ASSURANCE....104
12.1 Changes to the Protocol 104
12.2 Monitoring 104
12.3 Direct Access to Source Data/Documents for Audits and Inspections....105
13.0 ETHICS 106
13.1 IRB/IEC Approval 106
13.2 Written Informed Consent 106

14.0 DATA HANDLING AND RECORD KEEPING.....107
14.1 Data Collection Instruments and Source Documents 107
14.1.1 Study Records 107
14.1.2 Data Collection Instruments.....107
14.2 Retention of Essential Documents 107
15.0 CONFIDENTIALITY 109
16.0 PUBLICATION POLICY.....110
17.0 REFERENCES.....111
18.0 APPENDICES.....117

LIST OF TABLES

Table 1: Overall Survival, Progression Free Survival, and Response Rate for Patients with History of Brain Metastases (ITT Population).....31
Table 2: Treatment Emergent Adverse Events with a Frequency > 20%, Study 11-PIR-11 (BEACON, N = 425).....36
Table 3: Summary of TEAEs Leading to Study Drug Discontinuation by Preferred Term (> 1 Patient in NKTR-102 or TPC Treatment arm) (Safety Population) 38
Table 4: NKTR-102 Dose Modifications and Delays.....63
Table 5: Nomenclature.....73
Table 6: Criteria Definitions for Objective Tumor Response for Target Lesions ...79
Table 7: Criteria Definitions for Objective Tumor Response for Non-Target Lesions (RECIST).....80
Table 8: Overall Responses for Combinations of Tumor Responses per RECIST..80
Table 9: Criteria Definitions for Objective CNS Response for CNS Target Lesions (RANO-BM).....83
Table 10: Criteria Definitions for Objective CNS Response for Non-Target CNS Lesions (RANO-BM).....83
Table 11: Criteria Definitions for Objective CNS Response for CNS Lesions (RANO-BM) 84

[redacted]

LIST OF FIGURES

Figure 1: BEACON Study Kaplan-Meier Plot for Overall Survival Intent-to-Treat Population....26
Figure 2: Kaplan-Meier Plot for Overall Survival Intent-to-Treat Population with Brain Metastases History....28
Figure 3: Kaplan-Meier Plot for Overall Survival in Patients with Tumor in Brain at Baseline (N = 37)....29
Figure 4: Overall Survival by Graded Prognostic Assessment (GPA) Index....34
Figure 5: Simulated Plasma Concentration-Time Profiles of SN38 after Administration of NKTR-102 (Solid Line) or Irinotecan (Broken Line)..43

LIST OF APPENDICES

Appendix 1: Clinical Laboratory Assessments....117
Appendix 2: BEACON – Lancet Article, Perez, et al. 118
Appendix 3: Lancet Oncology Article, Lin, et al. 131

[redacted]

LIST OF ABBREVIATIONS

Abbreviation or Term	Definition
AE	adverse event
ALT	alanine transaminase
ANC	absolute neutrophil count
APC	aminopentane-carboxylic acid
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
BCBM	breast cancer brain metastases
BFI	Brief Fatigue Inventory
BMH	history of brain metastases
BN-20	brain neoplasms 20-question subscale
BP	blood pressure
BRCA 1	breast cancer 1
BRCA 2	breast cancer 2
BSA	body surface area
BTB	blood tumor barrier
BUN	blood urea nitrogen
CHW	Cui, Huang, & Wang
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
CBC	complete blood count
CBR	clinical benefit rate
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CR	complete response
CT	computed tomography
CYP3A4	cytochrome P450 3A4
DCI	data collection instruments

[redacted]

Abbreviation or Term	Definition
DoR	duration of response
DMC	data monitoring committee
DNA	deoxyribonucleic acid
eCRF	electronic case report form
eCOA	electronic clinical outcomes assessments
ECOG	Eastern Cooperative Oncology Group
EIAED	enzyme-inducing anti-epileptic activity
EMA	European Medicines Agency
EORTC	European Organisation for Treatment of Cancer
EOT	end of treatment
EPR	enhanced permeation and retention
EQ-5D-5L™	EuroQoL 5D
ER	estrogen receptor
ESMO	European Society for Medical Oncology
ESMO-MCBS	European Society for Medical Oncology magnitude of clinical benefit scale
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GPA	Graded Prognostic Assessment
HER2	human epidermal growth factor receptor 2
Hgb	hemoglobin
HR	hazard ratio
HR	Hormone receptor positive
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IHC	immunohistochemistry
IND	Investigational New Drug
INR	international normalized ratio
IRB	institutional review board

[redacted]

Abbreviation or Term	Definition
ITT	intent-to-treat
IV	intravenous
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
MBC	metastatic breast cancer
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NA	not applicable
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PD	progressive disease
PE	physical exam
PEG	polyethylene glycol
PET-CT	positron emission tomography – computed tomography
PFS	progression-free survival
PFS-BM	progression-free survival – brain metastases
PK	pharmacokinetic
PR	partial response
PT	prothrombin time
q8-12h	every 8 to 12 hours
q21d	every 21 days
q24h	every 24 hours
QLQ-C30	Quality of Life Core 30
RANO-BM	Response Assessment in Neuro-Oncology—Brain Metastases
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors

[redacted]

Abbreviation or Term	Definition
RR	respiration rate
RT	radiation therapy
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SGOT	serum glutamic-oxaloacetic transaminase
SN38	7-ethyl-10-hydroxy-camptothecin; the active metabolite of irinotecan
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOP	standard operating procedure
SRS	stereotactic radiosurgery; also called stereotactic radiotherapy
SUSAR	suspected unexpected serious adverse reaction
$T_{1/2}$	elimination half-life
TEAE	treatment-emergent adverse events
T_{max}	maximum concentration
TNBC	triple-negative breast cancer
TPC	Treatment of Physician's Choice
UGT1A1	uridine diphosphate-glucuronosyl transferase 1A1
ULN	upper limit of normal
US	United States
USAN	United States Adopted Name
V	volume of distribution
WBC	white blood cell
WBRT	whole brain radiation therapy
WCBP	Women of Child Bearing Potential

[redacted]

1.0 STUDY SYNOPSIS

Name of Sponsor:	Nektar Therapeutics
Name of Active Ingredient:	NKTR-102; etirinotecan pegol
Title of Study:	A Phase 3 Open-Label, Randomized, Multicenter Study of NKTR-102 versus Treatment of Physician's Choice (TPC) in Patients with Metastatic Breast Cancer Who Have Stable Brain Metastases and Have Been Previously Treated with an Anthracycline, a Taxane, and Capecitabine
Study Period:	Approximately 35 months
Objectives:	**Primary Objective:** To compare overall survival (OS) of patients who receive 145 mg/m^2 NKTR-102 given once every 21 days (q21d) with OS of patients who receive Treatment of Physician's Choice (TPC) selected from the following list of 7 single-agent intravenous (IV) therapies: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel. TPC drugs will be administered per standard of care. **Secondary Objectives:** • To compare the objective response rates (ORR) from NKTR-102 treatment with that of TPC; assessment of tumor outside the CNS will use the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; assessment of central nervous system (CNS) metastases will use the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) • To compare progression-free survival (PFS) from NKTR-102 treatment with that of TPC; assessment of tumor outside the CNS will use RECIST version 1.1; assessment of CNS metastases will use RANO-BM • To compare the clinical benefit rate (CBR) from NKTR-102 treatment with that of TPC (i.e., the proportion of patients having complete response [CR], partial response [PR], or stable disease [SD] for at least 4 months); CBR for peripheral lesions and for CNS lesions will be separately described • To compare the duration of response (DoR) from NKTR-102 treatment with that of TPC • [redacted] • To evaluate the safety profiles of NKTR-102 and TPC • To compare health-related quality of life (HRQoL) from NKTR-102 treatment with that of TPC using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core 30 (QLQ-C30) with the BN-20

[redacted]

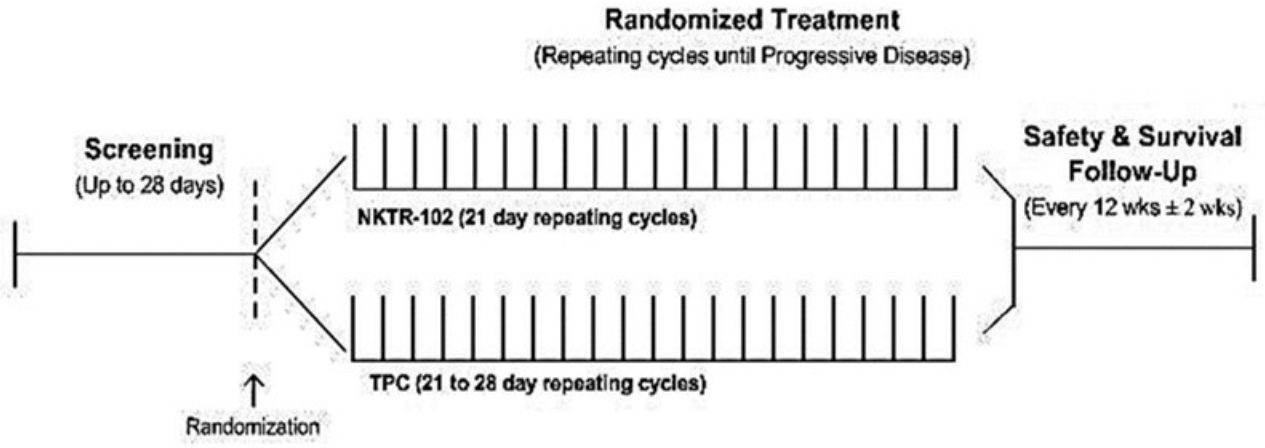
	questionnaire, the EuroQol 5D (EQ-5D-5L™) questionnaire, and the Brief Fatigue Inventory (BFI) • [redacted]
Study Design:	This is an open-label, randomized, two-group, multicenter, international Phase 3 study of NKTR-102 versus TPC in patients with breast cancer brain metastases (BCBM) who have stable brain metastases and have been previously treated with an anthracycline, a taxane, and capecitabine in either the adjuvant or metastatic setting (prior anthracycline may be omitted if not medically appropriate or contraindicated for the patient). In Group A, NKTR-102 will be administered at a dose level of 145 mg/m^2 on a q21d schedule as a 90-minute intravenous (IV) infusion on Day 1 of each treatment cycle. In Group B, TPC will be administered per standard of care. Patients randomized to TPC will receive single-agent IV chemotherapy, limited to choice of one of the following 7 agents: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel. This study will randomize up to 220 patients using a 1:1 randomization ratio and stratification based on geographic region, tumor receptor status, and Eastern Cooperative Oncology Group (ECOG) status. At Screening, the Investigator must determine which TPC will be offered to the patient. Data will be collected on subsequent anticancer therapies in both treatment groups from the time patients come off the study treatment until the time of primary data analysis for OS. An independent data monitoring committee (DMC) will assess interim safety and efficacy data and determine final number of death events needed to provide 80% conditional power based on the promising zone adaptive design (Mehta & Pocock, 2011).
Key Entry Criteria:	An eligible patient is an adult female or male with histologically-confirmed carcinoma of the breast. Patients may have metastatic disease that is either measurable or non-measurable by RECIST. Patients must have a history of brain metastases that are non-progressing. Brain metastases must have been previously treated with combination therapy (whole-brain radiation, stereotactic radiation and/or surgery) ≥ 14 days prior to randomization or single-agent modality ≥ 7 days prior to randomization. Patients must be sufficiently recovered from whole-brain radiation or stereotactic radiation and/or surgical resection with stable signs and symptoms of brain metastases per

	the investigator to randomize into the study (for patients who have undergone definitive therapy within 7-14 days prior to randomization, the baseline head imaging may be obtained up to 21 days following randomization). For patients who have received whole-brain radiation, or stereotactic radiation and/or surgical resection ≥ 28 days prior to randomization, the signs or symptoms of brain metastases must be stable ≥ 28 days prior to randomization and head imaging must be obtained within 28 days prior to randomization. Corticosteroids for patients with brain metastases may be used as long as patients are on a stable or decreasing dose for at least 7 days prior to randomization. Prior therapy (administered in the neoadjuvant, adjuvant, and/or metastatic setting) must include an anthracycline, a taxane, and capecitabine (prior anthracycline may be omitted if not medically appropriate or contraindicated for the patient). For triple-negative breast cancer, a minimum of 1 prior cytotoxic chemotherapy regimen must have been administered for the indication of metastatic disease. For hormone receptor-positive disease, a minimum of 2 cytotoxic chemotherapy regimens must have been administered for the indication of metastatic disease as well as at least 1 hormonal therapy. For human epidermal growth factor receptor 2 (HER2)-positive disease, a minimum of 2 cytotoxic chemotherapy regimens must have been administered for the indication of metastatic disease as well as at least 1 HER2-targeted therapy. The last dose of chemotherapy must have been administered within 6 months of the date of randomization into this study. Patients must have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 with demonstration of adequate organ function.
Criteria for Evaluation:	The primary efficacy endpoint for the study is OS. After discontinuation of therapy, all patients except those who withdraw consent must be followed (by contact via phone, clinic visit, or chart views) at least every 12 weeks (± 2 weeks) until death. If allowed by country regulatory authorities and/or consented to by the patient, study personnel may use public records to check for mortality for any patient considered lost to follow-up and for patients who withdraw consent for follow-up contact. Documented tumor measurements are required using magnetic resonance imaging (MRI) for brain imaging, and choice of computed tomography (CT) scans or MRI for thorax and abdomen assessment, in combination with physical examination and/or digital photography, as appropriate. Tumor assessments must be performed at Screening and every 8 weeks (± 7 days) through Week 24 from date of randomization, and every 12 weeks (± 7 days) thereafter until documented disease progression or death. To ensure that both groups of this study are assessed for progression in a similar manner, tumor assessments must be obtained at this interval, regardless of delays in chemotherapy due to toxicity. The same method of assessment and the same technique for acquisition of tumor assessment data must be used to characterize each identified and reported lesion at each measurement. All patients must undergo tumor assessments performed at the participating study center or at a radiology facility associated with the site. Tumor measurements will be evaluated locally and centrally per RECIST and RANO-BM criteria. Local assessments will be used for patient management and all tumor imaging (head, chest, abdomen and other as appropriate) and digital photography must be forwarded to a central imaging facility to permit blinded independent review.

[redacted]

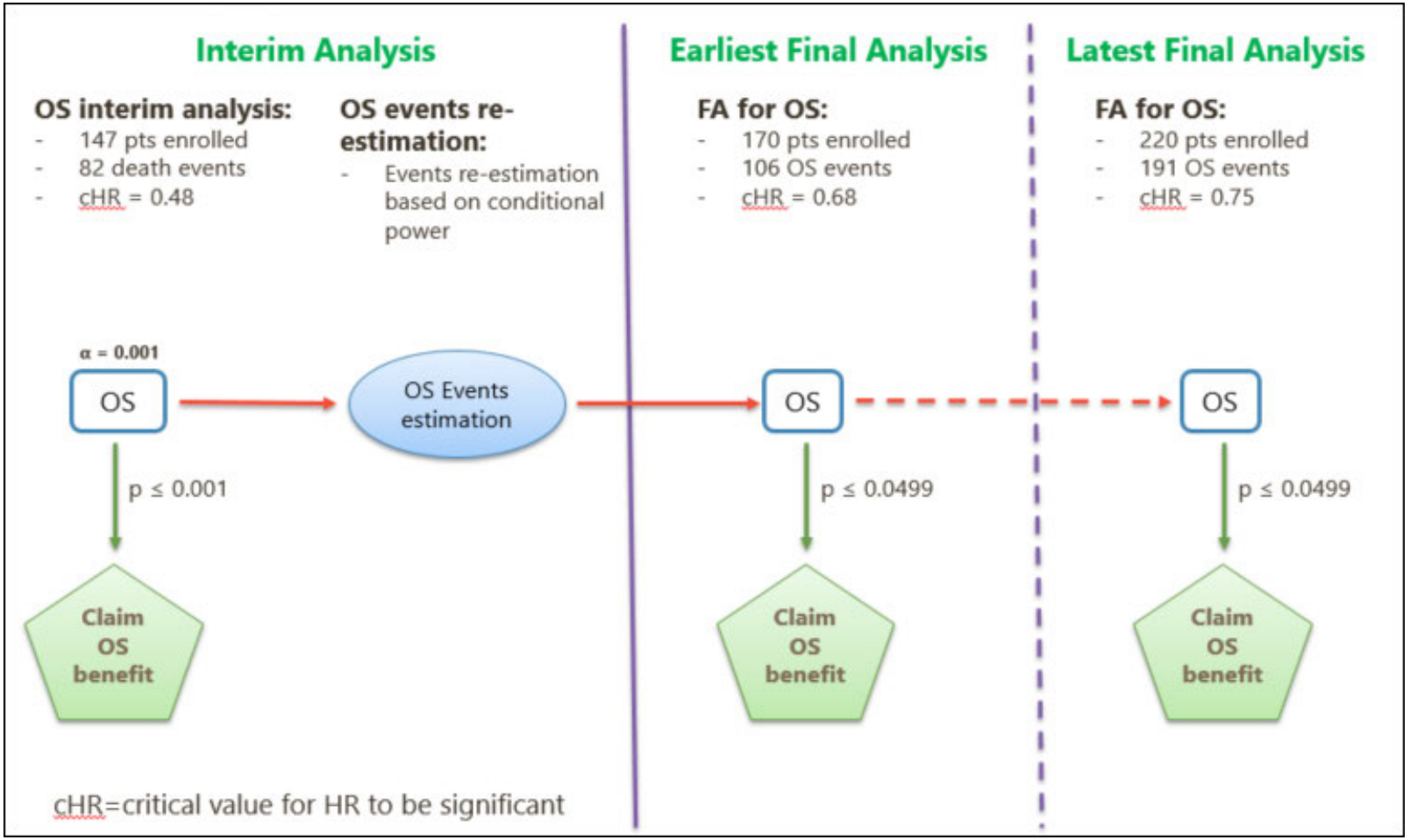
Statistical Plan and Methods:	The study is powered for detecting superiority of NKTR-102 compared with TPC in OS and up to 220 patients will be enrolled. The number of death events needed to provide 80% conditional power for the final analysis will be determined at an interim analysis when approximately 82 death events are available using the promising zone adaptive method (Mehta & Pocock, 2011). The minimum and maximum number of events for the final analysis will be 106 and 191, respectively. Two-sided α of 0.001 will be used to test efficacy at the interim analysis (efficacy zone-as part of promising zone design). One hundred ninety-one (191) events will be able to demonstrate statistical significance for any observed hazard ratio of 0.75 or better. The detailed event size adaptation rules based on conditional power are provided in an appendix to the DMC charter. One interim analysis and one final analysis will be conducted: • Interim Analysis (IA – OS interim [$\alpha = 0.001$] and death events re-estimation): when approximately 82 death events have been observed. • Final Analysis (FA - OS final [significant $p \leq 0.0499$]): timing will be determined at the time of IA using the promising zone adaptive method (Mehta & Pocock, 2011) to estimate the death events needed. The primary analysis of OS will be the Cui, Hung and Wang [CHW] test with pre-specified weights (Cui, Hung, & Wang, 1999) to ensure type I error control and the conventional test with equal weights for every patient will be conducted as a sensitivity analysis. If more than 10% of the study population (i.e., > 35 patients) received local treatment for CNS lesions (SRS, WBRT or surgery) during the study, the proportion of patients who received treatment for CNS lesions during the study will be compared between treatment groups using Fisher's exact test. The impact of treatment for CNS lesions on OS will be evaluated using a Cox regression model comparing patients who received treatment for CNS lesions with those who did not receive treatment for CNS lesions.

1.1 Study Schematic



[redacted]

1.2 Adaptive Design Study Flow



[redacted]

1.3 Schedule of Assessments

	Screening		Randomization	Cycle 1	Cycle 2+		End of Treatment (EOT)	Follow-up
				Day 1	Pre-Dose	Day 1		
	≤ 28 days prior to Randomization	≤ 14 days prior to Randomization		≤ 72 hours after Randomization	≤ 5 days prior to next cycle	± 3 days	30 ± 7 days after last dose	Every 12 wks ± 2 wks
Informed Consent	X							
Select TPC to be offered to patient	X							
Eligibility Criteria	X							
Medical History	X							
Prior Cancer Therapy, Surgery, and Radiotherapy	X							
Receptor status (ER, PR, and HER2), and HER2)	X							
Physical Exam - Complete	X							
Physical Exam - Symptom Directed				X	X		X	
Height	X							
Vital Signs (Temperature, BP, HR, RR, Weight)	X			X	X		X	
ECOG Performance Status		X						
Serum Pregnancy Test (WCBP only) [a]		X			X		X	
Central Lab: CBC with Differential [b]		X			Pre-dose		X	
Central Lab: Serum Chemistry [c]		X			Pre-dose		X	
Central Lab (optional): PT [d]		X						
Central Lab (optional): Urinalysis [d]		X						

[redacted]

	Screening		**Randomization**	**Cycle 1**	**Cycle 2+**		**End of Treatment (EOT)**	**Follow-up**
				Day 1	**Pre-Dose**	**Day 1**		
	≤ 28 days prior to Randomization	≤ 14 days prior to Randomization		≤ 72 hours after Randomization	≤ 5 days prior to next cycle	± 3 days	30 ± 7 days after last dose	Every 12 wks ± 2 wks
Randomization			X					
Body Surface Area (BSA)				X	X			
PK Blood Sample (Group A only; with consent)				Pre-dose	Pre-dose			
UGT1A1 Blood Sample (Group A only)				X				
Biomarker Blood Sample (all patients; with consent) [e]				Pre-dose	C2 only		X	
PEG-antibody Blood Sample (Group A only; with consent)				X	Pre-dose C2, C4 C6		X	
Dispense loperamide (Group A only)				X	As needed to maintain supply			
Chemotherapy: NKTR-102 or TPC[f]				X		X		
HRQoL (EORTC QLQ-C30 with BN-20, EQ-5D-5L™, and BFI)[g]	X			Pre-dose	X		X	
Tumor Assessments: Radiological Exams by RECIST and RANO-BM[h]	X			Q8w (± 7d) through Week 24, then every 12 weeks thereafter				
Concomitant Medications [i]	X							
Adverse Events [j]	X							

[redacted]

	Screening		Randomization	Cycle 1	Cycle 2+		End of Treatment (EOT)	Follow-up
				Day 1	Pre-Dose	Day 1		
	≤ 28 days prior to Randomization	≤ 14 days prior to Randomization		≤ 72 hours after Randomization	≤ 5 days prior to next cycle	± 3 days	30 ± 7 days after last dose	Every 12 wks ± 2 wks
Pharmacoeconomic questionnaires [g]					Pre-dose		X	
Survival Follow-Up[k]								X

Abbreviations: AE: adverse event; BFI: Brief Fatigue Inventory; BP: blood pressure; BRCA 1: breast cancer 1, early onset; BRCA 2: breast cancer 2, early onset; BSA: body surface area; CBC: complete blood count; CR: complete response; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Core 30; EOT: end of treatment; EQ-5D-5L™: EuroQol 5D; ER: estrogen receptor; HER2: human epidermal growth factor receptor 2; HR: heart rate; HRQoL: health-related quality of life; PK: pharmacokinetic; PR: partial response; PT: prothrombin time; RANO-BM: Response Assessment in Neuro-Oncology Brain Metastases; RECIST: Response Evaluation Criteria in Solid Tumors; RR: respiration rate; TPC: treatment of physician's choice; UGT1A1: uridine diphosphate-glucuronosyl transferase 1A1.

a. At Cycle 2 and beyond, urine or serum pregnancy test by local laboratory is acceptable if negative result is confirmed prior to dosing, provided that serum pregnancy test via the central laboratory is obtained simultaneously.

b. Central Laboratory results should be used to determine patient eligibility (Section 6.3); thereafter, central labs must be obtained prior to each cycle. If local lab results are used for re-treatment decisions, duplicate central lab tests must be submitted to the central laboratory.

c. All patients (Group A and B) must submit chemistry samples to the central lab for analysis. If local labs will also be obtained, patients randomized to Group A (NKTR-102) must have the following assessed prior to dosing (to check electrolytes and kidney function): bicarbonate/CO_2, calcium, chloride, potassium, sodium, and serum creatinine.

d. Samples (PT and urinalysis) should be collected pre-treatment only if indicated by clinical symptoms.

e. Biomarker blood sample to be collected prior to first dose.

f. NKTR-102 (145 mg/m^2 over 90 minutes via constant rate IV infusion); TPC may be in 21 or 28-day cycles as a single dose or at weekly intervals, as determined by the investigator.

g. Questionnaires should be completed on Day 1 of each Cycle prior to infusion and at End of Treatment visit.

h. Head imaging (MRI with contrast preferred per RANO-BM criteria); thorax and abdomen (CT with contrast preferred); pelvis if known disease. Tumor assessments continue through follow-up phase and stop when there is documented PD per RECIST. Confirmation of response, either PR or CR, is required. A confirmatory radiological exam should be performed ≥ 4 weeks after the criteria for response are first met. All tumor imaging (head, chest, abdomen and other as appropriate) and digital photography must be forwarded to a central imaging facility to permit blinded independent review (local assessment will be used for patient management).

i. Concomitant Medications taken from the time of Informed Consent through End of Treatment should be collected.

j. Only Serious Adverse Events related to study procedures should be collected from the time of Informed Consent through first dose. All AEs, regardless of relationship, that occur between Cycle 1 Day 1 through End of Treatment should be collected (sites should contact patients in both treatment groups at least weekly for the first 3 months while on study drug). Only AEs related to study drug should be collected from EOT through follow-up. New related SAEs that occur > 30 days after last dose of study treatment will be recorded.

k. After completion of therapy, all patients must be followed until death via phone contact, clinic visit, or patient chart review for every 12 weeks (± 2 weeks) until the end of study (or as directed by Sponsor).

[redacted]

2.0 INTRODUCTION

2.1 Background

Although the overall survival of patients with advanced breast cancer has improved over the last decade, the rising incidence of breast cancer brain metastases (BCBM) continues to be a major clinical problem with a poor prognosis and an unmet medical need for effective therapies. The prevalence of BCBM in unselected patients with advanced breast cancer disease has been estimated to be 30%, and up to 80% of these have concurrent extracranial disease (Sorlie, 2003; Kodack, 2015).

The cornerstone for treating patients having BCBM is radiotherapy and in select cases, surgery. While whole brain radiotherapy and surgery have been shown to substantially reduce brain metastases progression rates, there is no clear evidence of an effect on survival and patients are at risk of serious quality-of-life altering adverse effects such as memory loss (Soon, 2014). Although it is typically recommended that BCBM be treated with systemic chemotherapy before or after radiotherapy or surgery (Gil-Gil, 2013), there are no approved chemotherapy regimens specifically indicated for the management of BCBM, nor are there consensus-based recommendations for the general chemotherapeutic management of BCBM (guideline on the disease management of patients with human epidermal growth factor receptor 2 (HER2)+ breast cancer and brain metastases was recently published in 2014 [Ramakrishna, 2014]). In principle, clinicians have available the entire armamentarium of chemotherapeutics that are used in the treatment of metastatic breast cancer, however, unfortunately, chemotherapy results in minimal potency on brain metastases (Anderson, 2013; Steeg, 2011) due to the following limitations:

1. **Blood-tumor barrier:** Although compromised, the blood-tumor barrier is still effective in precluding efficient entry of chemotherapeutic agents into the brain metastases (Lockman, 2011);

2. **Efflux transporters:** Many of the chemotherapeutics approved for treatment of metastatic breast cancer are known substrates for efflux transporters (such as P-glycoprotein) that are highly expressed at the blood-tumor barrier. This ultimately results in poor distribution to both intra-cranial and extra-cranial lesions (Kemper, 2003; Schinkel, 1999; Wils, 1994; Taub, 2005; Lin, 2011; Polli, 2001; Shen, 2011; Taur, 2011);

3. **Resistance:** Metastatic tumors are either intrinsically resistant to therapy or eventually acquire resistance at some point during chemotherapy exposure due to numerous mechanisms. While various cytotoxic therapies are available for patients with breast cancer brain metastases, drug resistance is inevitable and response rates are low (Andreopoulou, 2013; Lalla, 2014; Seidman, 2011); and

4. **Cumulative toxicities:** Therapeutic options are limited for patients with advanced cancer when overlapping and/or cumulative toxicities (in particular, neuropathy, myelosuppression, fatigue, and cardiomyopathy) are present (Andreopoulou, 2013; Florea, 2013).

Thus, due to the paucity of brain-permeable chemotherapeutic agents, choice of therapy is often guided by an agent's activity against systemic disease. In fact, data from patients with BCBM suggest that control of systemic disease is strongly associated with improved outcomes (Lin, 2008; Melisko, 2008; Lin, 2013).

Unfortunately, treatment options for patients with central nervous system (CNS) relapse or progressive BCBM after surgery and radiotherapy approaches remain limited, with literature reviews of small prospective trials showing only modest response rates and short duration of benefit. Currently available chemotherapies distribute poorly to lesions in the brain due to difficulties penetrating the blood-tumor barrier (BTB) and because they are substrates of the efflux transporters expressed at the BTB. Unlike many other chemotherapeutics, NKTR-102 is not a substrate of such efflux transporters, and NKTR-102 has demonstrated enhanced permeation and retention (EPR) in pre-clinical models, resulting in high concentrations of its active metabolite (7-ethyl-10-hydroxy-camptothecin; the active metabolite of irinotecan [SN38]) in brain tumors.

In a mouse xenograft model of BCBM, NKTR-102 exhibited preferential accumulation (170-fold) in brain tumors over the corresponding plasma concentrations by seven days postdose. Once in the tumor, NKTR-102 served as reservoir for continued release of SN38, as reflected by a 30-fold higher concentration of SN38 in tumor tissue compared with plasma. In contrast, tumor accumulation and retention of SN38 were not observed after treatment with irinotecan.

In a mouse xenograft model of BCBM, NKTR-102 resulted in a median survival of 74 days, with 50% of animals surviving to the end of the 91-day study. Metastatic tumor burden was nearly eliminated in these animals. In contrast, irinotecan (administered at the same strength as NKTR-102) lacked efficacy in this model, as indicated by a median survival of 37 days, which was the same as observed in the vehicle control group (Adkins, 2015).

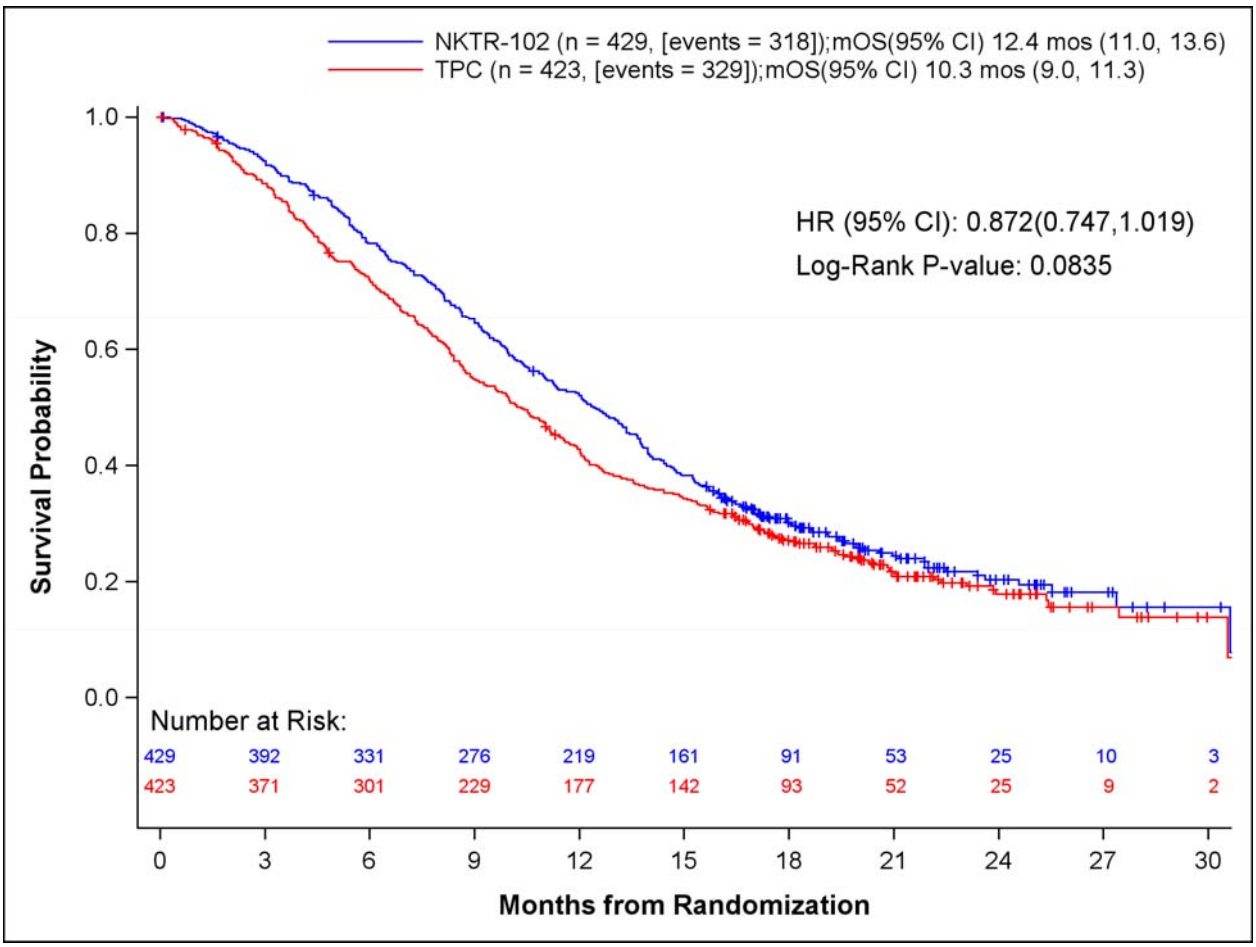
Patients with a history of stable brain metastases were included in the BEACON Study (BrEAst Cancer Outcomes with NKTR-102): A Phase 3 Open-Label, Randomized, Multicenter Study of NKTR-102 versus Treatment of Physician's Choice (TPC) in Patients with Locally Recurrent or Metastatic Breast Cancer Previously Treated with an Anthracycline, a Taxane, and Capecitabine. The inclusion of patients with breast cancer and brain metastases was based on the pre-clinical data suggesting potential benefit in this group of patients. This population was also pre-specified as a sub-group of interest in the BEACON study analysis plan.

[redacted]

2.2 BEACON Study Results in Patients with a History of Brain Metastases

In the BEACON study (Perez, 2015 [Appendix 2]), a total of 852 patients were randomized (1:1) to either NKTR-102 (145 mg/m^2 q21d) or TPC administered per standard of care. Patients in the TPC treatment group received one of the following intravenous (IV) single-agents: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel.
Figure 1 shows that single-agent NKTR-102 resulted in a 2.1 month increase in median overall survival benefit over the treatment of physician's choice (12.4 vs. 10.3 months; *P* = .0835) with a hazard ratio (HR) of 0.87 (95% confidence interval [CI], 0.747 to 1.019).

Figure 1: BEACON Study Kaplan-Meier Plot for Overall Survival Intent-to-Treat Population



[redacted]

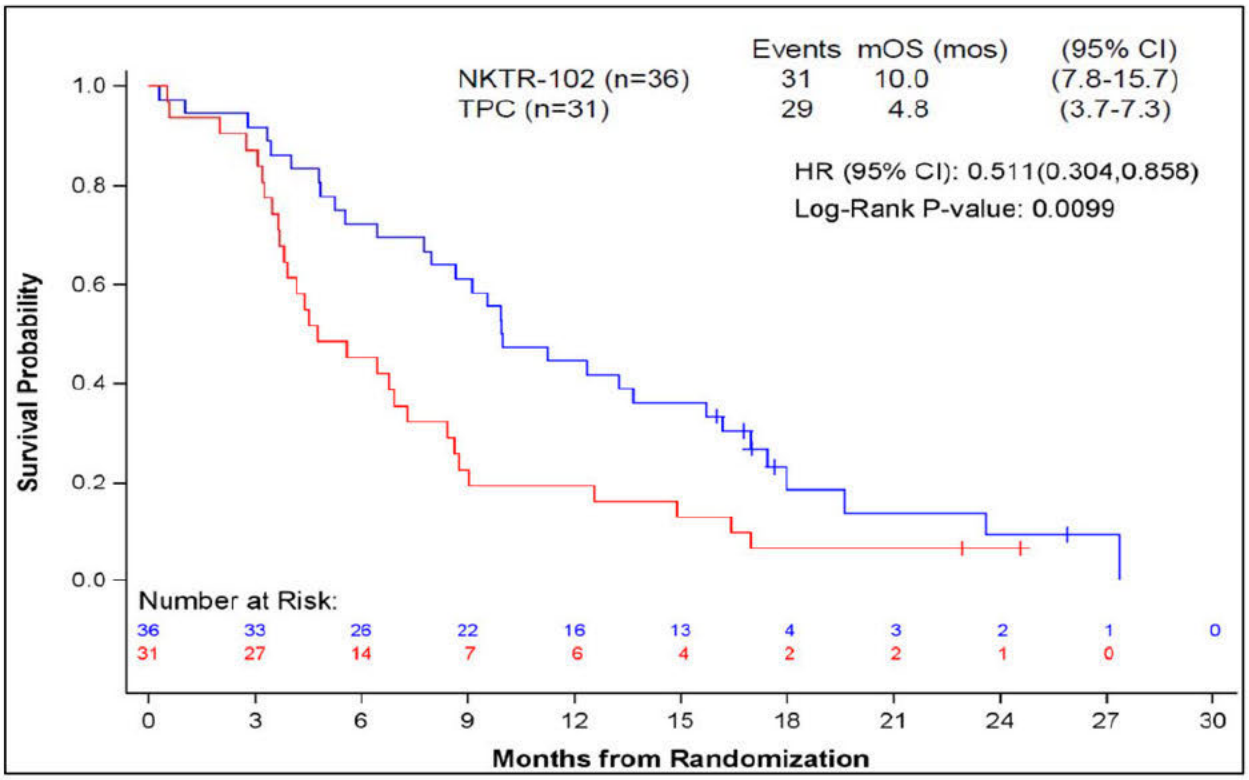
Although the study did not reach statistical significance for the primary efficacy endpoint, there was a clinically meaningful and statistically significant improvement in overall survival (OS) for the patients randomized to NKTR-102 who entered the study with a history of brain metastases at baseline in a pre-specified subset analysis.

A total of 67 patients with a history of baseline brain metastases were randomized to the BEACON study. Eligibility criteria required that these patients have had surgical resection, whole brain radiotherapy, and/or stereotactic radiation. Use of corticosteroids for brain metastases had to have been discontinued for at least 3 weeks prior to randomization, and signs or symptoms of brain metastases had to be stable for at least 28 days prior to randomization. No known progression of brain metastases (by imaging as assessed by Response Evaluation Criteria in Solid Tumors [RECIST]) was permitted, and patients with leptomeningeal disease or meningeal carcinomatosis were excluded.

Of the 67 patients in the BEACON BCBM subgroup, in the primary survival analysis, a total of 60 deaths had occurred, comprised of 31 (86%) in the NKTR-102 group and 29 (94%) in the TPC group. Pre-specified BCBM subgroup analyses demonstrated a significant improvement in survival with a doubling of survival in the NKTR-102 group (10.0 months) versus the TPC group (4.8 months). The estimated median overall survival of 4.8 months for patients with breast cancer brain metastases (BCBM) treated with TPC in the BEACON study was consistent with the reported median OS from previously published clinical studies. A review of the literature from selected clinical trials of systemic therapies for the treatment of BCBM report median OS in the range of 5.0 to 6.4 months (Freedman, 2011; Iwamoto, 2008; Lin, 2009; Christodoulou, 2005). The Kaplan-Meier curves for this subgroup are displayed in Figure 2. This significant reduction in death associated with NKTR-102 resulted in a HR of 0.51 (95% CI, 0.304 to 0.858; $P < 0.01$).

[redacted]

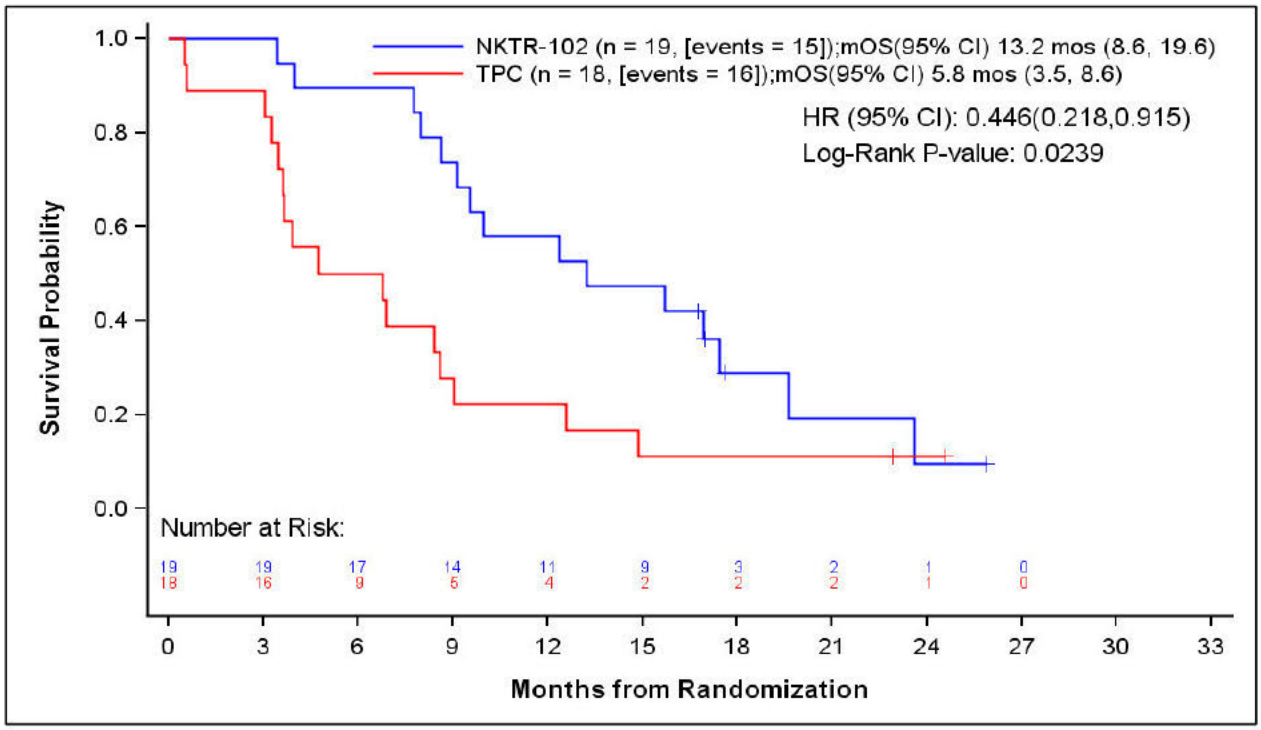
Figure 2: **Kaplan-Meier Plot for Overall Survival Intent-to-Treat Population with Brain Metastases History**



The trends in survival and response that favored NKTR-102 over TPC in all patients with a history of brain metastases (N = 67) were also observed (post hoc) in the subgroup of these patients (N = 37) with radiographic evidence of brain lesions at baseline. Figure 3 shows that median OS was 13.2 months (95% CI, 8.6 to 19.6) for the NKTR-102 arm (n = 19) and 5.8 months (95% CI, 3.5 to 8.6) for the TPC arm (n = 18) in this patient subgroup. Partial responses were observed in 5 of 32 (15.6%) patients in the NKTR-102 arm and 1 of 27 (3.7%) patients in the TPC arm. There were no complete responses in either treatment group.

[redacted]

Figure 3: **Kaplan-Meier Plot for Overall Survival in Patients with Tumor in Brain at Baseline (N = 37)**



In the BCBM subgroup, 44 (66%) of the 67 patients had liver metastases at study entry and 48 (72%) had a high burden of systemic disease (defined as those patients with 3 or more sites of metastatic disease). In these two subsets, NKTR-102 resulted in a survival advantage over TPC. For the patients with BCBM and liver metastases at study entry, etirinotecan pegol demonstrated a hazard ratio for survival of 0.53 [95% CI: 0.28, 0.999]); for BCBM patients with three or more sites of metastatic disease, the hazard ratio for survival was 0.48 [95% CI: 0.26, 0.89]). These findings are similar to the improvement in overall survival for these subgroups in the ITT population in BEACON, in which the hazard ratio for the 456 patients who had liver metastases at study entry equaled 0.73 [95% CI: 0.59, 0.89]) and 403 patients with three or more sites of metastatic disease had a hazard ratio of 0.77 [95% CI: 0.62, 0.95]).

NKTR-102 treatment was also associated with considerable improvement in 6- and 12-month survival rates. The 6-month rate was 72.2% for the NKTR-102 BCBM group compared with 45.2% for TPC BCBM; corresponding 12-month rates were 44.4% and 19.4%, respectively. Median progression-free survival (PFS) was 3.1 months for NKTR-102 and 2.7 months for TPC (HR, 0.840; 95% CI, 0.492 to 1.433; $P = 0.52$).

[redacted]

Progression-free survival rates at 6 months were 28.6% in the NKTR-102 BCBM group and 19.5% in the TPC BCBM group. In patients with evidence of stable brain lesions on radiographic scans at study entry, median OS was 13.2 months in the NKTR-102 group (n = 19) compared with 5.8 months for TPC group (n = 18); this, too, reached statistical significance (HR, 0.449; 95% CI, 0.218 to 0.915; $P = 0.02$). The proportion of patients alive at 6 and 12 months were 90% and 50%, respectively, in the NKTR-102 group compared with 58% and 22%, respectively, in the TPC group.

Among patients with measurable disease at baseline in the BEACON BCBM subgroup (NKTR-102, n = 32; TPC, n = 27), 5 patients (15.6%) had an objective response in the NKTR-102 group compared with 1 (3.7%) patient in TPC group. Of the remaining patients, approximately one-third of patients in each group had stable disease (SD); 44% of patients in the NKTR-102 group had progressive disease (PD) compared with 33% PD in the TPC group. The percent of patients with documented progression in target or non-target brain lesion(s) was similar between the 2 groups, i.e., 28% and 26%, respectively.

A post-hoc analysis of the survival data was completed according to the validated diagnosis-specific Graded Prognostic Assessment (GPA) index (Sperduto, 2012a; Sperduto, 2012b). Sperduto et al. evaluated a multi-institutional database of 400 patients with newly-diagnosed brain metastases from breast cancer. Three prognostic factors for survival were identified including Karnofsky Performance Status (KPS), tumor subtype (classified by human epidermal growth factor receptor 2, estrogen receptor, and progesterone receptor), and age. GPA numerical categories ranged from 0 to 4, with lower scores predictive of a worse prognosis following a diagnosis of brain metastases.

The 2 groups in the intent-to-treat (ITT) BEACON study population were balanced for these GPA indices (KPS, age, and tumor subtype) at baseline (Sperduto, 2012a; Sperduto, 2012b). Of the 67 patients in the history of brain metastases (BMH) subgroup (i.e., the subgroup with a history of brain metastases), 23 had a low GPA score (0 to 2) and 43 had a higher score (2.5 to 4.0). Slightly more patients in the NKTR-102 BMH group had a low (poorer) GPA score, 36% versus 32%; however, the mean (2.3) and median (2.5) GPA scores were the same for both treatment groups (Table 1). The median OS for patients with a GPA of 0 to 2 was 7.8 months for NKTR-102 and 3.8 months for TPC (HR, 0.265; 95% CI, 0.098 to 0.720; $P < 0.01$; Table 1). The median OS for patients with a GPA of 2.5 to 4 was 13.2 months for NKTR-102 and 6.9 months for TPC (HR, 0.541; 95% CI, 0.282 to 1.039; $P = 0.0616$); Kaplan-Meier curves are depicted in Figure 3. The same analyses were conducted for patients who had evidence of stable brain metastases at baseline. The same trend was seen in this smaller group (NKTR-102, n = 19; TPC, n = 18). The median OS for patients with a GPA of 0 to 2 was 9.6 months for NKTR-102 and 3.5 months for TPC; median OS for patients with a GPA of 2.5 to 4.0 was 16.8 months for NKTR-102 and 6.9 months for TPC (Figure 4). According to this validated prognostic index,

NKTR-102 was superior to TPC among patients with a history of brain metastases with a hazard ratio of 0.467 after adjusting for GPA in the Cox regression model.

Table 1: Overall Survival, Progression Free Survival, and Response Rate for Patients with History of Brain Metastases (ITT Population)

BMH Subgroup			
	NKTR-102 (n=36)	**TPC (n=31)**	**p-value**
Objective response rate Evaluable population [a] (95% CI) Complete response Partial response	5 (15.6%) n = 32 (5.3-32.8) 0 5 (15.6%)	1 (3.7%) n = 27 (0.1-19.0) 0 1 (3.7%)	0.2047
Stable disease	9 (28.1%)	9 (33.3%)	
Progressive disease	14 (43.8%)	9 (33.3%)	
Not evaluable	4 (12.5%)	8 (29.6%)	
Progressive disease in brain lesion [b]	9 (28.1%)	7 (25.9%)	
Overall survival (months) Median (95% CI)	 10.0 (7.8-15.7)	 4.8 (3.7-7.3)	 < 0.01
6-month OS rate	72.2%	45.2%	
12-month OS rate	44.4%	19.4%	
Progression-free survival (months) Median (95% CI)	 3.1 (1.8-4.0)	 2.7 (1.8-3.7)	 0.5234
3-month PFS rate	50.1%	50%	
6-month PFS rate	28.6%	19.5%	

[redacted]

Table 1: Overall Survival, Progression Free Survival, and Response Rate for Patients with History of Brain Metastases (ITT Population) (Cont'd)

Stable Brain Lesions at Study Entry			
	NKTR-102 (n=19)	**TPC (n=18)**	**p-value**
Objective response rate	4 (25%)	1 (6.3%)	0.3326
Evaluable population[a]	16	16	
95% CI	(7.3-52.4)	(0.2-30.2)	
Complete response	0	0	
Partial response	4 (25%)	1 (6.3%)	
Brain lesion status in responders[c]	3 SD; 1 CR	1 SD	
Stable disease	5 (31.3%)	6 (37.5%)	
Progressive disease	6 (37.5%)	4 (25%)	
Not evaluable	1 (6.3%)	5 (31.3%)	
Progressive disease in brain lesion	6 (37.5%)	6 (37.5%)	
Overall survival (months)			
Median	13.2	5.8	0.0239
95% CI	(8.6-19.6)	(3.5-8.6)	
6-month survival rate	89.5%	50%	
12-month survival rate	57.9%	22.2%	

[redacted]

Table 1: Overall Survival, Progression Free Survival, and Response Rate for Patients with History of Brain Metastases (ITT Population) (Cont'd)

Graded Prognostic Assessment (GPA)			
OS by GPA category – BMH Subgroup	**NKTR-102 (n=36)**	**TPC (n=31)**	**p-value**
0 to 2			
n	13	10	
Median, months	7.8	3.8	<0.01
2.5 to 4			
n	23	21	
Median, months	13.2	6.9	0.0616
OS by GPA category – Stable brain lesions at baseline	**NKTR-102 (n=19)**	**TPC (n=18)**	**p-value**
0 to 2			
n	6	5	
Median, months	9.6	3.5	0.0206
2.5 to 4			
n	13	13	
Median, months	16.8	6.9	0.0568

Abbreviations: BMH: history of breast cancer brain metastases; CI: confidence interval; CR: complete response; GPA: Graded Prognostic Assessment; OS: overall survival; PFS: progression-free survival; SD: stable disease; TPC: treatment of physician's choice

a. Efficacy evaluable population (measurable disease at baseline required).

b. Target or non-target lesions.

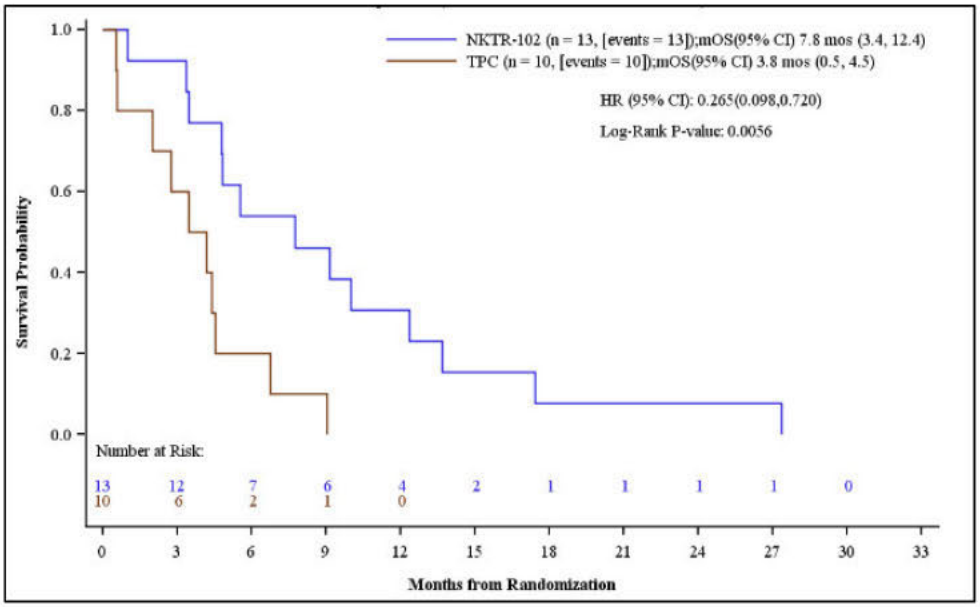
c. No responders in patients with baseline target lesions; all responding patients had non-target lesions.

[redacted]

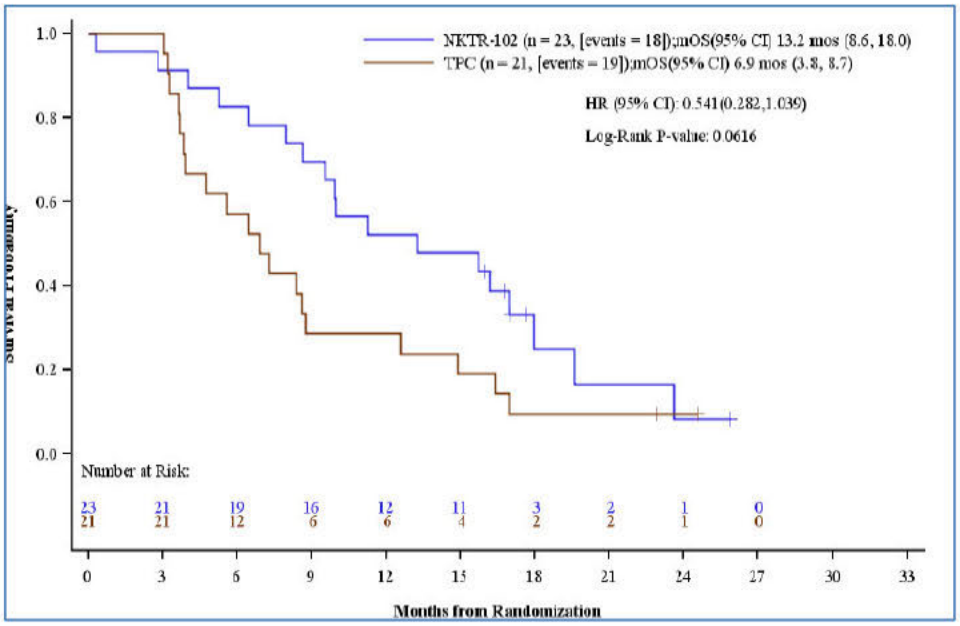
Figure 4: Overall Survival by Graded Prognostic Assessment (GPA) Index

BMH Subgroup

A. GPA 0-2



B. GPA 2.5-4



[redacted]

2.3 NKTR-102

NKTR-102 is a topoisomerase I inhibitor polymer conjugate that was engineered by attaching a polyethylene glycol (PEG) polymer to irinotecan molecules that are released following *in vivo* cleavage of a biodegradable linker. As a pro-drug of irinotecan, it was designed to improve both safety and efficacy by producing lower peak plasma concentrations and prolonging the half-life of irinotecan and its main active metabolite SN38 (37 days versus 2 days, respectively).

Irinotecan is a topoisomerase I inhibitor antineoplastic agent that is well characterized and widely used to treat colorectal and other gastrointestinal (GI) cancers. The active metabolite of irinotecan, SN38, interferes with deoxyribonucleic acid (DNA) replication and cell division by inhibiting topoisomerase I. Although irinotecan has shown single-agent objective responses in breast cancer in Phase 1 and 2 studies and has been approved for this indication in Japan, it is not approved by any regulatory authority in the European Union or United States (US) for the treatment of breast cancer.

Please refer to the NKTR-102 Investigator's Brochure for detailed preclinical and clinical study data. Please also see (Perez, 2015 [Appendix 2]) for further information on the BEACON study.

Additional evidence for NKTR-102's activity in CNS tumors was obtained in a study in 20 patients with heavily-pretreated (median of 3 prior therapies), high-grade glioma after recurrence on bevacizumab who were then treated with NKTR-102 (Nagpal, 2015). In this open-label study, 18 patients were diagnosed with glioblastoma multiforme; 3 of the 18 (17%) had a partial response, with two responses lasting for ≥ 18 months.

2.3.1 NKTR-102 Safety Profile

As of October 2015, 881 patients across all NKTR-102 clinical studies (completed and ongoing; single-agent and combination therapy) have received at least one dose of NKTR-102. Refer to the current version of the Investigator's Brochure for additional safety data.

Observations across all studies (including safety data from ongoing studies) have been generally consistent with regard to the overall safety profile of NKTR-102. Gastrointestinal toxicity, especially diarrhea, is the most common and clinically-significant toxicity. Other frequently observed adverse events (AEs) include nausea, vomiting, fatigue, decreased appetite, abdominal pain, constipation, and dehydration.

Diarrhea and dehydration secondary to diarrhea were the most common serious adverse events (SAEs) across all studies evaluating NKTR-102, occurring at frequencies of 9.7% and 4.1%, respectively. The incidence of treatment-emergent ≥ Grade 3 diarrhea in the Phase 3 BEACON study in patients with BCBM at the recommended dose and schedule was 9.6%; there were no

instances of Grade 4 diarrhea, dehydration, or vomiting. Prolonged severe diarrhea with dehydration leading to pre-renal azotemia and subsequent acute renal insufficiency has been fatal in 4 patients (1 patient in each of the Phase 2 studies in metastatic colorectal, ovarian, and breast cancers, and 1 patient in the Phase 3 BEACON study). Early onset cholinergic-mediated diarrhea has been observed with NKTR-102. Late-onset, severe diarrhea can occur and may be life-threatening if treatment is delayed. The median time to onset of Grade 3 diarrhea for NKTR-102 in the Phase 3 BEACON study was 43 days (range 3 to 488 days). Early, proactive, and aggressive intervention with anti-diarrheal therapy, IV hydration, and maintenance of electrolyte balance had a significant favorable effect on the clinical course of events, preventing volume depletion and the development of renal failure.

Myelosuppression, especially neutropenia, can occur in patients receiving NKTR-102; however, data from clinical studies evaluating NKTR-102 suggest a lower frequency and severity of neutropenia with NKTR-102 than with irinotecan. NKTR-102 administered at a dose level of 145 mg/m^2 in a q21d schedule in the Phase 3 BEACON study resulted in an overall neutropenia incidence of 21.4%; about one-third of these (7.5%) were ≥ Grade 3 neutropenia. 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.

Safety results from the Phase 3 BEACON study show a generally manageable safety profile for NKTR-102. Common toxicities (related and unrelated) with a frequency > 20% are listed by grade in Table 2.

Table 2: Treatment Emergent Adverse Events with a Frequency > 20%, Study 11-PIR-11 (BEACON, N = 425)

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Diarrhea	41.6%	14.8%	9.6%	-	-	66.1%
Nausea	36.9%	19.5%	3.5%	-	-	60.0%
Vomiting	26.4%	11.5%	2.8%	-	-	40.7%
Fatigue	14.6%	15.3%	4.5%	-	-	34.4%
Decreased appetite	19.5%	10.1%	1.2%	-	-	30.8%
Constipation	20.0%	6.1%	0.2%	-	-	26.4%
Headache	15.8%	5.4%	1.2%	-	-	22.4%
Asthenia	9.6%	10.1%	1.9%	-	-	21.6%
Abdominal pain	11.5%	8.7%	1.2%	-	-	21.4%
Neutropenia	2.1%	11.8%	5.4%	2.1%	-	21.4%

[redacted]

2.3.1.1 Study Drug Discontinuation due to Adverse Events and Physician Decision

A summary of the most common treatment-emergent adverse events (TEAEs) leading to study drug discontinuation (> 1 patient in the NKTR-102 treatment arm) is presented in Table 3. There was a higher overall incidence of TEAEs leading to discontinuation in the NKTR-102 treatment arm (11.1%) compared with TPC (6.7%), and there was a higher incidence of diarrhea leading to discontinuation in the NKTR-102 treatment arm (3.1%) compared with the TPC treatment arm (0.0%). The incidence of neuropathy leading to discontinuation was higher in the TPC treatment arm (2.2%) compared with the NKTR-102 treatment arm (0.2%).

Strict protocol-mandated diarrhea management guidelines were implemented in the BEACON study, including requirements for removal of patients from the study due to diarrhea. Guidelines were created based on the safety experience obtained in the prior Phase 2 program where Grade ≥ 3 diarrhea occurred at a rate of approximately 20%. Dose reductions were required to prevent the possibility of accumulation of active drug upon repeated dosing; occurrence of Grade ≥ 2 diarrhea was controlled by temporary discontinuation of NKTR-102. The BEACON protocol mandated discontinuation after the third occurrence of Grade ≥ 2 diarrhea. Because the incidence of Grade ≥ 3 diarrhea is less than 10% with the implementation of diarrhea management guidelines, and given that the median time to resolution for all Grades of diarrhea was 1.5 days, any subsequent studies will not require treatment discontinuation after 3 episodes of Grade ≥ 2 diarrhea.

Also of importance, a greater proportion of patients were removed from NKTR-102 (2.8%) for neutropenia compared with TPC (0.2%), despite the lower rate of Grade ≥ 3 neutropenia with NKTR-102 (9.6%) compared with that of TPC (30.6%). Comparing NKTR-102 with TPC, neutropenia was also different in terms of time to onset (median time to onset of 62 versus 17 days for the NKTR-102 and TPC arms, respectively). In addition, patients were required to be discontinued due to recurrent Grade 2 neutropenia in the NKTR-102 group due to the long elimination half-life (typically the TPC drugs required recurrent Grade 3 neutropenia, not ameliorated by growth factor support, in order to discontinue from therapy). In addition, the median time to onset of Grade ≥ 3 neutropenia was 120 days on NKTR-102 compared with 16 days on TPC, supporting the potential of this toxicity to be cumulative in nature.

Table 3: Summary of TEAEs Leading to Study Drug Discontinuation by Preferred Term (> 1 Patient in NKTR-102 or TPC Treatment arm) (Safety Population)

Preferred Term [a]	NKTR-102 (N = 425)	TPC (N = 406)
Total Number of TEAEs Leading to Study Drug Discontinuation [b]	47	27
Number of Patients With at Least One TEAE Leading to Study Drug Discontinuation	47 (11.1%)	27 (6.7%)
Diarrhea	13 (3.1%)	0
Neutropenia[c]	12 (2.8%)	1 (0.2%)
Pleural effusion	2 (0.5%)	2 (0.5%)
Vomiting	2 (0.5%)	0
Neuropathy[d]	1 (0.2%)	9 (2.2%)
Dyspnea	0	2 (0.5%)
Fatigue	0	2 (0.5%)

Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; TEAE: treatment-emergent adverse event; TPC: treatment of physician's choice

a. MedDRA v. 14.1
b. The total number of TEAEs counts all TEAEs for patients. A patient is counted only once within each summary level. The adverse event that was reported as the primary reason for study drug discontinuation is summarized.
c. Neutropenia includes neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis.
d. Neuropathy includes neuropathy peripheral, peripheral sensory neuropathy, paresthesia, neurotoxicity, neuralgia, peripheral motor neuropathy, and polyneuropathy.

A higher proportion of patients were withdrawn from treatment due to physician decision in the TPC arm (57/423; 13.5%) compared with the NKTR-102 arm (28/429; 6.5%). Typical reasons for clinical progression included symptoms of underlying disease such as increasing dyspnea, general deterioration, and reduced performance status. In the presence of clinical evidence suggesting progression, benefit/risk assessment may lead to discontinuation of treatments with less tolerable safety profiles (e.g., TPC).

The nature, scope, and severity of the safety findings to date with NKTR-102 are clinically manageable and consistent with findings common to treatments for patients with MBC.

2.3.2 Safety of NKTR-102 Compared with 7 TPC Agents in the BEACON Study

Given the known safety profiles of NKTR-102 and each of the treatments in the TPC arm administered in the BEACON study, adverse events of special interest included diarrhea and neutropenia. The incidence of AEs of special interest (diarrhea, neutropenia) was generally as expected, given the known safety profiles of the treatments in each treatment arm. There was a higher incidence and greater severity of gastrointestinal (GI) symptoms, particularly diarrhea associated with NKTR-102, and higher incidence and greater severity of events related to myelosuppression, particularly neutropenia associated with TPC.

Diarrhea

Of the 66.1% of patients in the NKTR-102 treatment arm who experienced diarrhea, most of the events were Grade 1 (41.6%) to Grade 2 (14.8%); 9.6% of patients randomized to NKTR-102 experienced Grade 3 diarrhea, and none experienced Grade 4 or 5 diarrhea. The overall median time to onset of Grade 2 or higher diarrhea was 39.5 days (range 1 to 471 days) in the NKTR-102 treatment arm, compared, with a median of 66.5 days (range 1 to 385 days) in the TPC treatment arm. The overall median time to onset of Grade 3 diarrhea in the NKTR-102 treatment arm was 43 days (range 3 to 488 days), compared with a median of 7 days (range 1 to 79 days) in the TPC treatment arm; 41 patients in the NKTR-102 treatment arm compared with 5 patients in the TPC treatment arm experienced Grade 3 diarrhea. Median duration of diarrhea of any grade was lower in the NKTR-102 treatment arm (1.5 days, range 1 to 52 days) than in the TPC treatment arm (3 days, range 1 to 123 days). Median duration of Grade ≥ 3 diarrhea was 6 days in the NKTR-102 treatment arm (range 1 to 31 days) and 4 days in the TPC treatment arm (range 1 to 21 days).

Dose reductions occurred in 47 patients (11.1%) in the NKTR-102 arm, with 63 patients (14.8%) receiving a dose delay due to diarrhea; the corresponding proportions of patients in these categories in the TPC treatment arm were 0.5% and 0.7%, respectively. The median NKTR-102 dose delay was 7 days (range 4 to 35 days).

Overall, 60.4% of patients in the NKTR-102 treatment arm and 12.1% of patients in the TPC treatment arm received concomitant medications belonging to the “anti-diarrheals, intestinal anti-inflammatory/anti-infective agents” ATC Level 2 drug class.

Neutropenia

In the BEACON study, the incidence of neutropenia was higher in the TPC treatment arm (175 patients, 43.1%) than in the NKTR-102 treatment arm (111 patients, 26.1%). Moreover, the neutropenia events were more severe in the TPC treatment arm, with 19.5% of patients experiencing Grade 3 neutropenia, 11.1% experiencing Grade 4 neutropenia, and 0.2% experiencing Grade 5 neutropenia, compared with 7.5%, 2.1%, and 0%, respectively, in the NKTR-102 treatment arm. Median time to onset for any grade neutropenia was 62 days (range 4 to 614 days) in the NKTR-102 treatment arm, compared with 17 days (range 1 to 225 days) in the TPC treatment arm. The median time to onset of Grade ≥3 neutropenia for patients treated with NKTR-102 was longer than for TPC (120 vs. 16 days).

Dose modification decisions varied between the two arms, in that NKTR-102 required dose delays and dose reductions due to Grade 2 neutropenia, and the TPC drugs were typically not delayed nor reduced unless the patient experienced Grade 3 neutropenia. Dose delays due to neutropenia occurred in 34 patients (8.0%) in the NKTR-102 treatment arm, compared with 81 patients (20.0%) in the TPC treatment arm; dose reductions due to neutropenia occurred in 61 patients (14.4%) in the NKTR-102 treatment arm, compared with 56 patients (13.8%) in the TPC treatment arm. The median NKTR-102 dose delay was 7 days (range 1 to 22 days); dose delay was not evaluable for the overall TPC arm because of the variety of TPC treatment regimens.

Overall, 51 patients (11.7%) in the NKTR-102 treatment arm and 110 patients (26.0%) in the TPC treatment arm received concomitant medications belonging to the “immunostimulants” (hematopoietic growth factors) ATC Level 2 drug class for neutropenia.

2.3.3 Safety Conclusions

In the BEACON study, NKTR-102 was associated with fewer Grade ≥ 3 toxicities compared with the TPC arm (48.0% versus 63.1%; $P < 0.001$). As expected, a higher incidence of GI events occurred in the NKTR-102 treatment arm, in particular mild-to-moderate diarrhea. In contrast, on the TPC arm, there was a higher incidence of myelosuppression and neuropathy. The differentiated mechanism of action and pharmacokinetics of a long-acting topoisomerase-I inhibitor (NKTR-102) not only resulted in a superior safety profile compared with TPC but in a safety profile substantially distinguished from currently-available therapies for MBC. This difference is critical, as sequential monotherapy by 2 agents with overlapping toxicities may result in clinically-significant treatment delays or further reduce available treatment options.

2.4 Comparator Drug

Breast cancer is a widely heterogeneous disease and there is no general consensus regarding the best approach for treating BCBM. Multiple prognostic factors such as a patient's functional status, tumor receptor status, number of brain lesions, and extent of systemic disease are taken into consideration when choosing treatment options. In clinical practice, physicians may subjectively base decisions on these factors due to the lack of generalized standard practice guidelines for the treatment of BCBM. Moreover, given that intracranial lesions are notoriously resistant to chemotherapeutics, it is not surprising that there are no approved agents, cytotoxic or targeted, for the treatment or prevention of BCBM (Lin, 2013; Hambrecht, 2011). Conventional chemotherapeutics in standard doses are used to treat BCBM in hormone receptor-positive and triple-negative disease (Lombardi, 2014; Lin 2013; Hambrecht 2011; Lim, 2012; Arslan, 2014; Gil-Gil, 2013).

Depending on the breast cancer subtype, up to 80% of breast cancer patients with brain metastasis have synchronous extracranial disease (Sorlie, 2003; Kodack, 2015), and data in patients with BCBM suggest that control of systemic disease is strongly associated with improved outcomes (Lin, 2008; Melisko, 2008; Lin, 2013).

Since this study is designed to be confirmatory to the BEACON study in evaluation of NKTR-102 treatment on a BCBM population, the treatment of physician's choice will remain the same as was used in BEACON and will include the following chemotherapeutic agents in the comparator group:

- Eribulin
- Vinorelbine
- Gemcitabine
- Paclitaxel
- Docetaxel
- Nab-paclitaxel
- Ixabepilone

[redacted]

2.5 Risks/Benefits and Population

There is no standard of care or universal chemotherapeutic approach for treating patients with BCBM after progression with an anthracycline, a taxane, and capecitabine. Choice of chemotherapeutic agent is driven by the nature and timing of prior therapy, extent of systemic and intracranial disease burden, cancer-related symptoms, patient preference, and availability of specific drugs in a given country. With an expected survival of < 1 year, current agents for treating BCBM patients are not optimal. New chemotherapeutic agents are urgently needed, especially agents with a non-overlapping mechanism of action to mitigate potential cross-resistance and reduce overlapping toxicities.

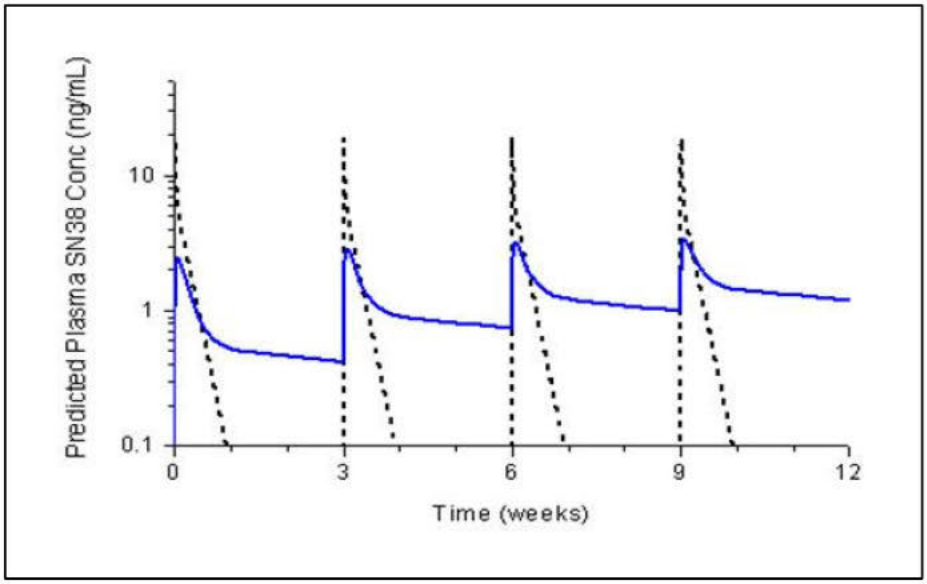
The encouraging survival findings among the BEACON study patients with a history of brain metastases who received NKTR-102 indicate that the potential benefit/risk profile justifies the exploration of NKTR-102 in this population.

2.6 Study and Dose Rationale

A single dose of 145 mg/m^2 NKTR-102 given every 21 days (q21d), the dose schedule used in the BEACON study, results in approximately the same plasma exposure to SN38 as a 350 mg/m^2 dose of irinotecan administered q21d. However, the exposure between dosing cycles with NKTR-102 is continuous and displays a markedly-reduced maximum concentration (C_{max}). In addition to the improved pharmacokinetic (PK) profile (Figure 5), NKTR-102 shows higher distribution and retention at sites of abnormal vasculature, allowing SN38 released from NKTR-102 to concentrate at metastatic sites of disease, including brain metastases. The combination of improved PK and preferential distribution and retention at sites of abnormal vasculature enable prolonged exposure of the tumor to the active metabolite, while reducing adverse effects without loss of efficacy.

[redacted]

Figure 5: **Simulated Plasma Concentration-Time Profiles of SN38 after Administration of NKTR-102 (Solid Line) or Irinotecan (Broken Line)**



Comparison of the simulated plasma concentration- time profiles of SN38 after irinotecan administration (350 mg/m^2; dashed line) with that after NKTR-102 administration (145 mg/m^2; solid line).
Sources: (Jameson, 2013; Xie, 2002).

[redacted]

3.0 STUDY OBJECTIVES

3.1 Primary Objective

To compare overall survival (OS) of patients who receive 145 mg/m^2 NKTR-102 given once every 21 days (q21d) with OS of patients who receive Treatment of Physician's Choice (TPC) selected from the following list of 7 single-agent intravenous (IV) therapies: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel. TPC drugs will be administered per the standard of care.

3.2 Secondary Objectives

- To compare the objective response rate (ORR) from NKTR-102 treatment with that of TPC; assessment of tumor outside the CNS will use the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; assessment of CNS metastases will use the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM)

- To compare progression-free survival (PFS) from NKTR-102 treatment with that of TPC; assessment of tumor outside the CNS will use RECIST version 1.1; assessment of CNS metastases will use RANO-BM

- To compare the clinical benefit rate (CBR) from NKTR-102 treatment with that of TPC (i.e., the proportion of patients having complete response [CR], partial response [PR], or stable disease [SD] for at least 4 months); CBR for peripheral lesions and for CNS lesions will be separately described

- To compare duration of response (DoR) from NKTR-102 treatment with that of TPC

- [redacted]

- To evaluate the safety profiles of NKTR-102 and TPC

[redacted]

- To compare health-related quality of life (HRQoL) from NKTR-102 treatment with that of TPC using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Core 30 (QLQ-C30) with the BN-20 questionnaire, the EuroQol 5D (EQ-5D-5L™) questionnaire, and the Brief Fatigue Inventory (BFI)
- [redacted]

[redacted]

4.0 STUDY DESIGN

This open-label, randomized, two-arm, multicenter, international, Phase 3 study of NKTR-102 in patients with BCBM who have stable brain metastases will evaluate single-agent NKTR-102 (145 mg/m^2 q21d) in patients who have previously received an anthracycline, a taxane, and capecitabine versus a comparator arm consisting of an active single-agent TPC.
For triple-negative breast cancer, patients must have received a minimum of 1 prior chemotherapy regimen for the indication of metastatic disease. For hormone receptor-positive disease, a minimum of 2 chemotherapy regimens must have been administered for the indication of metastatic disease, as well as at least 1 hormonal therapy. For HER2-positive disease, a minimum of 2 chemotherapy regimens must have been administered for the indication of metastatic disease as well as at least 1 HER2-targeted therapy. In Group A, NKTR-102 will be administered at a dose level of 145 mg/m^2 on a q21d schedule as a 90-minute intravenous (IV) infusion on Day 1 of each treatment cycle. In Group B, TPC will be administered per standard of care. Patients randomized to TPC will receive single-agent IV chemotherapy, limited to choice of one of the following 7 agents: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel.

Up to 220 patients will be randomized using a 1:1 randomization ratio. The following stratification factors for randomization were selected to balance the treatment groups for known factors that influence prognosis in patients with metastatic breast cancer and brain metastases:

- Geographic Region

  Stratification by geographic region (i.e., US versus the rest of the world) at randomization will be performed to balance the treatment groups for type of prior radiation therapy and differences in prior anticancer therapies or treatment of metastatic disease specific to each region.

  The standard of care for the treatment of brain metastases with radiation therapy is rapidly evolving. Recent Phase 3 randomized trial findings have shown that whole brain radiation therapy (WBRT) added to stereotactic radiation surgery (SRS) for a limited number of brain metastases (≤ 3 lesions) is associated with significantly worse cognitive function than SRS alone and no overall survival benefit despite better tumor disease control with the addition of WBRT (Brown, 2015). Multiple prospective trials have demonstrated the benefit of SRS for the treatment of a limited number of brain lesions where the definition of "limited" has been based on institutional preference and can vary from 3 to 10 lesions (Khuntia, 2015). A retrospective, longitudinal analysis of patients with breast cancer and brain metastases treated at 5 centers in the US found improved survival among patients who had fewer than 4 brain metastases that were less than 4 centimeters in size and were treated

with SRS alone versus WBRT (HR 0.54; 95% CI, 0.33-0.91) (Halasz, 2016). With increased access to precision radiosurgery systems, SRS alone for patients with limited disease has emerged as the new standard for care. Half of patients diagnosed with breast cancer and brain metastases have 3 lesions or fewer at initial diagnosis (Subbiah, 2015) and therefore, approximately 50% of patients with BCBM in the US will receive SRS alone as their first treatment. In a series of 1004 German patients, SRS was used in conjunction with surgery in 17% of patients and in 9% of patients without surgery (Witzel, 2015). The patients treated with SRS alone are closely monitored with frequent follow-up brain imaging studies to determine if additional radiosurgery or WBRT is needed for the presence of new lesions. Given the additional expense of active surveillance following SRS with multiple expensive follow-up imaging studies and the potential for repeat radiosurgical procedures, WBRT continues to play a role in the management of brain metastases in many parts of the world.

- Hormone and HER2 Receptor Status

  Stratification by tumor receptor status (triple negative breast cancer [TNBC], HER2+ and HR+/HER2-) at randomization is added to balance the treatment groups. Multiple studies have demonstrated differences in overall survival for patients with BCBM based on tumor subtype with TNBC associated with the worst prognosis and luminal subtype with the best prognosis (Niwinska, 2010, Anders 2010). Estrogen and progesterone receptor status should be determined by standard immunohistochemistry (IHC). HER2 receptor status should be determined by the local pathologist, using IHC and/or in situ hybridization and the local definition of positive/negative HER2 receptor status. TNBC status requires negative results for estrogen receptor, progesterone receptor and HER2 receptor expression by local pathology. Stratification should be based on the last available pathology report (for primary, local recurrence or metastatic site; if bone biopsy data are considered to be unreliable, results from a prior biopsy may be substituted).

  Of note, HER2-targeted therapy must be suspended in any patient with HER2-positive disease prior to randomization (HER2-targeted therapy may be re-started following discontinuation from the ATTAIN trial). Combination therapy with trastuzumab and either NKTR-102 or TPC is not permitted in this protocol. No safety data on the combination of NKTR-102 with trastuzumab currently exist. In order to investigate combination therapy, a separate study of NKTR-102 with trastuzumab is planned.

[redacted]

- ECOG Performance Status

  Stratification by Eastern Cooperative Oncology Group (ECOG) performance status at randomization is added to balance the treatment groups. Performance status is an independent prognostic factor for survival in BCBM. In a retrospective analysis of 196 patients with BCBM who received brain radiation from 2009-2013, an ECOG performance status of 1 was associated with worse overall survival compared with ECOG performance status of 0 (HR, 1.53; 95% CI 1.05 to 2.23; *P* = 0.028) (Crozier, 2015). ECOG 0 is defined as "Fully active, able to carry on all pre-disease performance without restriction". ECOG 1 is defined as "Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.

Additional secondary efficacy analyses will be undertaken to investigate the role of potential prognostics factors at baseline, including prior type of radiotherapy (SRS versus WBRT).

At Screening, the Investigator must determine which TPC will be offered to the patient and must enter the chosen agent into both the medical chart and the interactive response technology system. Data will be collected on subsequent anticancer therapies in both treatment groups from the time patients come off the study treatment until the time of primary data analysis for OS. Collected data will include any SRS, whole brain radiation therapy (WBRT), or surgery on CNS lesions. The duration of the study will be approximately 35 months. An independent data monitoring committee (DMC) will assess interim safety and efficacy data.

Treatment cycle length is either 21 days (Group A; NKTR-102) or 21 to 28 days (Group B; TPC).

A schematic of the study design is presented in Section 1.1; the Schedule of Assessments is presented in Section 1.3.

[redacted]

5.0 SELECTION OF STUDY POPULATION

Eligibility to the study is inclusive of patients with BCBM and any breast cancer tumor subtype. In a retrospective analysis of 189 consecutive patients with BCBM at a single clinical center, time to brain metastasis was assessed for 4 different subtypes: TNBC, HER2+ without trastuzumab before brain metastases, HER2+ with trastuzumab before brain metastases, and HR+/HER2- status. The median time to brain metastases for each group was as follows: 2.9 months, 5.8 months, 13.7 months, and 17.5 months, respectively. TNBC and HER2+ disease without trastuzumab use was independently associated with shorter times to brain metastases and was an independent risk factor for worse overall survival compared with patients having HR+/HER2- metastatic breast cancer (Ahn, 2013). Given the relatively short time to development of distant brain metastases among patients with TNBC, eligibility criteria for this population requires a minimum of 1 prior cytotoxic chemotherapy regimen administered for the indication of metastatic disease. For HR+ disease and/or HER2+ disease, a minimum of 2 prior cytotoxic chemotherapy regimens administered for the indication of metastatic disease is required.

Approximately 40-50% of patients with HER2-positive metastatic disease develop brain metastases over time, with a median number of total metastatic regimens equal to 5 (range 1–16). A German observational study documented improved survival with continued trastuzumab beyond progression (median 22.1 months with continued trastuzumab; median 14.9 months without continued trastuzumab; HR = 0.64; P = 0.00021) (Jackisch, 2014). The general treatment approach now includes the use of multiple lines of trastuzumab therapy; however the median number of trastuzumab-based regimens in the metastatic setting equaled only 3 (range 1-12), supporting the hypothesis that patients may receive single-agent cytotoxic chemotherapy at some point in their care (Olson, 2013). Given the high unmet medical needs of these patients, a combination therapy investigating the tolerability and pharmacokinetics of NKTR-102 and trastuzumab will be studied separately. Patients for whom continued trastuzumab would be considered standard of care should not be approached for consent to randomize in this trial. Patients who are responding to treatment for systemic disease but who develop brain metastases (including patients with brain-only metastases) are eligible to enroll, following definitive treatment of the CNS lesions. The timeframe between definitive therapy for brain metastases was set at 14 days for combination therapy (WBRT, stereotactic radiation and/or surgical resection) and 7 days for single-agent modality, as there can be an urgent need to provide systemic therapy for patients following these interventions. Provided the investigator believes that a patient has recovered from these CNS-directed therapies and otherwise meets all eligibility criteria, a patient may be enrolled in the trial.

Patients may receive any one of seven possible intravenous cytotoxic chemotherapy agents. The Principal Investigator should review the Summary of Product Characteristics (or local

Prescribing Guidelines) for the agent selected for the patient to ensure that the patient may safely receive the chosen drug. The Principal Investigator should review prohibited concomitant medications, contraindications, special warnings and precautions for use, and recommendations for dose modifications.

5.1 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study:

1. Each patient must be willing and able to comply with the protocol; the patient must provide written informed consent prior to study-specific screening procedures.

2. Female or male, age ≥ 18 years.

3. Have histologically-confirmed carcinoma of the breast (either the primary or metastatic lesions) for whom single-agent cytotoxic chemotherapy is indicated. Patients may have either measurable or non-measurable disease according to RECIST version 1.1.

4. Patients must have a history of brain metastases that are non-progressing. Brain metastases must have been previously treated with either combination therapy (whole-brain radiation with stereotactic radiation and/or surgery) ≥ 14 days prior to randomization, or single-agent modality (WBRT, stereotactic radiation or surgical resection alone, if combination therapy is contraindicated) ≥ 7 days prior to randomization; patients must be sufficiently recovered from whole-brain radiation, or stereotactic radiation and/or surgical resection, with stable signs and symptoms of brain metastases per the investigator to randomize into the study. For patients who have received whole-brain radiation, or stereotactic radiation and/or surgical resection ≥ 28 days prior to randomization, signs or symptoms of brain metastases must be stable for at least 28 days prior to randomization. Corticosteroids for this indication may be used as long as patients are on a stable or decreasing dose for at least 7 days prior to randomization.

5. For triple-negative breast cancer, a minimum of 1 prior cytotoxic chemotherapy regimen must have been administered for the indication of metastatic disease. For hormone receptor-positive disease (HER2-negative), a minimum of 2 cytotoxic chemotherapy regimens must have been administered for the indication of metastatic disease as well as at least 1 hormonal therapy. For HER2-positive disease, a minimum of 2 cytotoxic chemotherapy regimens must have been administered for the indication of metastatic disease as well as at least 1 HER2 targeted therapy (ado-trastuzumab emtansine is considered a cytotoxic chemotherapy regimen).

[redacted]

a. A "cytotoxic chemotherapy regimen" may be single-agent or combination therapy of at least 1 cycle of therapy. Treatment regimens for ipsilateral and/or contralateral recurrent disease (i.e., multiple adjuvant therapies) are permitted and are counted as 1 regimen.

b. Treatment with the same cytotoxic chemotherapy regimen without progressive disease (PD) by RECIST within 60 days following last dose of that regimen counts as 1 regimen; a single drug that is continued beyond the end of combination therapy without PD is counted as part of a single regimen.

c. A drug from a similar class that is substituted within a combination due to intolerance but not due to progression is also counted as a single regimen.

d. The following categories of drugs are not counted as "cytotoxic chemotherapy": biological agents (e.g., bevacizumab, trastuzumab, or pertuzumab), hormonal therapy, bone-targeting agents (eg., bisphosphonates, denosumab), immuno-oncology agents (CTLA4 inhibitors, checkpoint inhibitors), tyrosine kinase inhibitors, CDK4/6 inhibitors, HSP90 inhibitors, HDAC inhibitors, and mTOR inhibitors.

6. Have had prior therapy (administered in the neoadjuvant, adjuvant, and/or metastatic setting) with an anthracycline, a taxane, and capecitabine (prior anthracycline can be omitted if not medically appropriate or contraindicated for the patient).

7. Last dose of anticancer therapy must have been administered within 6 months of the date of randomization into this study.

8. All anticancer- and radiation therapy-related toxicities must be completely resolved or downgraded to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 Grade 1. Diarrhea must be completely resolved (returned to his/her expected baseline function) without supportive antidiarrheal medications. Stable sensory neuropathy must be resolved to Grade ≤ 2, and alopecia can be any grade.

9. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

10. Demonstrate adequate organ function obtained within 14 days prior to randomization and analyzed by the central laboratory as evidenced by:

    a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L without myeloid growth factor support for 7 days preceding the lab assessment;

[redacted]

b. Hemoglobin (Hgb) ≥ 9 g/dL (90 g/L); < 9 g/dL (< 90 g/L) is acceptable if hemoglobin is corrected to ≥ 9 g/dL (90 g/L) as assessed by the central laboratory by growth factor support or transfusion prior to randomization;

c. Platelet count ≥ 75 X 10^9/L without blood transfusions for 7 days preceding the lab assessment (for patients selecting vinorelbine, the screening platelet count should be greater than or equal to 100 X 10^9/L);

d. Bilirubin ≤ 1.5 X upper limit of normal (ULN), except for patients with a documented history of Gilbert's disease;

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

f. Serum creatinine ≤ 1.5 mg/dL (133 µmol/L) or calculated creatinine clearance ≥ 50 mL/min (using Cockcroft-Gault formula); creatinine clearance should be calculated using the patient's body weight in kilograms;

g. Women of childbearing potential (WCBP) must have a negative serum pregnancy test; this test is required of all women unless post-menopausal, defined as 12 consecutive months since last regular menses without an alternative medical cause or surgically sterile (permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy).

11. Women of childbearing potential (WCBP) must agree to use highly effective methods of birth control throughout the duration of the study until 6 months following the last dose of study drug. Acceptable methods are defined as those that result, alone or in combination, in a low failure rate (i.e., less than 1% per year) when used consistently and correctly, such as surgical sterilization, an intrauterine device, or hormonal contraception in combination with a barrier method. It is currently unknown whether NKTR-102 may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives should add a barrier method. In certain countries (if permitted by law), WCBP may agree to abide by heterosexual sexual abstinence during the time of participation in this study.

12. Males with female partners of child-bearing potential must agree to use a barrier contraception (e.g., condom with spermicidal foam/gel/film/cream/suppository) throughout the duration of the study until 6 months following the last dose of study drug; in addition to their female partner using either an intrauterine device or hormonal contraception and continuing until 6 months following the last dose of study drug. Male patients should not donate sperm until 6 months following the last dose of study drug. This criterion may be waived for male subjects who have had a vasectomy > 6 months before signing the informed consent form (ICF).

5.2 Exclusion Criteria

Patients who meet any of the following criteria will not be permitted entry to the study:

1. Have had their last dose of anticancer therapy (including HER2-targeted therapy) within 14 days prior to randomization.

2. Have undergone high-dose chemotherapy followed by stem cell transplantation (autologous or allogeneic).

3. Have had any major surgery within 28 days prior to randomization. This does not include surgical resection for CNS lesions, placement of a venous access device or peripherally-inserted central catheter, thoracocentesis, paracentesis, biopsy, and/or abscess drainage.

4. Concomitant use of any anticancer therapy or use of any investigational agent(s).

5. Have received prior treatment for cancer with a camptothecin-derived agent, e.g., irinotecan, irinotecan liposomal (Onivyde®, MM-398), topotecan, and investigational agents including but not limited to exatecan, rubitecan, gimatecan, karenitecan, and SN38 investigational agents such as EZN-2208, SN-2310, or AR-67.

6. Have brain metastases amenable to local therapy but without completion of such therapy (surgical resection, whole brain RT, or stereotactic radiation). An investigator may choose to not irradiate equivocal CNS lesions.

7. Have lesions on imaging, by cerebrospinal fluid or with neurological findings that the investigator believes is consistent with leptomeningeal disease or meningeal carcinomatosis.

8. Have chronic or acute GI disorders resulting in diarrhea of any severity grade; patients who are using chronic daily anti-diarrheal supportive care to control diarrhea in the 28 days prior to randomization (patients who have ingested anti-diarrheal medications in the week prior to randomization but are generally without diarrhea may still proceed to randomization; anti-diarrheal medications should be withdrawn and re-initiated only based on the guidelines in Table 4 NKTR-102 Dose Modifications and Delays).

9. Female patients who are pregnant or lactating, who plan to get pregnant, or who have a positive serum pregnancy test prior to randomization.

10. Taking any enzyme-inducing anti-epileptic drugs (EIAEDs) within 14 days of randomization, including phenytoin, carbamazepine, oxcarbazepine, or phenobarbital.

11. Receiving pharmacotherapy for hepatitis B or C, tuberculosis, or HIV.

12. Have known cirrhosis.

13. Prior malignancy (other than breast cancer) unless diagnosed and definitively treated more than 5 years prior to randomization. Patients with non-melanoma skin cancer are not excluded.

14. Severe/uncontrolled illness within the previous 28 days prior to randomization.

15. Require daily use of oxygen supplementation in the 28 days prior to randomization, defined as oxygen use for 7 or more consecutive days.

16. Significant known cardiovascular impairment (New York Heart Association Classification of Heart Failure > grade 2, unstable angina, myocardial infarction within the 6 months prior to randomization, or uncontrolled cardiac arrhythmia).

17. Any other significant co-morbid conditions that in the opinion of the Investigator would impair study participation or cooperation.

18. Prior randomization into this study.

19. Prior treatment with NKTR-102.

20. Have psychiatric illness, social situation, or geographical situation that would preclude informed consent or limit compliance with study requirements, as determined by the Investigator.

21. Known intolerance or hypersensitivity to any of the products used in this study or their excipients.

22. For patients selecting vinorelbine or gemcitabine as the TPC agent, patients may not receive yellow fever vaccine in the 28 days prior to randomization.

5.3 Removal of Patients from Study Therapy or Assessments

Patients may choose to discontinue participation in the study at any time, for any reason, and without prejudice to further treatment.

Study drug therapy must be stopped for any of the following reasons:

- Progressive disease per RECIST version 1.1 and/or RANO-BM
  - Exception: Patients with progressive disease but with stable or improved clinical performance status may continue to be treated with study drug if perceived to be beneficial to the patient by the Investigator. Neurological deterioration and the need for higher doses of steroids will not be considered progressive disease in the absence of radiographic evidence of progressive disease per RECIST
  - Exception: Progression of non-target CNS lesions captured on magnetic resonance imaging (MRI) does not require removal on study in the absence of extra-cranial progression.
- An adverse event causing unacceptable toxicity to the patient
- Death
- Physician decision
- Withdrawal of consent for treatment by the patient
- Withdrawal of consent for treatment and any subsequent follow-up by the patient
- Non-compliance
- Pregnancy
- Lost to Follow-Up
- Study terminated by Sponsor

[redacted]

If a patient withdraws consent for the analysis of biological specimens (such as PK and biomarkers), any samples not analyzed will be destroyed or returned if the analysis has not already been performed; if analysis has been performed, data pertaining to the analysis will not be removed from the database.

Patients are to be followed for efficacy outcomes until the end of the study and for safety outcomes until resolution or permanent sequelae of all toxicities attributable to the study drug. In the event of withdrawal from study participation, the study staff or Investigator must make every effort to have the patient return for the End of Treatment visit.

Sites should obtain survival information on all patients unless the patient has not consented to ongoing collection of that information. If allowed by country regulatory authorities and/or consented to by the patient, study personnel may use public records to check for mortality for any patient considered lost to follow-up and for patients who withdraw consent for follow-up contact.

6.0 TREATMENT PLAN

In Group A, NKTR-102 will be administered at a dose level of 145 mg/m^2 on a q21d schedule as a 90-minute IV infusion on Day 1 of each treatment cycle. In Group B, TPC will be administered per standard of care.

Cross-over from Group B to Group A is not permitted. Data regarding subsequent anticancer therapies, radiation therapies, and CNS surgeries will be collected in both treatment groups from the time the patient completes therapy until the time of primary data analysis for OS. After completion of therapy, all patients must be followed until death via phone contact, clinic visit, or patient chart review for every 12 weeks (± 2 weeks) until the end of study (or as directed by Sponsor to support interim and final efficacy analyses). If allowed by country regulatory authorities and/or consented to by the patient, study personnel may use public records to check for mortality for any patient considered lost to follow-up and for patients who withdraw consent for follow-up contact.

6.1 Study Assessments

Refer to the Schedule of Assessments (Section 1.3) for the details and timing of assessments to be completed.

Group A: site personnel should contact patients approximately weekly for the first 3 months while on study drug (and as needed thereafter based on clinical symptoms) to assess whether the patient is experiencing adverse events.

Group B: depending on the TPC dosing schedule, patients may return to the clinic as frequently as weekly for administration of cytotoxic chemotherapy. Local laboratory assessment may be required by institutional guidelines to determine whether retreatment may safely occur. Site personnel should contact patients approximately weekly for the first 3 months while on study drug (and as needed thereafter based on clinical symptoms) to assess whether the patient is experiencing adverse events.

6.2 Physical Examinations, Vital Signs, and BSA

Full physical examination will include examination of all major organ systems in the following categories: general, head, eyes, ears, mouth/throat, neck, heart, lungs, abdomen, lymph nodes, joints, extremities, integumentary, and neurologic. On Day 1 of each Cycle visit and End of Treatment visit, a symptom-directed physical examination may be performed. Clinically significant findings on physical examination or vital sign assessment should be captured as AEs.

Sites should use their own formula to calculate body surface area.

[redacted]

6.3 Clinical Laboratory Assessments

Clinical laboratory tests will be conducted according to the Schedule of Assessments (Section 1.3). Clinical laboratory tests (Appendix 1) will be performed by a designated central laboratory. Central laboratory results must be used to determine patient eligibility. In situations where central laboratory results are unavailable for eligibility determination, the Medical Monitor may approve of substitution of local laboratory results (a repeat full set of central laboratory results must be obtained prior to Cycle 1 Day 1).

For treatment decisions at Cycle 2 and beyond, blood draw for the central laboratory may be obtained up to 5 days prior to the scheduled day of treatment. Urinalysis and coagulation samples should also be collected pre-treatment if indicated by clinical symptoms. Depending on the turn-around time for each center, the results of these safety laboratory tests may not be available prior to the scheduled treatment. If the results are not available, or, at the discretion of the Investigator, local laboratory results obtained from blood draws as part of the institutional standard of care closest to the start time of the next infusion may be used to determine eligibility for retreatment.

Treatment decisions require results for the following tests (both Group A and B): hemoglobin, ANC, and platelets. In addition, Group A patients require testing for electrolytes (bicarbonate/CO_2), calcium, chloride, potassium, sodium, and serum creatinine). Additional requirements for Group B patients should follow institutional guidelines.

If the patient does not meet treatment criteria, the patient can be reassessed within 7 days. Any additional blood drawn must be sent to the central laboratory.

6.4 Tumor Assessments

All patients must undergo tumor assessments at the participating study center or at a radiology facility associated with the site. Tumor assessments will be conducted according to the Schedule of Assessments (Section 1.3). Tumor response evaluation is described in Section 8.6. All tumor imaging (head, chest, abdomen and other as appropriate) and digital photography must be forwarded to a central imaging facility to permit blinded independent review (local assessment will be used for patient management). Details regarding shipment of images are provided separately in the Imaging Manual.

Radiologic exams for all patients will include imaging of the brain (MRI with contrast is preferred) and the thorax and abdomen (CT with contrast is preferred), as well as digital photograph of any superficial / cutaneous lesions. Additional anatomical sites will be assessed if indicated. Selection of target lesions per RECIST version 1.1 by the Investigator (or radiologist) must occur prior to randomization (CNS lesions should not be selected as non-target lesions for

assessment by RECIST, as these are assessed separately using RANO-BM criteria). For patients with cutaneous disease, digital photography of skin lesions is required. Bone scans (radionuclide scans) are not required within 28 days prior to randomization if used only to assess non-measurable disease (i.e., data from the most recent scan may be used to assess bony non-target lesions).

Radiographic measurements must be performed to RECIST and RANO-BM specifications, as appropriate. A head imaging protocol by MRI is provided in Appendix 3 (Lin, 2015). This imaging protocol is not required for all sites and all patients. However, the minimal acceptable MRI should be performed on a 1.5 Tesla scanner, and include a Localizer/Scout sequence, 3D T1 (pre-contrast), contrast injection (unless medically contraindicated), T2 and 3D T1 (post-contrast). The gap thickness should be set at least double the size of the smallest CNS lesion. A similar gap thickness guidance should be used for head imaging by CT. If a site will perform dynamic-contrast enhanced MRI (in addition to or in place of the imaging protocol in Appendix 3), these images should also be forwarded to the central imaging facility.

To establish baseline disease, imaging should occur within 28 days prior to randomization. For patients whose CNS lesion(s) undergo definitive treatment in the 14 days (for combination therapy of WBRT with SRS and/or surgical resection) or in the 7 days (for single-modality therapy) prior to randomization, it is preferred that "baseline" is established after treatment of the CNS lesion(s) and prior to randomization. If this is not possible, baseline head imaging should occur as soon as possible after randomization (baseline head imaging must occur within the first 21 days after randomization).

Radiological exams (MRI and/or CT) are required every 8 weeks (± 7 days) starting at the date of randomization and continuing through the third on-study assessment (approximately Week 24); radiological exams should continue every 12 weeks (± 7 days) thereafter, until PD is noted. Radiological exams should not be delayed for toxicity. Patients who reach the End of Treatment visit without PD must continue to undergo radiological assessment. Depending on whether the EOT visit occurs prior to or after Week 24, the imaging interval should be every 8 weeks (± 7 days) or every 12 weeks (± 7 days) until PD by RECIST occurs. Confirmation of response, either PR or CR, is required. A confirmatory radiological exam should be performed ≥ 4 weeks after the criteria for response are first met. Scanning thereafter should continue at an 8-week or 12-week interval based on the date of the early confirmatory scan. To ensure both groups of this study are assessed for progression in a similar manner, tumor assessments must be obtained at this interval, regardless of delays in chemotherapy due to toxicity. Positron emission tomography-CT (PET-CT) may be obtained, but only CT data will be used to determine response and/or progression by RECIST.

Assessment of non-target bone disease by radionuclide bone scan should be scheduled as per institutional guidelines.

6.5 Health Related Quality of Life Assessments and Pharmacoeconomics

All patients will complete the EORTC QLQ-C30, version 3.0 with the BN-20 subscale, the EQ-5D-5L™, and the BFI on Day 1 prior to infusion for each cycle and at the End of Treatment visit. If possible, patients should complete the questionnaire in the same setting each time. If a patient completes a full set of questionnaires and has his/her study drug treatment delayed due to toxicity or administrative reasons, the patient should not be asked to complete a repeat set of questionnaires on the day that the study drug is actually infused.

In addition, data regarding selected parameters of health care utilization, including doctor visits (other than the oncologist), hospital admission and ICU stays will be collected.

6.6 Survival Follow-Up

Follow-up for survival information may be conducted via phone, clinic visit, or patient chart review approximately every 12 weeks (± 2 weeks) following the End of Treatment visit or as directed by the Sponsor. If allowed by country regulatory authorities and/or consented to by the patient, study personnel may use public records to check for mortality for any patient considered lost to follow-up and for patients who withdraw consent for follow-up contact. Data will be collected on subsequent anticancer therapies in both treatment groups from the time patients come off the study treatment until the time of primary data analysis for OS. Collected data will include any systemic chemotherapy, radiation, stereotactic radiosurgery (SRS), whole brain radiation therapy (WBRT), or surgery on CNS lesions. Cause of death (if secondary to progressive disease) will be captured to specify whether this was primarily due to progression of extra-cranial or progression of intra-cranial disease.

During follow-up contacts, patients will be asked about subsequent anticancer therapy and the first occurrence of disease progression, if not identified during study treatment. For any toxicity attributed by the Investigator to study drug, the Investigator will assess the patient to determine whether the toxicity is continuing, has resolved, or has 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).

Follow-up contacts will continue until death, withdrawal from the study by patient, patient is lost to follow up, or study termination by Sponsor.

[redacted]

6.7 Group A: NKTR-102 Treatment Guidelines

6.7.1 Treatment Criteria for NKTR-102

Prior to initiation of treatment cycles, patients must meet specific laboratory requirements with respect to hematopoietic function (Hgb ≥ 8.0 g/dL or 80 g/L; absolute neutrophil count (ANC) ≥ 1.5 X 10^9/L; platelets ≥ 50 X 10^9/L). Should an investigator wish to retreat a patient whose ANC is below 1.5 X 10^9/L but ≥ 1.3 X 10^9/L, Medical Monitor approval is required. The blood drawn must be sent to the central laboratory. Treatment decisions may be made using local or central lab results (if local lab results are used for treatment decisions, duplicate blood draws for central lab analysis must also occur). Diarrhea must be fully resolved for at least 7 days (or returned to baseline function) without supportive antidiarrheal measures prior to treatment. Serum creatinine and electrolytes (sodium, potassium, chloride, calcium, and bicarbonate/CO_2) must be tested prior to treatment; if such testing yields Grade 3 or higher toxicities, the patient should be treated for the toxicity (for example, IV hydration and/or correction of electrolyte abnormalities), and the toxicity must resolve to within normal limits or baseline levels prior to treatment. Grade 3 or higher non-hematologic treatment-related toxicities must resolve to baseline or Grade 1; continued treatment with NKTR-102, even with dose reduction, is not permitted without such resolution.

Dose reductions and dose delays may be implemented for patients who experience recurrent or specific severe toxicities that are classified as possibly related or related to NKTR-102 by the Investigator (Table 4).

6.7.2 Dose Modifications due to Treatment-Related Toxicity

All AEs will be assessed according to the NCI-CTCAE version 4.03. 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 treatment, treatment may be delayed, followed by an additional evaluation to determine feasibility of treatment. Initiation of subsequent doses may be delayed for a maximum of 28 days to allow recovery from any toxicity to permit treatment (with the delay calculated from the scheduled date of the next infusion).

Patients who require treatment delays of > 28 days due to unresolved toxicity must be withdrawn from treatment unless continuing in the study would be of benefit for the patient in the opinion of the investigator. In such cases, continuation of treatment must be discussed with the Medical Monitor and the reason for continuation must be approved.

[redacted]

Dose escalation for NKTR-102 is not permitted. Patients who undergo dose reduction of NKTR-102 due to observed toxicity may not be re-escalated to the previous dose level upon resolution of the toxicity. NKTR-102 doses for an individual patient may be reduced to 120 mg/m^2, then to 95 mg/m^2 based on conditions listed in Table 4. If additional toxicities warrant further dose reductions and the Investigator believes the patient is deriving clinical benefit from NKTR-102, the patient may continue on treatment with further dose reductions (for example to 70 mg/m^2), following discussion with and approval by the Medical Monitor.

[redacted]

Table 4: NKTR-102 Dose Modifications and Delays

Toxicity Grade	Dose Modifications and Delays for Day 1 of Cycle
Diarrhea	
Any Grade	Prior to retreatment, confirm with the patient that diarrhea is no longer present for ≥ 7 days without having received supportive care, including anti-diarrheal medication. Treatment may be delayed up to 28 days
Grade 1	Maintain dose level; consider prophylactic anti-diarrheal supportive care
Grade 2	After 1st occurrence: maintain dose level; consider prophylactic anti-diarrheal supportive care After 2nd occurrence: reduce dose to 120 mg/m^2 and use prophylactic anti-diarrheal supportive care After ≥ 3rd occurrence: retreatment may be attempted at 120 mg/m^2 provided that adequate treatment with anti-diarrheal medication and supportive care has been given to the patient (re-instruct the patient on supportive care)
Grade 3	After 1st occurrence: reduce dose to 120 mg/m^2 and use prophylactic anti-diarrheal supportive care After 2nd occurrence: reduce dose to 95 mg/m^2 and use prophylactic anti-diarrheal supportive care After ≥ 3rd occurrence: retreatment may be attempted at 95 mg/m^2 provided that adequate treatment with anti-diarrheal medication and supportive care has been given to the patient (re-instruct the patient on supportive care)
Grade 4	After 1st occurrence: reduce dose to 95 mg/m^2 and use prophylactic anti-diarrheal supportive care After ≥ 2nd occurrence: retreatment may be attempted at 95 mg/m^2 provided that adequate treatment with anti-diarrheal medication and supportive care has been given to the patient (re-instruct the patient on supportive care)
Dehydration	
Grade 1	Maintain dose level; consider prophylactic anti-diarrheal or anti-emetic supportive care.
Grade 2	After 1st occurrence: maintain dose level; use prophylactic anti-emetic or anti-diarrheal supportive care After 2nd occurrence: reduce dose to 120 mg/m^2 and use prophylactic anti-emetic or anti-diarrheal medication and supportive care After ≥ 3rd occurrence: retreatment may be attempted provided that adequate treatment with anti-emetic and anti-diarrheal medication has been given to the patient (re-instruct the patient on use of anti-diarrheal medication and supportive care)

Table 4: NKTR-102 Dose Modifications and Delays (Cont'd)

Toxicity Grade	Dose Modifications and Delays for Day 1 of Cycle
Dehydration (cont'd)	
Grade 3	Treatment must be delayed until the toxicity recovered to baseline or Grade ≤ 1. Treatment may be delayed up to 28 days After 1st occurrence: reduce dose to 120 mg/m^2 and use prophylactic anti-emetic or anti-diarrheal medication and supportive care After 2nd occurrence: reduce dose to 95 mg/m^2 and use prophylactic anti-emetic or anti-diarrheal medication and supportive care After ≥ 3rd occurrence: retreatment may be attempted at 95 mg/m^2 provided that adequate treatment with anti-emetic and anti-diarrheal medication has been given to the patient (re-instruct the patient on use of anti-diarrheal medication and supportive care)
Grade 4	Treatment must be delayed until the toxicity recovered to baseline or Grade ≤ 1. Treatment may be delayed up to 28 days After 1st occurrence: reduce dose to 95 mg/m^2 and use prophylactic anti-emetic or anti-diarrheal medication and supportive care After 2nd occurrence: stop treatment with NKTR-102
Nausea/Vomiting/Abdominal Pain	
Grade 1/2	Maintain dose level; consider prophylactic anti-emetic supportive care.
Grade 3	Treatment must be delayed until the toxicity recovered to baseline or Grade ≤ 1. Treatment may be delayed up to 28 days After 1st occurrence: reduce dose to 120 mg/m^2 and use prophylactic anti-emetic medication and supportive care After 2nd occurrence: reduce dose to 95 mg/m^2 and use prophylactic anti-emetic medication and supportive care After ≥ 3rd occurrence: retreatment may be attempted at 95 mg/m^2 provided that adequate treatment with anti-emetic medication has been given to the patient (re-instruct the patient on use of anti-emetic medication supportive care)
Grade 4	Treatment must be delayed until the toxicity recovered to baseline or Grade ≤ 1. Treatment may be delayed up to 28 days After 1st occurrence: reduce dose to 95 mg/m^2 and use prophylactic anti-emetic or anti-diarrheal medication and supportive care After ≥ 2nd occurrence: retreatment may be attempted at 95 mg/m^2 provided that adequate treatment with anti-emetic medication has been given to the patient (re-instruct the patient on use of anti-emetic medication supportive care)

Table 4: NKTR-102 Dose Modifications and Delays (Cont'd)

Toxicity Grade	Dose Modifications and Delays for Day 1 of Cycle
Neutropenia/Febrile Neutropenia	
Grade 1 (ANC ≥ 1500/mm^3, < 2000/mm^3)	Maintain dose level.
Grade 2 (ANC ≥ 1000/mm^3, < 1500/mm^3)	If present on a treatment day, hold therapy until toxicity resolves to ANC ≥ 1500/mm^3. (Should the Investigator wish to continue treatment with ANC ≥ 1300/mm^3 and ≤ 1500/mm^3, Medical Monitor approval is required). Treatment may be delayed up to 28 days After 1st occurrence: reduce dose to 120 mg/m^2 and consider prophylactic growth factor therapy After 2nd occurrence: reduce dose to 95 mg/m^2 and consider prophylactic growth factor therapy After ≥ 3rd occurrence: retreatment may be attempted at 95 mg/m^2 provided that adequate supportive care has been given to the patient, and the physician believes it is in the best interest of the patient
Grade 3 (ANC ≥ 500/mm^3, < 1000/mm^3)	If present on a treatment day, hold therapy until toxicity resolves to ANC ≥ 1500/mm^3. Treatment may be delayed up to 28 days After 1st occurrence: reduce dose to 120 mg/m^2 and consider prophylactic growth factor therapy After 2nd occurrence: reduce dose to 95 mg/m^2 and consider prophylactic growth factor therapy After ≥ 3rd occurrence: retreatment may be attempted at 95 mg/m^2 provided that adequate supportive care has been given to the patient and the physician believes it is in the best interest of the patient
Grade 4 (ANC < 500/mm^3)	If present on a treatment day, hold therapy until toxicity resolves to ANC ≥ 1500/mm^3. Treatment may be delayed up to 28 days After 1st occurrence: reduce dose to 120 mg/m^2 and consider prophylactic growth factor therapy. Consider antibiotics (oral fluoroquinolones) even in the absence of fever or diarrhea After 2nd occurrence: reduce dose to 95 mg/m^2 and consider prophylactic growth factor therapy. Consider antibiotics (oral fluoroquinolones) even in the absence of fever or diarrhea After 3rd occurrence: stop treatment with NKTR-102

[redacted]

Table 4: NKTR-102 Dose Modifications and Delays (Cont'd)

Toxicity Grade	Dose Modifications and Delays for Day 1 of Cycle
Neutropenia/Febrile Neutropenia (cont'd)	
Febrile Neutropenia Grade 3 or 4 (ANC < 1000/mm^3 with a single temperature of ≥ 38.3°C (101°F) or a sustained temperature of ≥ 38°C (100.4°F) for more than one hour	If present on treatment day, hold therapy until toxicity is ≤ Grade 1. Treatment may be delayed up to 28 days After 1st occurrence: reduce dose to 120 mg/m^2 and consider prophylactic growth factor therapy After 2nd occurrence: reduce dose to 95 mg/m^2 and consider prophylactic growth factor therapy After 3rd occurrence: stop treatment with NKTR-102
Non-Hematological Toxicities (except fatigue/asthenia)	
Grade 1/2	Maintain dose level; consider supportive care.
Grade 3	Treatment must be delayed until the toxicity recovered to baseline or Grade ≤ 1. Treatment may be delayed up to 28 days After 1st occurrence: reduce dose to 120 mg/m^2 and use prophylactic anti-emetic medication and supportive care After 2nd occurrence: reduce dose to 95 mg/m^2 and use prophylactic anti-emetic medication and supportive care 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 the patient on supportive care)
Grade 4	Treatment must be delayed until the toxicity recovered to baseline or Grade ≤ 1. Treatment may be delayed up to 28 days After 1st occurrence: reduce dose to 95 mg/m^2 and consider hospital admission After ≥ 2nd occurrence: retreatment may be attempted provided that adequate supportive care has been given to the patient (re-instruct the patient on supportive care)

Abbreviations: ANC: absolute neutrophil count; Hgb: hemoglobin

6.7.3 Antidiarrheal Therapy

Patients randomized to NKTR-102 (Group A) may experience diarrhea. Diarrhea must be treated promptly with loperamide. Loperamide will be dispensed to NKTR-102 patients between randomization and Cycle 1 Day 1 and throughout the study for their use at home.

[redacted]

Depending on the country, loperamide may be supplied by the Sponsor as part of the study. Patients who are documented to have their own supply of loperamide (starting on or before Cycle 1 Day 1) may use this in place of sponsor-supplied loperamide. 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 or higher 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 or higher diarrhea was 3.5 days and the median time to resolution of Grade 3 diarrhea was 6 days. There were no incidents of Grade 4 diarrhea.

Patients randomized to Group A 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 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.

6.7.3.1 Diarrhea Prophylaxis

Table 4 describes the initiation of prophylactic anti-diarrheal supportive care *after* observation of diarrhea in a prior cycle. In the absence of constipation and *prior* to any observation of diarrhea, prophylactic use of loperamide may also be initiated based on the investigator's judgment and patient preference 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, in the absence of constipation. The 7-day prophylactic regimen is repeated with each subsequent cycle starting after the dose until Cycle 6. Starting after the Cycle 6 dose in the absence of constipation, the recommended loperamide regimen is 2 mg every 8 to 12 hours (q8-12h) and continuing for 7 days, in the absence of constipation.

[redacted]

The 7-day prophylactic regimen is repeated after the dose in each subsequent cycle following Cycle 6.

6.7.3.2 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. Alternate anti-diarrheal supportive care, such as diphenoxylate atropine, may be attempted if loperamide does not ameliorate the diarrhea within 48 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 (e.g., positive stool test for *C. difficile*).

6.7.4 Antiemetic Therapy

If a patient experiences nausea and/or vomiting, the patient may be given prophylactic antiemetic treatment prior to the next dose of NKTR-102. An Investigator may, at his/her discretion, prescribe prophylactic antiemetics prior to the first dose of NKTR-102, if this is believed to be in the patient's best interests. The patient must be carefully monitored throughout the study period and be given adequate fluid and electrolyte replacement to prevent dehydration and electrolyte imbalance.

[redacted]

6.7.5 Use of Growth Factor Support and Transfusions

Upon NKTR-102 administration, patients may experience neutropenia, though its frequency and severity appears to be less than that seen with Camptosar® (irinotecan) administration.

Patients must demonstrate an ANC $\geq 1.5 \times 10^9$/L prior to treatment with NKTR-102. Patients who do not meet treatment criteria for ANC should return to clinic within 3 to 7 days for reassessment. If any patients continue not to meet treatment criteria for ANC, they should return to clinic at weekly intervals for reassessment.

Prophylactic use of growth factor support is not generally required; however, use of growth factor support in a setting of neutropenia is permitted. For example, if a patient required growth factor support during a previous cycle, a patient may be administered prophylactic growth factor support during a subsequent cycle at the Investigator's discretion (Section 6.7.2). Use of growth factor support must follow American Society of Clinical Oncology guidelines, European Society for Medical Oncology (ESMO) guidelines, or standard of care at the local institution.

Patients may receive transfusions (platelets or blood products) at the Investigator's discretion. A patient who has a treatment value of Hgb < 8.0 g/dL (80 g/L) or platelets $< 50 \times 10^9$/L may receive a transfusion; however, treatment must be delayed for 7 days (post-transfusion) and patients must meet treatment criteria prior to resuming treatment.

6.7.6 Hypersensitivity

Hypersensitivity and hypersensitivity-like reactions have been reported in association with the administration of NKTR-102. The hypersensitivity reaction may be secondary to NKTR-102, irinotecan or the PEG-backbone. Flushing, swollen tongue, and "hypersensitivity reactions" occur more commonly on the day of infusion than at other times. The events tend to be of mild to moderate severity, with the exception of a single previously reported Grade 3 hypersensitivity reaction. Treatment, when indicated, has included antihistamines and corticosteroids. These events tend to resolve rapidly. PEG-hypersensitivity reactions may include symptoms of pruritus, tingling, flushing, urticaria, angioedema, hypotension and bronchospasm (Wenande, 2016).

In the case of patients reporting mild allergic reactions, re-administration of NKTR-102 may be performed. Recommended interventions to mitigate recurrence of symptoms include premedication with an antihistamine and/or corticosteroid (oral or IV), and/or slowing the rate of infusion to 180 minutes. Patients showing evidence of an anaphylactic reaction should not receive subsequent NKTR-102.

6.8 Group B: Treatment of Physician's Choice (TPC)

Selection of a TPC therapy should be based on what would have been offered to that patient were they not participating in this NKTR-102 study. Agents that are not routinely available in the pharmacy at each medical center will not be considered as available TPC therapy. The Investigator must have prior clinical experience with the TPC agent in the treatment of a patient with breast cancer.

The TPC agent selected must be indicated at Screening.

6.8.1 Dose Modifications due to Toxicity

All AEs will be assessed according to the NCI-CTCAE version 4.03. In event of multiple toxicities, dose delays and modifications should occur in accordance with the highest toxicity observed per the recommendations and guidelines provided in the approved label/prescribing information for that drug.

6.8.2 Supportive Care

Supportive care (including, but not limited to, growth factor support, blood product transfusions, antiemetics, and antidiarrheal medications) can be administered at the discretion of the Investigator.

6.9 Concomitant Treatments

All prescription and over-the-counter (OTC) medications, vitamin and mineral supplements, and/or herbal therapies taken by the patient from Informed Consent through the End of Treatment visit will be collected.

6.9.1 Permitted Concomitant Treatments

The treatments listed below are permitted while on study.

- Stereotactic radiation for new or existing brain lesions; patients with a total of ≤ 10 CNS lesions may receive stereotactic radiation, provided that it is available and that the Investigator feels stereotactic radiation is in the best interest of the patient. In addition, a patient who develops isolated CNS progression can be given the option to have their CNS disease treated with whole-brain radiotherapy or surgery, and remain on protocol therapy (see Section 5.3). Patients who undergo additional CNS-directed therapy on-study should continue to undergo head imaging following therapy at the pre-specified interval.

- Palliative and supportive care for disease-related symptoms.
- Corticosteroids are permitted to be initiated on-study for control of symptoms (for example, nausea/vomiting or neurological symptoms). For patients who entered the study on a stable dose of corticosteroids, this dose may be adjusted on-study as needed by the investigator.
- Standard therapies for concurrent medical conditions, including antiemetic prophylaxis and early interventional antidiarrheal therapy; atropine may be used, as indicated, for cholinergic reactions; and prophylactic antiemetic(s) may be given if felt to be in the patient's best interests, starting from Cycle 1 Day 1 and at each subsequent cycle if needed.
- Prophylactic or therapeutic use of loperamide may be used as described in Section 6.7.3.1 and Section 6.7.3.2.
- Standard TPC premedications such as H1 and H2 antihistamines prior to ixabepilone administration; antihistamines and/or corticosteroids prior to taxane administration.
- Premedication with an antihistamine and/or a corticosteroid is allowed in subsequent cycles following occurrence of a self-limiting NCI-CTCAE version 4.03 Grade 1 to Grade 3 allergic/hypersensitivity reaction to a prior infusion (Group A or Group B patients).
- Limited exposure/duration radiation therapy (RT) to treat pain is permitted; RT use must be recorded.
- Bisphosphonates and denosumab are permitted; the dose and schedule should be similar to that used prior to randomization into this protocol.
- Vitamin and mineral supplements and/or herbal therapies are permitted as long as the agent is not considered "investigational", and their use should be recorded.

6.9.2 Prohibited Concomitant Treatments

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 medications contraindicated by the Prescribing Information for the chosen TPC

[redacted]

- Any concurrent chemotherapy, radiotherapy (except for RT as described in Section 6.9.1), hormonal therapy (including megestrol acetate unless used for appetite stimulation), immunotherapy, or other systemic therapy for cancer

- Enzyme-inducing anti-epileptic drugs (EIAEDs) including phenytoin, carbamazepine, oxcarbazepine, or phenobarbital

Investigators must monitor patients randomized to Group A (NKTR-102) for use of potent cytochrome P450 3A4 (CYP3A4) inducers or inhibitors, because these agents may induce or inhibit irinotecan or SN38 metabolism. Some of these agents are OTC medications (e.g., St John's Wort); patients must provide a complete list of all concomitant medications as part of the screening process. In addition, certain agents permitted in TPC may also have potential drug interactions with CYP3A4 inducers or inhibitors (e.g., docetaxel).

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

[redacted]

7.0 INVESTIGATIONAL PRODUCT(S)/STUDY DRUGS

7.1 Group A: NKTR-102 (etirinotecan pegol)

The drug substance NKTR-102, 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).

Table 5: Nomenclature

Proprietary name	Onzeald ®
International Non-proprietary Name (INN) /United States Adopted Name (USAN):	etirinotecan pegol
Compound Number/Name:	NKTR-102
Sponsor:	Nektar Therapeutics
Chemical classification:	Topoisomerase 1 Inhibitor

Abbreviation: INN: International Nonproprietary Name; USAN: United States Adopted Name

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 before IV infusion with commercially-available 5% Dextrose Injection (w/w%) or 0.9% Sodium Chloride for Injection. The pH of the formulation is in the range of 3.2 to 4.2, and the storage condition is 2°C to 8°C. The period of use/shelf life of the drug product clinical supplies are managed by an interactive response technology (IRT) system and may be printed on the clinical labels based on country regulations. Both 5% Dextrose Injection and 0.9% Sodium Chloride for Injection will be locally sourced at each clinical site.

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 1.1 g NKTR-102, equivalent to 100 mg of irinotecan with a 5% overfill; (5 mg IRT). A NKTR-102 dose of 145 mg/m^2 is based on irinotecan equivalents.

Each vial and carton will be labeled to comply with local regulations.

The instructions for reconstitution and administration of the investigational drug product (NKTR-102 for Injection) are described in detail in the Pharmacy Manual.

[redacted]

7.1.1 NKTR-102 Dosage and Administration

Body surface area (BSA) will be determined before the start of each cycle, based on institutional guidelines and will be capped at 2.4 m^2. In the instance where there are no institutional guidelines, use baseline height and most recent weight to calculate BSA. Each patient's NKTR-102 dose will be determined by multiplying the most recent BSA by the starting dose of 145 mg/m^2. NKTR-102 for Injection will be administered as an IV infusion over 90 minutes (± 15 minutes). Premedications are not required to be administered prior to the initial infusion, but may be used for an individual patient, as needed and as described in Section 6.7.3, Section 6.7.4, Section 6.7.5, and Section 6.7.6.

7.2 Group B: Treatment of Physician's Choice (TPC)

Patients randomized to TPC will receive single-agent chemotherapy, limited to one of the following 7 agents: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel. TPC must consist of single-agent IV therapy, not combination therapy. Choice of Group B agent (TPC) for an individual patient will depend on what TPC drug products are available at each medical center. For TPC products without generic versions (e.g., eribulin, ixabepilone, and nab-paclitaxel), the branded product must be commercially available at the medical center. Selection of a TPC drug product should be based on what would have been offered to the patient within that medical center if the patient were not participating in a clinical study.

Depending on local health authority guidelines, the TPC drug product will be obtained by the center through commercial supply, the site pharmacy, or through a central repository. Depending on source of supply, the packaging and labeling will vary. Nektar will only supply Group B (TPC) drug product from a central source if TPC cannot be procured locally, and if that drug product has been approved by the local Competent Authority and is a commercially-available drug supplied through the central repository and that will be labeled to meet local country requirements.

TPC drugs must be reconstituted and administrated per their respective Prescribing Information.

[redacted]

8.0 PHARMACOKINETIC, PHARMACOGENOMIC, BIOMARKER, AND EFFICACY MEASUREMENTS

[redacted]

[redacted]

8.5 Efficacy Assessments

All patients must undergo tumor assessments at the participating study center or at a radiology facility associated with the site. Interpretation of all radiologic assessments will be performed by the site investigator or radiologist. The radiologic evaluation performed locally will guide treatment decisions and will continue until PD. In addition, all tumor imaging (including digital photographs) will be forwarded to the Central Imaging Facility for independent blinded review.

8.6 Tumor Response Evaluation per RECIST

8.6.1 Measurements of Response

The revised RECIST 1.1 guidelines (Eisenhauer, 2009) will be used to determine response and progression for extra-cranial disease (CNS metastases should not be selected as non-target lesions for assessment by RECIST).

Patients with measurable disease (according to RECIST) will be evaluated for response or progression (Section 6.4). For the purposes of this study, patients will be evaluated every 8 weeks (± 7 days) through Week 24 and every 12 weeks (± 7 days) thereafter, from date of randomization until documented disease progression or death.

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable based on the definitions provided below.

8.6.1.1 Measurable Disease

Measurable disease is defined by the presence of at least one measurable lesion that can be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm); when CT scans have slice thickness > 5 mm, the minimum size for a measurable lesion must be twice the slice thickness. Patients must have a history of brain metastases that are non-progressing upon study entry, therefore, no CNS lesions can be considered as target lesions

for RECIST 1.1. CNS lesions will, however, be measured at baseline and at all timepoints on study.

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm). Only the short axis will be measured and followed at baseline and in follow-up (Schwartz, 2009).

8.6.1.2 Non-Measurable Disease

All other lesions, including small lesions (longest diameter < 10 mm, or pathological lymph nodes ≥ 10 mm and < 15 mm on the short axis) as well as truly non-measurable lesions, are considered non-measurable disease. Lesions considered truly non-measurable include ascites, pleural or pericardial effusion, lymphangitic involvement of skin or lung, or abdominal masses/abdominal organomegaly identified by physical exam (PE) that is not measurable by reproducible imaging techniques.

8.6.2 Specifications by Methods of Measurements

The same method of assessment and the same technique should be used to characterize each lesion at baseline and throughout the study. Imaging-based evaluation must always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but is/are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and are ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). When lesions can be evaluated by both clinical exam and imaging, imaging evaluation must be undertaken, because it is more objective and may also be reviewed at the end of the study.

CT, MRI: CT is the best currently-available and reproducible method for measuring lesions selected for response assessment. If a slice thickness > 5 mm is used for CT scanning, then the minimum longest diameter for a target lesion will be twice the slice thickness. Magnetic resonance imaging is preferred for imaging of the head.

Tumor markers: Tumor markers may be obtained per institutional guidelines; however, tumor markers cannot be used to assess objective tumor response or PD. Details on tumor markers will not be captured in the database.

Cytology and histology: These techniques can be used to differentiate between PR and CR in rare cases when the nature of a residual lesion is in question. The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if

the measurable tumor has met the criteria for response or stable disease (SD) in order to differentiate between response (or SD) and PD.

8.6.2.1 Baseline Documentation of 'Target' and 'Non-Target' Lesions

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this estimate as a comparator for subsequent measurements.

Any lesion that meets the definition of measurable disease (Section 8.6.1.1) should be identified as a "Target Lesion" and will be measured at baseline (for this protocol, "target lesions" are extra-cranial lesions only). When > 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 total (and a maximum of 2 lesions per organ) that are representative of all involved organs will be identified as target lesions and will be recorded and measured at baseline. This means that in instances where patients have only 1 or 2 organ sites involved, a maximum of 2 and 4 lesions, respectively, will be recorded. Target lesions will be selected by size (based on their longest diameter) and whether they lend themselves to reproducible repeated measurements. Occasionally, the largest lesion does not lend itself to reproducible measurement; in this circumstance, the next-largest lesion that can be measured reproducibly will be selected. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Pathological nodes that are defined as measurable may be identified as target lesions; however, only the short axis of these nodes will contribute to the baseline sum. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if complete response criteria are met, because a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions. All other pathological nodes will be considered non-target lesions.

While on study, all lesions (nodal and non-nodal) recorded at baseline will have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, if the lesion is believed to be present and is faintly seen but is too small to measure with any accuracy, a default value of 5 mm will be assigned.

A sum of the diameters (longest diameter for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and will be reported as the baseline sum of diameters. The baseline sum of diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other extra-cranial lesions (or sites of disease) including pathological lymph nodes will be identified as "non-target lesions" and will also be recorded at baseline. Measurements are not required and these lesions will be followed as present, absent, unequivocal progression, or new lesions.

8.6.3 Evaluation of Target Lesions

Definitions of the criteria used to determine objective tumor response for target lesions are seen in Table 6.

Table 6: Criteria Definitions for Objective Tumor Response for Target Lesions

Tumor Response	Criteria Definition
Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease	At least a 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. Note: The appearance of 1 or more new lesions is considered progression.
Stable Disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

8.6.4 Evaluation of Non-Target Lesions

To be eligible for this study, CNS lesions must have undergone prior definitive treatment, be documented as non-progressing in the baseline scan and are therefore considered non-target lesions. Although measurement of CNS lesions is requested, these lesions will be assessed qualitatively as other non-target lesions.

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are in Table 7. While some non-target lesions may actually be measurable, they need not be measured and instead will be assessed only qualitatively at the time points of radiographic assessments.

Table 7: Criteria Definitions for Objective Tumor Response for Non-Target Lesions (RECIST)

Tumor Response	Criteria Definition
Complete Response	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD	Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease	Unequivocal progression of existing non-target lesions. (Note: The appearance of 1 or more new lesions is also considered progression).

A patient who develops isolated CNS progression can be given the option to have their CNS disease treated with whole-brain radiotherapy, SRS or surgery, and remain on protocol therapy (see Section 5.3).

8.6.5 Evaluation of Best Overall Response per RECIST

The best overall response is the best response recorded from the start of the randomization until disease progression/recurrence per RECIST, taking as reference for PD the smallest measurements recorded since the treatment started. The patient's best response assignment will depend on the achievement of both measurement and RECIST criteria.

Table 8 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with and without the appearance of new lesions.

Table 8: Overall Responses for Combinations of Tumor Responses per RECIST

Target Lesions	Nontarget Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Nonprogressive disease	No	PR
SD	Nonprogressive disease	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR: complete response; PD: progression of disease; PR: partial response; SD: stable disease.

[redacted]

Confirmation of Response: Confirmation of response, either PR or CR, is required. A confirmatory radiological exam should be performed ≥ 4 weeks after the criteria for response are first met.

Note: Patients with a global deterioration of their health status requiring discontinuation of treatment without objective evidence of disease progression at that time will be classified as having symptomatic deterioration. Every effort must be made to document objective progression, even after discontinuation of treatment.

Date of PD: This is the earliest date of the imaging method to determine PD, or, if the patient is followed by PE, the date of the PE showing PD. The date of global deterioration or symptomatic deterioration will not be used as the date of PD.

8.7 Response Assessment Criteria for Brain Metastases per RANO-BM Criteria

8.7.1 Measurements of CNS Response (RANO-BM)

The criteria proposed from the RANO group (Lin, 2015) will be utilized to assess the disease progression in CNS metastases only. To be eligible for this study, CNS lesions must have undergone prior definitive treatment, be documented as non-progressing in the baseline scan and are therefore considered non-target lesions. Date of CNS lesion progression is the earliest date of the imaging method used to determine CNS lesion progression per RANO-BM Criteria.

8.7.1.1 Measurable Disease (RANO-BM)

CNS lesions, although considered to be non-target lesions, will undergo baseline and serial assessment on study using bidimensional measurements. (This is a modification of the RANO-BM criteria, made to better understand any intracranial effects of NKTR-102 and TPC).

8.7.1.2 Non-Measurable Disease (RANO-BM)

Lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, and cystic-only lesions are considered non-measurable disease.

8.7.2 Specification of Methods of Measurements

The same method of assessment and the same technique should be used to characterize each lesion at baseline and throughout the study. Consistent use of imaging techniques across all imaging timepoints is important to ensure that the assessment of interval appearance, disappearance of lesions, or change in size is not affected by changes in technique.

Gadolinium-enhanced MRI is the most sensitive and reproducible method available to measure

CNS lesions for response assessment and is the preferred imaging technique. MRI (preferably with use of thin section imaging) is the default standard imaging technique. CT with contrast can be substituted for MRI upon discussions between the Principal Investigator and Medical Monitor.

8.7.3 Baseline Documentation of Target/Non-Target Lesions (RANO-BM)

While on study, all CNS lesions recorded at baseline will have their actual measurements recorded at each subsequent evaluation.

A sum of the diameters for all CNS lesions will be calculated and will be reported as the baseline sum of longest diameters. The baseline sum of diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other CNS lesions (e.g., lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, and cystic-only lesions) should be identified as "non-target lesions" and should also be recorded at baseline. Measurements are not required and these lesions should be classified as present, absent, or unequivocal progression.

8.7.4 Evaluation of CNS Target Lesions (RANO-BM)

Table 9 gives criteria definitions for objective CNS response for target CNS lesions by RANO-BM. (As there are no target lesions in the CNS in this protocol, this table is provided for completeness only).

[redacted]

Table 9: Criteria Definitions for Objective CNS Response for CNS Target Lesions (RANO-BM)

Tumor Response	Criteria Definition
Complete response	Disappearance of all CNS target lesions sustained for at least 4 weeks with no new lesions, no use of corticosteroids, and patient is stable or improved clinically
Partial response	At least a 30% decrease in the sum longest diameter of CNS target lesions, taking as reference the baseline sum of longest diameters sustained for at least 4 weeks, no new lesions; stable to decreased corticosteroid dose; stable or improved clinically
Progressive disease	At least a 20% increase in the sum of longest diameters of CNS 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%, at least 1 lesion must increase by an absolute value of 5 mm or more to be considered progression
Stable disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter while on study

Abbreviations: CNS: central nervous system; RANO-BM: Response Assessment in Neuro-Oncology-Brain Metastases

8.7.5 Evaluation of Non-Target CNS Lesions (RANO-BM)

Table 10 gives criteria definitions for objective CNS response for non-target CNS lesions by RANO-BM.

Table 10: Criteria Definitions for Objective CNS Response for Non-Target CNS Lesions (RANO-BM)

Tumor Response	Criteria Definition
Complete response	Requires disappearance of all enhancing CNS non-target lesions and no new CNS lesions
Non-complete response or non-progressive disease	Persistence of 1 or more non-target CNS lesion or lesions
Progressive disease	Unequivocal progression of existing enhancing non-target CNS lesions, or new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumor-related non-enhancing (T2/FLAIR) CNS lesions

Abbreviation: CNS: central nervous system; RANO-BM: Response Assessment in Neuro-Oncology-Brain Metastases

[redacted]

8.7.6 CNS Response Criteria for CNS Lesions Proposed by RANO-BM

Table 11 gives CNS response criteria for CNS lesions proposed by RANO-BM. As only non-target CNS lesions will be observed in this study at baseline, the best response by RANO-BM for CNS lesions will be CR (if all CNS lesions identified on the baseline scan disappear). Measurements are being captured on non-target CNS lesions to perform an exploratory analysis on change in the dimensions of CNS lesions comparing the two groups.

Table 11: Criteria Definitions for Objective CNS Response for CNS Lesions (RANO-BM)

	Complete Response	Partial Response	Stable Disease	Progressive Disease
Target lesions	None	≥ 30% decrease in sum longest distance relative to baseline	< 30% decrease relative to baseline but < 20% increase in sum longest distance relative to nadir	≥20% increase in sum longest distance relative to nadir [a]
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal progressive disease [a]
New lesion(s)[b]	None	None	None	Present [a]
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable [c]
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse [a]
Requirement for response	All	All	All	Any [c]

a. Progression occurs when this criterion is met.

b. A new lesion is one that was not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, e.g., because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion.

c. Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

[redacted]

9.0 ASSESSMENT OF SAFETY OR ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Close attention to the accurate and complete capture of all adverse events ***for both treatment groups*** is a critical component of this phase 3 trial. The previous Phase 3 trial (BEACON) demonstrated fewer Grade 3 or higher adverse events, comparing NKTR-102 with TPC, both in the ITT population and in the subgroup with a history of stable brain metastases. As the two treatment groups are anticipated to have different safety profiles, study personnel must review patients at each contact for any clinically significant signs or symptoms that may reflect potential adverse events.

9.1 AE Definition and Assessment

An AE is defined as any untoward medical occurrence in a clinical investigation patient who was 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, including overdose. 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 treatment, or require follow-up.

For patients enrolled in Group A and receiving NKTR-102, an unexpected AE is one of a type not consistent in nature or severity with information in the current Investigator's Brochure for NKTR-102. For patients enrolled in Group B and receiving an approved drug as TPC, an unexpected AE is one of a type not consistent in nature or severity with information present in the current approved label or prescribing information for that TPC drug.

An AE does not include:

- A medical or surgical procedure (e.g., 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 that do not worsen or increase in severity or frequency after the administration of study medication

- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery for a condition that has not worsened on study, or 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
- Pregnancy

9.2 Monitoring AEs

All AEs will be assessed by the Investigator and recorded, including the date of onset and resolution, severity, relationship to NKTR-102 or TPC, outcome, and action taken with NKTR-102 or TPC. Adverse events will be reported starting immediately after the patient has been administered the first dose of study treatment (NKTR-102 or TPC) through 30 days after the last dose of study treatment.

An event occurring after the patient has provided informed consent but before the first dose of study treatment will be collected as medical history unless the event is serious and attributed to protocol-mandated procedures by the Investigator. Under the latter circumstance, the event will be reported as a serious adverse event (SAE) to Nektar Drug Safety or designee.

Example 1:

Hospitalization for thrombophlebitis associated with a blood draw for assessments required prior to dosing per protocol is a serious event that is related to protocol-mandated procedures. In this scenario, the event of "thrombophlebitis" will be reported as an SAE, and it will be documented as being "unrelated" to study drug.

Example 2:

An ankle sprain following an unexpected fall from a flight of stairs while at home, after the patient has provided informed consent, but before the first dose of study drug, is clearly unrelated to any protocol-mandated procedures and would therefore be recorded as medical history.

9.3 Grading of AEs

The assessment of severity and seriousness are not to be considered synonymous. The severity is grading the intensity of an event. The seriousness of an event is based on the patient/event outcome or action criteria. All AEs will be assessed for severity using the NCI-CTCAE

version 4.03. Severity for all AEs except diarrhea and neutropenia will be recorded according to the highest severity grade a patient experiences for the duration of that AE. Adverse events of special interest (diarrhea and neutropenia AEs) will be reported with an individual start and stop date for each level of severity; see Section 9.6.

Grade 1 = Mild; event results in mild or transient discomfort, not requiring intervention or treatment or needing only minimal intervention or treatment; does not limit or interfere with daily activities, e.g., insomnia, mild headache

Grade 2 = Moderate; event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment, e.g., fever requiring antipyretic medication

Grade 3 = Severe; event results in significant symptoms that prevents normal daily activities; may require hospitalization or invasive intervention

Grade 4 = Life threatening or disabling

Grade 5 = Death

9.4 Causality Relationship of AEs

The relationship of each AE to the study treatment will be evaluated by the Investigator using the following definitions:

- Not related: The AE is clearly not related to the investigational agent(s); the AE can be explained to be likely related to other factors such as concomitant medications or the patient's clinical state

- Possibly related: The AE may be related to the investigational agent(s); a plausible temporal sequence exists between the time of administration of the investigational product and the development of the AE, and it follows a known pattern of response to the investigational product; the reaction may have been produced by the patient's clinical state or by other concomitant therapies or interventions

- Related: The AE is clearly related to the investigational agent(s); a plausible temporal sequence exists between the time of administration of the investigational product and the development of the AE, and it follows a known pattern of response to the investigational product; the occurrence of this AE can be confirmed with a positive re-challenge test or with supporting laboratory data

The causality criteria of "related" and "possibly related" will be considered "related" to the study medication for regulatory reporting requirements.

9.5 AE Reporting and Follow-up

All ongoing AEs assessed as "unrelated" to study treatment will be followed until resolution or until 30 days after last dose of study treatment, whichever is earlier. In case the AE has not completely resolved up to 30 days after last dose of study treatment, the final outcome of these ongoing unrelated AEs will be captured as "Not Recovered/Not Resolved" or "Recovered/ Resolved", whichever is applicable. For adverse events of special interests, an additional category of "Recovering/Resolving" may be used.

All ongoing AEs assessed as "related" to study treatment will be followed until they stabilize or resolve; until the Investigator assesses them as chronic or stable; start of new cancer therapy; patient lost to follow-up; or patient death, whichever comes first.

Any new AEs occurring more than 30 days after last dose of study treatment or End of Treatment will not be captured, except for serious adverse events that are assessed by the Investigator as "related" to study treatment. All new "related" SAEs occurring > 30 days after the last dose of study treatment will be recorded and appropriate SAE forms must be completed and provided to Nektar Drug Safety or designee.

All new "related" SAEs occurring > 30 days after the last dose of study will be followed until they stabilize or resolve, until the Investigator assesses them as chronic or stable, until the start of new cancer therapy, until the patient is lost to follow-up, or until patient death, whichever comes first.

9.6 Adverse Events of Special Interest (AESI)

An AESI is defined as:

- Diarrhea
- Neutropenia ("neutropenia" will include patients with an event characterized by "neutropenia," "decreased neutrophils," "febrile neutropenia," "neutropenic infection", "neutropenic colitis" and "neutropenic sepsis")
- Others to be determined

[redacted]

AESI will be reported with an individual start and stop date for each level of severity. In addition, an additional category of "Recovering/Resolving" may be used for the outcome of an AESI (for example, when Grade 3 neutropenia becomes Grade 2 neutropenia).

9.7 Serious AE Definition

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening, i.e., in the opinion of the Investigator, the AE places the patient at immediate risk of death from the event as it occurred; it does not include a reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of an existing hospitalization that occurs during the course of a patient's participation in a clinical study, except for those due to the following:
  - A surgery or procedure that was planned before the patient entered the study and that is part of the planned study procedure
  - Nonmedical reasons, in the absence of an AE
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed above

Death is an outcome of an AE, but death is not an AE in itself. All deaths must be reported, regardless of causality. An efficacy failure is not considered an SAE. "Life-threatening" means that the patient was at immediate risk of death from the event as it occurred; this does not include an event that might have led to death if it had occurred with greater severity. "Inpatient hospitalization" means the patient has been admitted to a hospital for medical reasons for any length of time. The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not as the individual signs/symptoms.

9.8 Serious AE Reporting

All SAEs regardless of causality attribution, with an onset within **30 days** after the patient's last dose of study treatment, will be reported to Nektar Therapeutics Drug Safety or its designee within **24 hours** of when the site becomes aware of the event. In addition, SAEs that are assessed by the Investigator as both being related to study treatment and occurring **> 30 days** after last dose of study treatment will also be reported to Nektar Therapeutics Drug Safety or its designee within **24 hours** of when the site becomes aware of the event.

To fulfill this responsibility to report an SAE that has occurred, the Investigator must complete the SAE Report Form, assess the causality relationship to the study treatment as applicable (either NKTR-102 or TPC), and send the completed SAE form via email or fax to Nektar Therapeutics Drug Safety or its designee. A follow-up report and any additional records (such as hospital records, consultant reports, and autopsy findings) will be emailed or faxed to Nektar Therapeutics Drug Safety or designee within **24 hours** of receipt. Any medication or other therapeutic measures used to treat the event will be recorded.

Reporting of SAEs to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be done in accordance with the standard operating procedures (SOPs) and policies of IRBs/IECs. Adequate documentation must be provided to Nektar Therapeutics showing that the IRB/IEC was properly notified. SAEs will be reported by Nektar Therapeutics or its designee to the Regulatory Authorities, per local regulations.

9.9 Serious AE Follow-up

All study treatment-related SAEs that have not resolved within 30 days of last dose of study treatment, will be followed until any of the following occur (whichever comes first):

- The event resolves
- The event has stabilized
- The event returns to baseline, if a baseline value is available
- It becomes apparent that it is unlikely that any additional information can be obtained (e.g., patient or health care practitioner refuses to provide additional information or is lost to follow-up after duly diligent follow-up efforts)
- The patient dies or is lost to follow-up

All ongoing SAEs assessed as "unrelated" to study medication will be followed until resolution or until 30 days after last dose of study medication, whichever is earlier. In cases where an unrelated SAE has not completely resolved in up to 30 days after last dose of study treatment, the final outcome of these ongoing SAEs will be captured as "Not Recovered/Not Resolved" or "Recovered/Resolved", whichever is applicable.

9.10 Disease Progression – Not Reportable as an AE

It is anticipated that during this study a proportion of patients will experience disease progression prior to study discontinuation. Progressive disease in some patients may result in hospitalization or death. Such events leading to hospitalization or death of a study patient are typically considered "serious," requiring submission of an SAE report. However, since disease progression is an endpoint for this study, reporting the term "disease progression" as either an adverse event or a serious adverse event is not necessary. When progressive disease is characterized by a constellation of signs and symptoms with no principal clinical manifestation, the condition may be considered as "disease progression" without a requirement to report it as an AE or SAE.

However, if there are separate identifiable clinical manifestations of the disease progression, e.g., pleural effusion or weight loss, these manifestations are reportable as adverse events. Such an event should be recorded on the AE eCRF and, if the event meets any of the "serious" criteria, it must also be reported on the SAE form.

9.11 Pregnancy

The Sponsor must be notified within **24 hours** of the initial report and any follow-up reports of a male patient's female partner, or a female patient becoming pregnant during the course of the study, and for 6 months after the last dose of the study drug. Pregnancy, although reportable, is not considered an AE/SAE unless a female patient or male patient's female partner experiences signs or symptoms of pregnancy complications; however, the contact information for pregnancy reporting is the same as for SAE reporting. Females who become pregnant will be followed every trimester until the outcome of the pregnancy is known. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects in the offspring.

If a female patient or a male patient's female partner becomes pregnant, administration of the study drug must be discontinued immediately, and the Sponsor must be notified within 24 hours of the initial report of the pregnancy.

[redacted]

9.12 Expedited Reporting of SAEs

For the study treatment, NKTR-102, a suspected unexpected serious adverse reaction (SUSAR) is an SAE that is considered "unexpected", because it is not listed in the current Investigator's Brochure or is not listed at the specificity or severity that has been observed. For Group B, related SAEs will be forwarded to the respective manufacturer via email. The manufacturer will determine the reportability of the related SAE report. All SUSARs deemed related to NKTR-102 are subject to expedited reporting by the Sponsor to the applicable regulatory authorities, the IRB/IEC, and the Investigators. With this requirement, the Investigator or site personnel must report all SAEs to Nektar Drug Safety or designee within **24 hours** of first becoming aware of the event.

Fatal or life-threatening SUSARs will be reported by the Sponsor to the Regulatory Authorities as soon as possible, but no later than 7 calendar days after the Sponsor or Sponsor's designee has first knowledge of an adverse event that meets the minimum criteria for expedited SAE reporting. IRBs/IECs and Investigators will be notified within 7 calendar days. Non-fatal and non-life-threatening SUSARs will be reported to the Regulatory Authorities, the IRB/IEC, and the Investigators as soon as possible, but no later than 15 calendar days after the Sponsor or Sponsor's designee has first knowledge of the minimum criteria for expedited reporting.

All efforts will be made to ensure that the following information will be obtained and included in the report:

- The suspected investigational medicinal product (NKTR-102 or TPC)
- An adverse event that meets serious criteria
- An identifiable patient (e.g., study and patient code number)
- A causal relationship
- An identifiable reporter

Reporting of SUSARs to all applicable Regulatory Authorities will be done by Nektar or its designee as per local country and regional regulations.

Reporting of SUSARs to the central IRB/IEC will be done by Nektar or its designee in accordance with the SOPs and policies of the IRB/IEC. Reporting of SUSARs to all participating clinical Investigators will be done by Nektar or its designee as per local regulations. Local IRB reporting requirements will be met by the applicable clinical site personnel as per

[redacted]

their institutional guidelines. Adequate documentation must be provided to Nektar or its designee showing that the local IRB/IEC was properly notified.

Cross reporting of SUSARs occurring in other ongoing clinical studies that are evaluating study treatment NKTR-102 will be done for all applicable Regulatory Authorities, central IRB/IECs, and Investigators participating in this study by Nektar or its designee.

[redacted]

10.0 STATISTICAL METHODOLOGY

10.1 General Considerations

The study has been powered for detecting superiority of NKTR-102 compared with TPC for the primary efficacy endpoint of OS. Patients will be randomized in a 1:1 ratio to one of the two study groups with stratification based on geographic region, tumor receptor status (HER2+, HR+/HER2-, and TNBC) and ECOG (0 vs. 1). The primary efficacy endpoint for the study is OS. After discontinuation of therapy, all patients except those who withdraw consent must be followed (by contact via phone or clinic visit) every 12 weeks (± 2 weeks) until death unless a patient has specifically withdrawn consent to be followed for survival. If allowed by country regulatory authorities and/or consented to by the patient, study personnel may use public records to check for mortality for any patient who withdraws consent for follow-up contact.

Baseline will be the last assessment prior to randomization unless otherwise defined in Section 6.4 (head imaging that occurs after randomization) or the Statistical Analysis Plan (SAP).

All patients must have tumor measurements performed, with radiographic measurements performed to RECIST specifications. Patients will be evaluated for response every 8 weeks (± 7 days) from date of randomization through Week 24, every 12 weeks (± 7 days) thereafter until documented disease progression or death. The RECIST criteria will be used to determine response or progression during the study. Grading for best response or progression will be categorized as CR, PR, SD, or PD. In addition, RANO-BM criteria will be used to assess CNS lesions.

10.2 Determination of Sample Size

The study is powered for detecting superiority of NKTR-102 compared with TPC in OS and up to 220 patients will be enrolled. The number of death events needed to provide 80% conditional power for the final analysis will be determined at an interim analysis when approximately 82 death events are available using the promising zone adaptive method (Mehta & Pocock, 2011). The minimum and maximum number of death events for the final analysis will be 106 and 191, respectively. Two-sided α of 0.001 will be used to test efficacy at the interim analysis (efficacy zone-as part of promising zone design). One hundred ninety-one (191) death events will be able to demonstrate statistical significance for any observed hazard ratio of 0.75 or better, which corresponds to a median difference of approximately 2 months if the OS median for TPC is 6 months and the proportional hazard model assumption is approximately met. The detailed event size adaptation rules based on conditional power will be provided in an appendix to the DMC charter.

10.3 Interim and Final Analyses

One interim analysis and one final analysis will be conducted:

- Interim Analysis (IA – OS interim [$\alpha = 0.001$] and death events re-estimation): when approximately 82 death events have been observed.
- Final Analysis (FA - OS final [significant $p \leq 0.0499$]): timing will be determined at the time of IA using the promising zone adaptive method (Mehta & Pocock, 2011) to estimate the death events needed.

The primary analysis of OS will be the Cui, Hung and Wang [CHW] test with pre-specified weights (Cui, Hung, & Wang, 1999) to ensure type I error control and the conventional test with equal weights for every patient will be conducted as a sensitivity analysis. Details are described in the SAP.

A Data Monitoring Committee (DMC) Charter will be approved and finalized by the independent DMC members prior to the initiation of any interim analysis; the DMC Charter and meeting minutes will be submitted as part of the final Clinical Study Report. The DMC will review and make recommendations consistent with the overall clinical trial design for one formal interim efficacy and safety analysis when approximately 82 death events have been observed. Two-sided α of 0.001 will be used to test efficacy in OS at this interim analysis (falling into the efficacy zone of the promising zone adaptive design). If OS does not reach statistical significance, event size needed for the final OS analysis will be determined based on conditional power per the adaptation rules described in the DMC charter appendix, "Event Size Adaption Rule for Clinical Study Protocol 15-102-14."

See Section 1.2 for the adaptive design study flow chart.

10.4 Analysis Populations

Safety Population: All patients who are randomized and receive at least 1 dose (or partial dose) of study drug (NKTR-102 or TPC) will be included in the safety population; safety analyses will be conducted based on this population.

Intent-to-Treat (ITT) Population: All patients who are randomized in the study will be included in the ITT population; the primary endpoint OS and secondary efficacy analyses (except ORR and DoR) will utilize the ITT population.

Response Evaluable Population: All patients who are randomized in the study with measurable disease in the periphery by RECIST at baseline (as determined by the Investigator) will be included in the Response Evaluable Population; the secondary endpoint analyses of ORR and DoR will utilize the Response Evaluable Population.

[redacted]

PK Population: Those patients with sufficient PK sampling to permit PK analysis

Biomarker Population: Those patients with sufficient biomarker data to permit analysis

10.5 Demographic and Baseline Disease Characteristics

Demographic and baseline disease characteristic data will be summarized for each treatment group by presenting frequency distributions and/or descriptive statistics (mean, standard deviation, median, range, and relevant percentiles). Formal statistical tests comparing treatment groups will not be provided.

10.6 Treatment Compliance

Compliance will be assessed by overall dose intensity and the proportion of patients having dose reductions at each specified visit by treatment group. The reasons for dose reductions will be tabulated.

10.7 Efficacy Analyses

10.7.1 Primary Endpoint - Overall Survival

Overall survival is defined as the time from the date of randomization to the date of death from any cause. Patients will be followed until their date of death or until final database closure. Patients who are lost-to-follow-up or are alive at the time of analysis will be censored at the time they were last known to be alive or at the date of event cut-off for OS analysis.

The primary analysis of OS will be the CHW test with pre-specified weights (Cui, Hung, & Wang, 1999) and the conventional test with equal weights for every patient will be conducted as a sensitivity analysis. The median survival times and their 95% confidence intervals as well as survival curves will be estimated using the Kaplan-Meier method and will be summarized by treatment group. The two-sided significance level for superiority at final analysis of OS will be 0.0499.

A single hazard ratio (NKTR-102/TPC) and its 95% confidence interval will be calculated using a Cox regression model adjusting for geographic region, tumor receptor status, and ECOG.

If more than 10% of study population (i.e., more than 35 patients) have received stereotactic radiosurgery (SRS, WBRT or surgery) during the study, the proportion of patients that received SRS during the study in different treatment groups will be compared using Fisher's exact test. The impact of SRS use on OS will be evaluated using a Cox regression model comparing patients who received SRS with those who did not receive SRS.

Additional secondary efficacy analyses will be undertaken, including the differences in survival outcome depending on prior type of radiotherapy received (SRS versus WBRT), extent of tumor burden at study entry (2 or fewer versus 3 or more sites of disease) and the impact of liver metastases on survival difference between the two arms. In addition, the overall survival analysis will be repeated with all patients selecting ixabepilone as the TPC agent removed from the analysis.

10.7.2 Secondary Endpoints

Analysis for secondary endpoints will not include any adjustment for multiplicity. Statistical tests will be two-sided with a type I error rate of 0.05.

10.7.2.1 Progression-Free Survival (Outside the CNS)

Progression-free survival (PFS) is defined as the time from the date of randomization to the earliest evidence of documented PD or of death from any cause. The date of global deterioration or symptomatic deterioration will not be used as the date of PD. Disease progression for tumors outside the CNS will be assessed by the investigator according to RECIST. The primary analysis of PFS will be performed based on censoring criteria as described in Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics – Appendix 3 (Table A) (FDA, 2007). Two sensitivity analyses of PFS will be performed based on the censoring criteria with considerations of informative censoring as described in European Medicines Agency (EMA) Guideline on the Evaluation of Anticancer Medicinal Products in Man – Appendix 1 (EMA, 2012). The methodology of handling missing scans are described in the SAP. Progression-free survival will be compared with a two-sided, log-rank test with the same stratification factors that were used for randomization. Kaplan-Meier median PFS times and their 95% confidence intervals as well as PFS curves will be summarized by treatment group.

A single hazard ratio (NKTR-102/TPC) and its 95% confidence interval will be calculated using a Cox regression model adjusting for geographic region, tumor receptor status, and baseline ECOG status.

10.7.2.2 Progression-Free Survival in Brain Metastasis

Progression-free survival in brain metastasis (PFS-BM) is defined as the time from the date of randomization to the earliest evidence of documented PD per RANO-BM in brain metastases or death from any cause. The PD will also be determined by the investigator's assessments. The same statistical methods that were used for PFS will be used for PFS-BM.

For patients with CNS metastases at baseline, time to disease progression in the CNS will be separately calculated. For patients without CNS metastases at baseline, time to disease recurrence in the CNS will be separately calculated.

10.7.2.3 Progression-Free Survival (Overall)

Progression-free survival (CNS and peripheral) is defined as the time from the date of randomization to the earliest evidence of documented PD in either the CNS or peripheral (using RANO-BM) or death from any cause. The PD will be determined by both the investigator's and the central imaging facility assessments. The same statistical methods that were used for PFS and PFS-BM will be used for PFS (Overall).

10.7.2.4 Objective Response Rate

Objective response rate (ORR) will be defined as the proportion of patients with a confirmed CR or PR (RECIST for lesions outside the CNS; RANO-BM for CNS lesions) based upon the best response as assessed by the central imaging facility. As a secondary analysis, ORR will be calculated based on the Investigator assessment of response. The analysis of ORR will be performed based on Fisher's exact test between the 2 treatment groups. Clopper-Pearson exact two-sided 95% confidence limits will be calculated for the proportion of patients with ORR in each treatment group. The analysis of ORR will be conducted for the Response Evaluable Population analysis set.

10.7.2.5 Clinical Benefit Rate

Clinical benefit rate will be defined as the proportion of patients having a CR, PR, or SD for at least 4 months (≥ 120 days). The SD duration of 4 months is selected to reflect the shorter life expectancy of study population, e.g., the median OS for the TPC arm in patients with history of brain metastases was 4.8 months from the BEACON trial. Clinical benefit rate will be compared between the treatment groups using a Cochran Mantel-Haenszel test stratified by the randomization factors. Clopper Pearson exact two-sided 95% confidence limits will be calculated in determining the CBR of each group.

In addition, the clinical benefit rate (CBR) in the brain will be defined as the proportion of patients having a CR or SD for at least 4 months (≥ 120 days) per RANO-BM in the CNS. Clinical benefit rate in the brain will be compared between the treatment groups using a Cochran Mantel-Haenszel test stratified by the randomization factors. Clopper Pearson exact two-sided 95% confidence limits will be calculated in determining the CBR of each group. CBR will be calculated based on both the central imaging facility assessment of response, progression and stability of disease, as well as the investigator's assessment of these parameters.

[redacted] [redacted]

10.7.2.6 Duration of Response

Duration of response (DoR) outside the CNS will be defined as the time from first documented CR or PR until the earliest evidence of disease progression per RECIST v1.1 or death from any cause. Kaplan-Meier median duration of response curves will be summarized by treatment group. DoR will be calculated based on the central imaging facility assessment of response and progression, as well as the investigator's assessment of response and progression.

[redacted]

10.7.2.8 HRQoL

The EORTC QLQ-C30 module with the BN-20 subscale, the EQ-5D-5L™, and the BFI will be used to measure the health outcome, quality of life, and assess the symptoms and side effects of treatment and their impact on everyday life. The instrument will be scored according to the developer instructions. Missing items will be imputed based on the developer instructions.

At each assessment point, summary statistics of absolute scores and changes from baseline will be calculated by treatment group for each subscale. Changes from baseline will be compared between treatment groups using Repeated Measures Linear Mixed Effects and Generalized Linear Mixed Models Analyses.

The SAP provides details regarding the HRQoL analysis.

[redacted]

[redacted]

10.9 Safety Analyses

For patients in the Safety Population, the safety analysis will be summarized by treatment group (NKTR-102 and TPC) and further tabulated for each TPC drug for patients who are assigned to the TPC group.

10.9.1 Adverse Events and Deaths

The frequency of treatment emergent adverse events (TEAEs) and SAEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class. The maximum NCI CTCAE grade and frequency of AEs will be summarized.

A TEAE is defined as an AE that was not present prior to treatment with study drug but appeared following treatment, or was present at treatment initiation but worsened during treatment. An AE that was present at treatment initiation but resolved and then reappeared while the patient was on treatment is a TEAE (regardless of the intensity of the AE when the treatment was initiated). The treatment-emergent period will be defined as the period of time from the date of the first dose of study drug up to 30 days after the date of the last dose of study drug or the day prior to the initiation of subsequent anticancer treatment, whichever occurs first.

Treatment-emergent AEs and SAEs will also be tabulated by NCI CTCAE version 4.03 Grade and by relationship to study drug. Adverse events leading to permanent discontinuation of study drug and/or leading to death will be listed and tabulated.

[redacted]

[redacted]

10.10 Missing Data

Statistical considerations and methodology for handling missing data are detailed in the SAP.

10.11 Method of Randomization

Patients will be randomized in a 1:1 ratio to one of the 2 study groups stratified by geographic region, tumor receptor status (HER2+, HR+/HER2-, and TNBC), and ECOG performance status (0 vs. 1) using a randomized permuted block scheme.

[redacted]

The block sizes will not be known to the Investigator. Patients will be considered randomized into the study only after they are assigned a randomization number, after which study treatment administration may begin.

11.0 STUDY OR STUDY SITE TERMINATION

The sponsor has the right to suspend or terminate the study at any time. The study may be suspended or terminated for any reason.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor will implement and maintain quality control and quality assurance procedures with written SOPs to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements.

12.1 Changes to the Protocol

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by ***BfArM and*** IRB/independent ethics committee (IEC except when necessary to eliminate immediate hazards to the patient or when the change(s) involve only logistical or administrative aspects of the study. Any deviation may result in the patient having to be withdrawn from the study and rendering that patient nonevaluable.

All protocol deviations and the reasons for such deviations are to be documented in the source documents and reported to the sponsor.

12.2 Monitoring

In accordance with Code of Federal Regulations 21 CFR 312.56, ICH GCP, and local regulations, the clinical monitor will periodically inspect all electronic case report forms (eCRFs), study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times during and after completion of the study. As required by 21 CFR 312 Subpart D (Responsibilities of Sponsors and Investigators), ICH GCP, and local regulations, the monitoring visits provide the sponsor with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of eCRFs; ensure that all protocol requirements, applicable Food and Drug Administration (FDA), International Conference on Harmonisation (ICH) GCP, and local regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records that are required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) for the patients in this study. The names and identities of all research patients will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by the sponsor. The Investigational New Drug Application (IND) regulations and ICH E6 guidelines also require the Investigator to allow authorized representatives of the sponsor, IRB/IEC, FDA, and other relevant regulatory authorities direct access to study source records, and to inspect and make copies of the same records. The names and identities of the patients need not be divulged to the sponsor; however, the records must nevertheless be available to be inspected for review. This can be accomplished by blacking out the patient's name and replacing the name with the patient's study identification number. If these requirements are in conflict with local regulatory restrictions or institutional

requirements, the Investigator must inform the sponsor of these restrictions before initiation of the study.

12.3 Direct Access to Source Data/Documents for Audits and Inspections

The sponsor or designees may conduct auditing activities of a clinical site at any time during or after completion of the study. The Investigator will be informed of such activities.

Representatives of the FDA or other regulatory agencies, including IRB/IEC representatives, may also conduct an inspection or perform an audit of the study. The investigator(s)/institution(s) will permit trial-related audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents and study records. If informed of such an inspection, the Investigator should notify the sponsor immediately. The Investigator will ensure that the inspectors and auditors have access to the clinical supplies, study site facilities, and laboratory, and that all data (including original source documentation) and all study files are available, if requested.

13.0 ETHICS

This study will be conducted to be consistent with the principles that have their origin in the Declaration of Helsinki and in accordance with FDA regulations (21 CFR § 11, 50, 54, 56, and 312), with the current ICH GCP guidelines (ICH E6), as well as with any and all applicable federal, state, and/or local laws and regulations.

13.1 IRB/IEC Approval

Before enrollment of patients into the study, as required by FDA (21 CFR § 56), ICH GCP, applicable regulatory authority requirements, and local regulations, the current protocol and ICF will be reviewed and approved by an appropriate IRB or IEC. A letter documenting the IRB or IEC approval must be received by the sponsor before the initiation of the study at a clinical site. Amendments to the protocol will be subject to the same requirements as the original protocol.

The Investigator, sponsor or designee will submit a progress report at least once yearly to the IRB or IEC. However, the frequency of these reports will depend on IRB or IEC requirements. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB or IEC per the IRB or IEC requirements, and in compliance with FDA regulations, applicable regulatory authority requirements, and ICH GCPs.

The Investigator, the sponsor, or designee shall promptly notify the IRB or IEC of any SAEs, SUSARs, or any other information that may affect the safe use of the study drug(s) during the study, per the IRB or IEC local requirements, and in compliance with FDA regulations, country and local regulatory authority regulations, and in compliance with FDA regulations and ICH GCPs.

13.2 Written Informed Consent

Written informed consent must be obtained from each patient before entering the study. Patients will be informed of the nature of the study and the ICF must be presented to each patient in the language in which the patient is fluent.

Informed consent will be obtained and documented by each patient prior to the conduct of any protocol-specific procedures. Procedures that were performed for standard of care prior to signing informed consent may be used for screening purposes (e.g., chest/abdomen CT, full physical exam) as long as the procedures were completed within the 28-day screening period; bone scan data obtained prior to this screening period may be used. Signed and dated ICFs will be retained by the Investigator with the study records. Each patient will be given a copy of the signed and dated ICF.

14.0 DATA HANDLING AND RECORD KEEPING

14.1 Data Collection Instruments and Source Documents

14.1.1 Study Records

During the study, the investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail). The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. The investigator/institution should, at a minimum, maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 section 8) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

14.1.2 Data Collection Instruments

Data collection instruments (DCIs) (e.g., eCRFs, electronic clinical outcomes assessments [eCOA], and paper forms) will be used in this study. These instruments are used to transmit the information collected during the performance of this study to the sponsor or sponsor's designee and regulatory authorities. The Investigator must review the DCIs for completeness and accuracy and must approve all data, including any changes made. Furthermore, the Investigator retains full responsibility for the appropriateness and accuracy of all data collected in the DCIs.

14.2 Retention of Essential Documents

For sites in the US: All records and documents pertaining to the study including, but not limited to, those outlined above (Section 14.1.1) will be maintained by the Investigator for a period of at least 2 years after FDA approval of the drug or at least 2 years after withdrawal of the IND under which this study was conducted, whichever is longer.

For sites outside the US: Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution when these documents no longer need to be retained.

To avoid any possible errors, the Investigator will contact the sponsor before transferring or destroying any study records. The Investigator will also promptly notify the sponsor in the event of accidental loss or destruction of any study records.

15.0 CONFIDENTIALITY

Subject confidentiality will be maintained per local legal and regulatory requirements and applicable US federal regulations and ICH GCP guidelines. To comply with GCP guidelines and requirements, subject records will be reviewed during monitoring visits and audits conducted by the sponsor, sponsor's representatives, or health authorities. During these activities, every reasonable effort will be made to keep medical information, including subject identifying information, as confidential as possible as required by law.

16.0 PUBLICATION POLICY

All data are the property of the sponsor. Any formal presentation or publication of data from this study will be considered for joint publication by the sponsor personnel and Investigator(s).

The Investigator may be required to sign the clinical study report if it is to be used in a registration submission to the health authorities of some countries.

17.0 REFERENCES

1. Adkins CE, Nounou MI, Hye T, et al. NKTR-102 Efficacy versus irinotecan in a mouse model of brain metastases of breast cancer. BMC Cancer. 2015;15:685

2. Ahn HK, Park YH, Lee SJ. 2013. Clinical implication of Time To Brain Metastasis (TTBM) according to breast cancer subtypes. SpringerPlus. 2013;2(1):136.

3. Anders CK, Deal AM, Miller R, et al. The Prognostic Contribution of Clinical Breast Cancer Subtype, Age, and Race Among Patients With Breast Cancer Brain Metastases. Cancer. 2010;117(8):1602-1611.

4. Anderson A, Choy C, Neman J, et al. Metastatic breast cancer to the brain: A clinical primer for translational investigation. In: Madame Curie Bioscience Database [Internet]. Austin (TX): Landes Bioscience. 2013 Available at: http://www.ncbi.nlm.nih.gov/books/NBK154381/.

5. Andreopoulou E and Sparano JA. Chemotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer: An overview. Current Breast Cancer Reports. 2013;5(1):42-50.

6. Arslan C, Dizdar O, Altundaq K. Chemotherapy and biological treatment options in breast cancer patients with brain metastasis: an update. Expert Opinion on Pharmacotherapy. 2014;15(12):1643-1658.

7. Bendell JC, Domchek SM, Burstein HJ, et al. Central Nervous System Metastases in Women who Receive Trastuzumab-Based Therapy for Metastatic Breast Carcinoma. Cancer. 2003;97(12):2972-2977.

8. Brown PD, Asher AL, Ballman KV, et al. NCCTG N0574 (Alliance): A Phase III randomized trial of whole brain radiation therapy (WBRT) in addition to radiosurgery (SRS) in patients with 1 to 3 brain metastases. Neuro-Oncology. 2015;17(suppl5):v45.5-v46

9. Christodoulou C, Bafaloukos D, Linardou H, et al. Temozolomide (TMZ) combined with cisplatin (CDDP) in patients with brain metastases from solid tumors: A hellenic cooperative oncology group (hecog) Phase II study. J of Neurooncol. 2005;71(1):61-65.

10. Crozier JA, Cornell LF, Rawal B, et al. Breast cancer brain metastases: Comprehensive review of tumor extent, histology and treatment on survival. Journal of Clinical Oncology. 2015;33 (supple; abstract 1059).

[redacted]

11. Cui L, Hung JHM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics 1999; 55: 853-857.

12. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer Supplements. 2009;45(2):228-247.

13. Florea A-M and Büsselberg D. Breast cancer and possible mechanisms of therapy resistance. Journal of Local and Global Health Science. 2013;(2013):2.

14. Freedman RA, Bullitt E, Sun L, et al. A Phase II study of sagopilone (ZK 219477; ZK-EPO) in patients with breast cancer and brain metastases. Clinical Breast Cancer. 2011;11(6):376-383.

15. Gil-Gil MJ, Martinez-Garcia M, Sierra A, et al. Breast cancer brain metastases: A review of the literature and a current multidisciplinary management guideline. Clinical and Translational Oncology. 2013;16(5):436-446.

16. Halasz LM, Uno H, Hughes M, et al. Comparative Effectiveness of Stereotactic Radiosurgery Versus Whole-Brain Radiation Therapy for Patients With Brain Metastases From Breast or Non–Small Cell Lung Cancer. Cancer. 2016.

17. Hambrecht A, Jandial R, Neman J. Emerging role of brain metastases in the prognosis of breast cancer patients. Breast Cancer (Dove Med Press). 2011;3:79-91.

18. Iwamoto FM, Omuro AM, Raizer JJ, et al. 2008. A Phase II trial of vinorelbine and intensive temozolomide for patients with recurrent or progressive brain metastases. J Neurooncol. 2008;87(1):85-90.

19. Jackisch C, Welslau M, Schoenegg W, Selbach J, Harich HD, Schröder J, Schmidt M, Göhler T, Eustermann H, Ringel R, Hinke A. Impact of trastuzumab treatment beyond disease progression for advanced/metastatic breast cancer on survival - results from a prospective, observational study in Germany. Breast. 2014 Oct;23(5):603-8.

20. Jameson GS, Hamm JT, Weiss GJ, et al. Multicenter, Phase I, dose-escalation study to assess the safety, tolerability, and pharmacokinetics of etirinotecan pegol in patients with refractory solid tumors. Clinical Cancer Research. 2013;19(1)268-278.

21. Kemper EM, van Zandbergen AE, Cleypool C, et al. Increased penetration of paclitaxel into the brain by inhibition of p-glycoprotein. Clinical Cancer Research. 2003;9(7):2849-2855.

[redacted]

22. Khuntia D. Contemporary review of the management of brain metastasis with radiation. Hindawi Publishing Corporation. Advances in Neuroscience. 2015;2015:1-3.

23. Kodack DP, Askoxylakis V, Ferraro G, et al. Emerging strategies for treating brain metastases from breast cancer. Cancer Cell. 2015;27(2):163-175.

24. Lalla D, Carlton R, Santos E, et al. Willingness to pay to avoid metastatic breast cancer treatment side effects: Results from a conjoint analysis. SpringerPlus. 2014;3(1):350.

25. Lim E, Lin NU. New insights and emerging therapies for breast cancer brain metastases. Oncology (Williston Park). 2012;26:652-659, 663.

26. Lin NU. Breast cancer brain metastases: New directions in systemic therapy. Ecancermedicalscience. 2013;7:307.

27. Lin NU, Claus E, Sohl J, et al. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer: High incidence of central nervous system metastases. Cancer. 2008;113(10):2638-2645.

28. Lin NU, Diéras V, Paul D, et al. Multicenter Phase II study of lapatinib in patients with brain metastases from her2-positive breast cancer. Clinical Cancer Research. 2009;15(4):1452-1459.

29. Lin NU, Lee EQ, Aoyama H, et al. Response assessment criteria for brain metastases: proposal from the RANO group. Lancet Oncology. 2015;16(6):e270-e278.

30. Lin X, Skolnik S, Chen X, et al. Attenuation of intestinal absorption by major efflux transporters: Quantitative tools and strategies using a caco-2 model. Drug Metabolism and Disposition. 2011;39(2):265-274.

31. Liu Y, and Hu M. Testing multiple primary endpoints in clinical trials with sample size adaptation. Pharmaceut. Statist. 2016, 15: 37–45.

32. Lockman PR, Mittapalli RK, Taskar KS, et al. Heterogeneous blood-tumor barrier permeability determines drug efficacy in experimental brain metastases of breast cancer. Clinical Cancer Research. 2011;16(23):5664-5678.

33. Lombardi G, Di Stefano AL, Farina P, et al. Systemic treatments for brain metastases from breast cancer, non-small cell lung cancer, melanoma and renal cell carcinoma: An overview of the literature. Cancer Treat Reviews. 2014;40(8):951-959.

[redacted]

34. Melisko ME, Moore DH, Sneed PK, et al. Brain metastases in breast cancer: Clinical and pathologic characteristics associated with improvements in survival. J Neurooncol. 2008;88(3):359-365.

35. Mehta C, Pocock SJ. Adaptive increase in sample size when interim results are promising: A practical guide with examples. Statistics in Medicine 2011; 30: 3267-3284.

36. Nagpal S, Recht CK, Bertrand S, et al. Phase II pilot study of single-agent etirinotecan pegol (NKTR-102) in bevacizumab-resistant high grade glioma. J. Neurooncol. 2015;123(2):277-282.

37. Niwinska A, Murawska M, Pogoda K. Breast cancer brain metastases: differences in survival depending on biological subtype, RPA RTOG prognostic class and systemic treatment after whole-brain radiotherapy (WBRT). Annals of oncology. 2010;21(5):942-948.

38. Olson EM, Najita JS, Sohl J, Arnaout A, Burstein HJ, Winer EP, Lin NU. Clinical outcomes and treatment practice patterns of patients with HER2-positive metastatic breast cancer in the post-trastuzumab era. Breast. 2013; Aug;22(4):525-31.

39. Perez EA, Awada A, O'Shaughnessy J, et al. Etirinotecan pegol (NKTR-102) versus treatment of physician's choice in women with advanced breast cancer previously treated with an anthracycline, a taxane, and capecitabine (BEACON): a randomised, open-label, multicentre, Phase 3 trial. The Lancet Oncology. 2015;16(15):1556-1568.

40. Polli JW, Wring SA, Humphreys JE, et al. Rational use of in vitro p-glycoprotein assays in drug discovery. Journal of Pharmacology and Experimental Therapeutics. 2001;299(2):620-628.

41. Ramakrishna N, Temin S, Chandarlapaty S, et al. Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. Journal of Clinical Oncology. 2014;32(19):2100-2108.

42. Schinkel AH. P-glycoprotein, a gatekeeper in the blood-brain barrier. Advanced Drug Delivery Reviews. 1999;36(2-3):179-194.

43. Seidman AD. How long is long enough? Journal of Clinical Oncology. 2011;29(16):2129-2130.

[redacted]

44. Schwartz LH, Bogaerts J, Ford R, et al. Evaluation of lymph nodes with RECIST 1.1. European Journal of Cancer. 2009;45:261-267.

45. Shen H, Lee FY, Gan J. Ixabepilone, a novel microtubule-targeting agent for breast cancer, is a substrate for p-glycoprotein (p-gp/MDR1/ABCB1) but not breast cancer resistance protein (BCRP/ABCG2). Journal of Pharmacology and Experimental Therapeutics. 2011;337(2):423-432.

46. Soon YY, Tham IW, Lim KH, et al. Surgery or radiosurgery plus whole brain radiotherapy versus surgery or radiosurgery alone for brain metastases. The Cochrane Library. 2014;3.

47. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA. 2003;100(14):8418-8423.

48. Sperduto PW, Kased N, Roberge D, et al. Effect of tumor subtype on survival and the graded prognostic assessment (GPA) for patients with breast cancer and brain metastases. International Journal of Radiation Oncology *Biology* Physics. 2012a;82(5):2111-2117.

49. Sperduto PW, Kased N, Roberge D, et al. Summary report on the Graded Prognostic Assessment: An accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. Journal of Clinical Oncology. 2012b;30(4):419-425.

50. Steeg PS, Camphausen KA and Smith QR. Brain metastases as preventive and therapeutic targets. Nature Reviews Cancer. 2011;11(5):352-363.

51. Subbiah IM, Lei X, Weinberg JS, et al. Validation and development of a modified breast graded prognostic assessment as a tool for survival in patients with breast cancer and brain metastases. Journal of Clinical Oncology. 2015;33(20):2239-2245.

52. Taub ME, Podila L, Ely D, et al. Functional assessment of multiple p-glycoprotein (p-gp) probe substrates: Influence of cell line and modulator concentration on p-gp activity. Drug Metabolism and Disposition. 2005;33(11):1679-1687.

53. Taur JS, DesJardins CS, Schuck EL, et al. Interactions between the chemotherapeutic agent eribulin mesylate (E7389) and p-glycoprotein in CF-1 abcb1a-deficient mice and caco-2 cells. Xenobiotica. 2011;41(4):320-326.

54. Wenande E, Garvey LH. Immediate-type hypersensitivity to polyethylene glycols:a review. Clin Exp Allergy. 2016 Jul;46(7):907-22.

[redacted]

55. Wils P, Phung-Ba V, Warnery A, et al. Polarized transport of docetaxel and vinblastine mediated by p-glycoprotein in human intestinal epithelial cell monolayers. Biochemical Pharmacology. 1994;48(7):1528-1530.

56. Witzel I, Loibl S, Laakmann E, et al. et al. Brain metastases in breast cancer network Germany (BMBC, GBG 79): First analysis of 548 patients from the multicenter registry. San Antonio Breast Cancer Symposium 2015 – Poster P6-17-08.

57. Xie R, Mathijssen RH, Sparreboom A, et al. Clinical pharmacokinetics of irinotecan and its metabolites: A population analysis. Journal of Clinical Oncology. 2002;20(15):3293-3301.

58. Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Food and Drug Administration Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. May, 2007.

59. Appendix 1 to the Guideline on the Evaluation of Anticancer Medicinal Produces in Man. European Medicines Agency Science Medicines Health. December, 2012.

18.0 APPENDICES

APPENDIX 1: CLINICAL LABORATORY ASSESSMENTS

<table>
<tr><th>Hematology</th><th>Chemistry</th><th>Coagulation</th></tr>
<tr><td rowspan="2">• Hemoglobin
• Hematocrit
• RBC parameters (including MCV, MCHC, MCH, RBCC and RBC Morphology)
• WBC
• Platelet count
• Neutrophils including bands (absolute)
• Lymphocytes (absolute)
• Monocytes (absolute)
• Eosinophils (absolute)
• Basophils (absolute)</td><td rowspan="2"><u>Liver function tests</u>
• AST (SGOT)
• ALT (SGPT)
• Albumin
• Total bilirubin
• Total protein
• Alkaline phosphatase

<u>Kidney function tests</u>
• BUN (urea)
• Creatinine

<u>Electrolytes</u>
• Sodium
• Potassium
• Chloride
• Calcium
• Bicarbonate/CO_2
• Phosphorus

<u>Miscellaneous</u>
• Random Glucose (screening only)*
• LDH
• Serum pregnancy (for WCBP)</td><td>• PT by INR</td></tr>
<tr><td>Urinalysis

<u>Urine Macro Panel</u>
• Color & Clarity
• Specific Gravity
• pH
• Protein
• Glucose
• Ketones
• Bilirubin
• Urobilinogen
• Blood
• Nitrite
• Leukocyte esterase
• Microscopic</td></tr>
<tr><td colspan="3">Minimal acceptable laboratory safety tests for local lab to assess suitability for retreatment of NKTR-102:</td></tr>
<tr><td>Hematology</td><td>Chemistry</td><td>Coagulation</td></tr>
<tr><td>• Hemoglobin
• Platelet count
• Neutrophils including bands (absolute)</td><td>• Creatinine
• Urine pregnancy (for WCBP)
<u>Electrolytes</u>
• Sodium
• Potassium
• Chloride
• Calcium
• Bicarbonate</td><td>NA</td></tr>
</table>

Abbreviations: ALT: alanine transaminase; aPTT: activated partial thromboplastin time; AST: aspartate aminotransferase; BUN: blood urea nitrogen; INR: international normalized ratio; LDH: lactate dehydrogenase; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; NA: not applicable; PT: prothrombin time; RBC: red blood cell; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase; WBC: white blood cell; WCBP: women of child-bearing potential.

* Random glucose is to be done non-fasting.

[redacted]

APPENDIX 2: BEACON – LANCET ARTICLE, PEREZ, ET AL.

Etirinotecan pegol (NKTR-102) versus treatment of physician's choice in women with advanced breast cancer previously treated with an anthracycline, a taxane, and capecitabine (BEACON): a randomised, open-label, multicentre, phase 3 trial

Edith A Perez, Ahmad Awada, Joyce O'Shaughnessy, Hope S Rugo, Chris Twelves, Seock-Ah Im, Patricia Gómez-Pardo, Lee S Schwartzberg, Veronique Diéras, Denise A Yardley, David A Potter, Audrey Mailliez, Alvaro Moreno-Aspitia, Jin-Seok Ahn, Carol Zhao, Ute Hoch, Mary Tagliaferri, Alison L Hannah, Javier Cortes

Lancet Oncol 2015; 16: 1556–68
Published Online October 16, 2015
http://dx.doi.org/10.1016/S1470-2045(15)00332-0
See Comment page 1453

Mayo Clinic, Jacksonville, FL, USA (E A Perez MD, A Moreno-Aspitia MD); Medical Oncology Clinic, Jules Bordet Institute, Brussels, Belgium (A Awada MD); Baylor-Sammons Cancer Center, Texas Oncology, US Oncology, Dallas, TX, USA (J O'Shaughnessy MD); University of California, San Francisco, CA, USA (H S Rugo MD); University of Leeds and St James's University Hospital, Leeds, UK (C Twelves MD); Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, South Korea (S-A Im MD); Vall d'Hebron Institute of Oncology, Barcelona, Spain (P Gómez-Pardo MD, J Cortes MD); The West Clinic, Memphis, TN, USA (L S Schwartzberg MD); Institut Curie, Paris, France (V Diéras MD); Sarah Cannon Research Institute, Nashville, TN, USA (D A Yardley MD); University of Minnesota Department of Medicine and Masonic Cancer Center, Minneapolis, MN, USA (D A Potter MD); Centre Oscar Lambret, Lille, France (A Mailliez MD); Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea (J-S Ahn MD); Nektar Therapeutics, San Francisco, CA, USA (C Zhao MS, U Hoch MD, M Tagliaferri PhD, A L Hannah MD)

Summary

Background New options are needed for patients with heavily pretreated breast cancer. Etirinotecan pegol is a long-acting topoisomerase-I inhibitor that prolongs exposure to, but reduces the toxicity of, SN38 (the active metabolite of irinotecan). We assessed whether etirinotecan pegol is superior to currently available treatments for patients with previously treated, locally recurrent or metastatic breast cancer.

Methods In this open-label, multicentre, randomised phase 3 study (BEACON; BrEAst Cancer Outcomes with NKTR-102), conducted at 135 sites in 11 countries, patients with locally recurrent or metastatic breast cancer previously treated with an anthracycline, a taxane, and capecitabine (and two to five previous regimens for advanced disease) were randomly assigned (1:1) centrally via an interactive response system to etirinotecan pegol (145 mg/m² as a 90-min intravenous infusion every 3 weeks) or single-drug treatment of physician's choice. Patients with stable brain metastases and an Eastern Cooperative Oncology Group performance status of 0–1 were eligible. Randomisation was stratified with a permuted block scheme by region, previous eribulin, and receptor status. After randomisation, patients and investigators were aware of treatment assignments. The primary endpoint was overall survival in the intention-to-treat population. This study is registered with ClinicalTrials.gov, number NCT01492101.

Findings Between Dec 19, 2011, and Aug 20, 2013, 852 patients were randomly assigned: 429 to etirinotecan pegol and 423 to treatment of physician's choice. There was no significant difference in overall survival between groups (median 12·4 months [95% CI 11·0–13·6] for the etirinotecan pegol group *vs* 10·3 months [9·0–11·3] for the treatment of physician's choice group; hazard ratio 0·87 [95% CI 0·75–1·02]; p=0·084). The safety population includes the 831 patients who received at least one dose of assigned treatment (425 assigned to etirinotecan pegol and 406 to treatment of physician's choice). Serious adverse events were recorded for 128 (30%) patients treated with etirinotecan pegol and 129 (32%) treated with treatment of physician's choice. Fewer patients in the etirinotecan pegol group had grade 3 or worse toxicity than those in the treatment of physician's choice group (204 [48%] *vs* 256 [63%]; p<0·0001). The most common grade 3 or worse adverse events were diarrhoea (41 [10%] in the experimental group *vs* five [1%] in the control group), neutropenia (41 [10%] *vs* 125 [31%]), and peripheral neuropathy (two [<1%] *vs* 15 [4%]). Three patients in the etirinotecan pegol group died of treatment-related adverse events (pneumonia, myelodysplastic syndrome, and acute renal failure) and two in the treatment of physician's choice group (neutropenic sepsis and septic shock).

Interpretation This trial did not demonstrate an improvement in overall survival for etirinotecan pegol compared to treatment of physician's choice in patients with heavily pre-treated advanced breast cancer. The toxicity profile noted in the etirinotecan pegol group differed from that in the control group. In view of the frequency of cross-resistance and overlapping toxicities noted with many available drugs and the need for effective drugs in highly refractory disease, etirinotecan pegol may warrant further research in some subgroups of patients.

Funding Nektar Therapeutics.

Introduction

Chemotherapy is a mainstay of treatment for metastatic breast cancer. It prolongs survival and can improve quality of life, but the use of sequential single-agent regimens requires careful balancing of safety and effectiveness.[1] The development of cumulative toxic effects, such as neuropathy and cardiotoxicity, and the emergence of resistant or refractory disease, ultimately restricts the use of the drugs used in the metastatic setting, including anthracyclines, taxanes, and

[redacted]

U Hoch PhD, M Taglaferri MD; Sebastopol, CA, USA
(A L Hamrah MD); and Ramon y Cajal University Hospital, Madrid, Spain (J Cortes)

Correspondence to:
Dr Edith A Perez, Mayo Clinic, 4500 San Pablo Rd, Jacksonville, FL 32224, USA
perez.edith@mayo.edu

Research in context

Evidence before this study

At the time that this study design was finalised in 2010, we searched PubMed, with the search terms "advanced breast cancer", "phase 3 clinical trial", "taxane", "anthracycline", "capecitabine", and major oncology society meeting websites, which showed no standard of care or universal chemotherapeutic approach for treatment of patients with advanced breast cancer who progress after an anthracycline, taxane, and capecitabine. Choice of chemotherapeutic drug was driven by the nature and timing of previous therapy, extent of disease burden, cancer-related symptoms, patient and clinician preference, and availability of specific drugs in a given country or region. Available drugs produced suboptimum outcomes and an expected survival of less than 1 year. An urgent need existed for new chemotherapeutic drugs, especially those with a non-overlapping mechanism of action to ensure no cross-resistance and reduce overlapping toxicities.

Added value of this study

It had been postulated that a drug with a different mechanism of action and non-overlapping toxicities might improve survival in patients with heavily advanced disease, especially when most of the commonly used drugs are microtubule-targeting agents. Although we did not demonstrate a significant difference between groups in overall survival, the overlapping adverse event profile and improved global quality of life are encouraging.

Implications of all the available evidence

Although there was no difference in overall survival between groups in the overall population, the suggestion of benefit with etirinotecan pegol in the predefined subgroups of patients with advanced breast cancer and a history of brain metastases and liver metastases deserves further investigation in clinical trials, as does the investigation of predictive biomarkers such as circulating tumour cells that have the potential to identify appropriate patients for treatment with this novel drug.

capecitabine. New treatments with novel mechanisms of action and non-overlapping toxicity profiles are urgently needed, particularly for patients with heavily pretreated, resistant, or refractory disease.

Etirinotecan pegol is a unique, long-acting topoisomerase-I inhibitor designed to improve the pharmacokinetics and distribution of the prodrug irinotecan. Etirinotecan pegol contains a large-chain polyethylene glycol (PEG) core to which four molecules of irinotecan are attached via a cleavable ester-based linker.[3] The linker slowly hydrolyses in vivo to release irinotecan, which is subsequently converted to SN38, the active metabolite of irinotecan. The high molecular weight of etirinotecan pegol (nominal molecular weight 22 kDa) limits its ability to freely cross intact vasculature into healthy tissues but promotes extravasation through the leaky tumour microvasculature, consistent with the enhanced permeation and retention effect shown for macromolecules.[4] In non-clinical models, tumour localisation of etirinotecan pegol via enhanced permeation and retention was pronounced and resulted in high and sustained tumour exposure to SN38.[3] Sustained exposure to this S-phase specific drug could enhance antitumour activity, while avoiding the high plasma levels of irinotecan and SN38 that are associated with toxicity in current clinical practice.[3,5]

In the initial phase 1 study, the mean half-life of SN38 was extended from 2 days with conventional irinotecan to 50 days with etirinotecan pegol, and fewer cases of early-onset cholinergic diarrhoea and neutropenia were noted relative to irinotecan-treated historical controls.[6,7] A randomised phase 2 study assessing two schedules of etirinotecan pegol (145 mg/m² every 14 or 21 days) reported that the drug produced substantial antitumour activity in patients who had received a median of two previous regimens for metastatic breast cancer.[8] Objective responses were noted in 29% of patients, including two complete responses with each schedule. Activity was seen in subsets of patients with particularly poor prognoses, including those with triple-negative breast cancer (objective response in 39%) and visceral disease (objective response in 30%). Although the trial was not designed to formally compare the two treatment schedules, patients randomly assigned to the every 3-week regimen had less toxicity and slightly extended median progression-free survival and overall survival than the 2-week schedule, which led to the selection of the every 3-week dosing regimen for further clinical development.

We aimed to assess whether etirinotecan pegol given every 3 weeks is superior to single-drug treatment of physician's choice with respect to overall survival in patients with heavily pretreated, locally recurrent, or metastatic breast cancer.

Methods

Study design and participants

This open-label, multicentre, randomised phase 3 study (BEACON; BrEAst Cancer Outcomes with NKTR-102) was conducted at 135 sites in 11 countries (the UK, the USA, Canada, France, Spain, Belgium, the Netherlands, Italy, Germany, Russia, and South Korea; appendix). Medical centres included a mix of community and academic centres (about half of each).

See Online for appendix

Eligible patients were 18 years and older with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 who had histologically or cytologically confirmed breast cancer for whom

single-drug chemotherapy was indicated. An estimated minimum life expectancy was not stipulated but would be expected to be at least 6 months. Patients could have measurable (by Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) or non-measurable locally recurrent or metastatic disease. Other entry criteria included: having had a minimum of two previous cytotoxic regimens for advanced disease and no more than five previous cytotoxic regimens for breast cancer (in any setting; all therapy before metastatic disease was counted as one regimen; all patients must have had previous treatment with an anthracycline [unless contraindicated or not medically appropriate]), a taxane, and capecitabine (Patients with known HER2-positive tumours should have been treated with trastuzumab and patients with oestrogen-receptor positive disease should have been treated with previous hormonal therapy); resolution of chemotherapy-related and radiotherapy-related toxicities to grade 1 or less (according to National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] version 4.0), except for diarrhoea (grade 0 without supportive antidiarrhoeal drugs), stable sensory neuropathy (grade ≤2), and alopecia (any grade); and adequate marrow, renal, and hepatic organ function. Patients were not required to have documented progressive disease before study entry, but the last dose of cytotoxic chemotherapy for the treatment of breast cancer must have been given within 6 months of randomisation. Patients were required to have an absolute neutrophil count of $1·5 \times 10^9$ cells per L or greater without myeloid growth factor support for 7 days; haemoglobin 99 g/L or greater; platelet count 75×10^9 platelets per L or greater without blood transfusions for 7 days; total bilirubin less than or equal to 1·5× upper limit of normal (ULN); alanine aminotransferase and aspartate aminotransferase less than or equal to 2·5× ULN (for patients with liver metastases ≤5× ULN); alkaline phosphatase 3 or less× ULN (for patients with liver metastases, ≤5× ULN); serum creatinine 133 µmol/L or less or calculated creatinine clearance 50 mL/min or greater (with Cockcroft-Gault formula). Women of childbearing potential must have had a negative serum pregnancy test. Patients with stable brain metastases (by symptoms and imaging) were eligible, provided that local therapy was completed and corticosteroid use for this indication was discontinued at least 3 weeks before randomisation.

The main exclusion criteria were: receipt of the final dose of intravenous chemotherapy within 21 days (42 days for nitrosoureas or mitomycin C); oral cytotoxic chemotherapy, radiotherapy, biological therapy, or investigational therapy within 14 days; hormonal therapy within 7 days before randomisation; or previous treatment for cancer with a camptothecin derivative (eg, irinotecan, topotecan, camptothecin, or SN38 investigational drugs). Patients with chronic or acute gastrointestinal disorders resulting in diarrhoea of any severity grade or who were on chronic antidiarrhoeal supportive care (more than 3 days per week) to control diarrhoea in the 28 days before randomisation were excluded. Other major exclusion criteria included concomitant use of biological drugs, including antibodies (eg, bevacizumab, trastuzumab, or pertuzumab) or any investigational drugs for the treatment of cancer and any comorbid conditions that in the investigator's opinion would impair study participation or cooperation.

The study was conducted according to the provisions of the Declaration of Helsinki and in accordance with International Conference on Harmonisation Good Clinical Practice standards, US Food and Drug Administration regulations, as well as any and all applicable federal, state and/or local laws and regulations. All patients provided written informed consent, and study approval was obtained by the relevant institutional review board or independent ethics committee at each site.

Randomisation and masking

Before randomisation, investigators specified which treatment of physician's choice regimen would be offered to each patient as part of the informed consent process, and provided that choice to the independent contract research organisation (CRO; Quintiles, Durham, NC, USA) responsible for creating and administering the randomisation scheme. Patients were then randomised centrally (1:1) via an interactive response system to one of two treatment groups: etirinotecan pegol or the registered treatment of physician's choice regimen for each individual patient. Randomisation was stratified with a permuted block scheme by geographical region (North America or Europe *vs* South Korea); previous eribulin use (yes *vs* no); and receptor status (based on local review of triple-negative breast cancer *vs* HER2-positive *vs* other). Investigators were unaware of the block sizes (of 4) used in the randomisation. Treatments were open-label; patients and investigators were both aware of treatment group assignment in this open-label study.

Procedures

Etirinotecan pegol was given at a dose of 145 mg/m² every 21 days until disease progression, unacceptable toxicity, withdrawal by patient, loss to follow up, or death, as a 90-min intravenous infusion; body-surface area was capped at 2·4 m² for dose calculation. The control group allowed investigators to choose one of seven cytotoxic drugs commonly used in this setting at the time the study was designed. The drugs were specified in the protocol to be one of the following (where commercially available): eribulin (manufactured by NerPharMa, Nerviano, Italy; locally sourced for USA), ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel. For sites outside of the

[redacted]

USA, treatment of physician's choice drugs were supplied by the funder; US sites used local commercial supply for treatment of physician's choice drugs. Treatment of physician's choice was given according to local practice, with the exceptions of eribulin and ixabepilone, which were given in accordance with local product labelling. Patients were discontinued from the study for disease progression, unacceptable toxicity, patient withdrawal of consent, investigator decision, loss to follow-up, death, patient non-compliance, or study termination by the funder. Crossover to etirinotecan pegol was not allowed.

Dose delays, reductions, and discontinuations due to toxic effects were defined in the protocol (appendix) for etirinotecan pegol but made according to the prescribing information or local practice guidelines for treatment of physician's choice. Before each cycle of etirinotecan pegol, patients were required to have haemoglobin 80 g/L or greater, absolute neutrophil count $1 \cdot 5 \times 10^9$ cells per L or greater, and platelet count 50×10^9 platelets per L or greater. Diarrhoea had to have resolved to CTCAE grade 0 for at least 7 days without supportive antidiarrhoeal measures; serum creatinine and electrolyte levels had to return to baseline or grade 1 before retreatment. Etirinotecan pegol treatment was delayed until these crtieria were met. A treatment delay of 14 days or more but 28 days or less due to a drug-related toxicity mandated a dose reduction could be reduced to 120 mg/m², then to 95 mg/m² at next treatment cycle initiation. Dose re-escalation was not allowed in subsequent cycles. Patients who required treatment delays of more than 28 days due to unresolved toxicity were withdrawn from treatment, unless, in the investigator's opinion and approved by the medical monitor, study continuation was of benefit for the patient. Loperamide was dispensed to all patients in the etirinotecan pegol group for the treatment of diarrhoea (average dose 2·7 mg [range 1–20 mg]), along with institutional review board-approved or institutional ethics committee-approved instructions written in the local language. The use of prophylactic antidiarrhoeal drugs was prohibited. Use of loperamide was initiated at the first onset of diarrhoea or loose stool and continued until resolution of this toxicity.

Tumour assessments were done at screening and every 8 weeks (give or take 7 days) from date of randomisation until documented disease progression or death. To ensure that both study groups were assessed for progression in a similar manner, tumour assessments were obtained at this interval regardless of delays in chemotherapy. The same method of assessment (CT scans or MRI) and the same technique for acquisition of tumour assessment data were used to characterise each identified and reported lesion at each measurement. Progression and response by imaging were assessed locally by the investigator. Laboratory assessments were done at baseline, on day 1 of each treatment cycle, and at the end-of-treatment visit.

Patients were asked to complete two validated questionnaires designed to assess health-related quality of life, including the EORTC QLQ-C30 and its associated breast cancer subscales, the BR23. Questionnaires were completed at baseline and every 8 weeks thereafter until progressive disease.

Circulating tumour cells were isolated from participating patients for investigation of their use to predict response to treatment. Serial 7·5 mL whole blood samples were drawn and shipped ambient to ApoCell (Houston, TX, USA) for further processing. Peripheral blood mononuclear cells were harvested with the Ficoll-Paque gradient separation method. An iCys laser scanning cytometer (CompuCyte, Westwood, MA, USA) equipped with iCys 3.4.12 image analysis software was used for quantitation. Circulating tumour cell samples

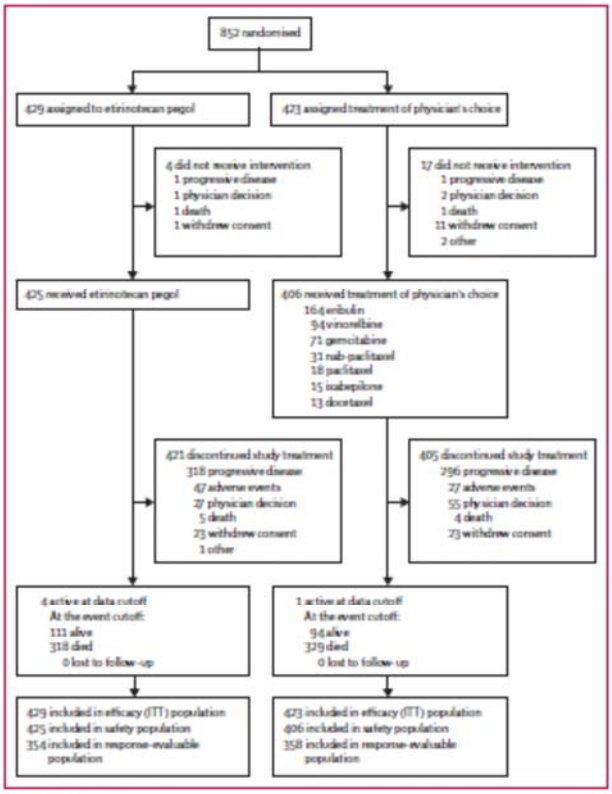


Figure 1: Trial profile
ITT=intention to treat.

[redacted]

were analysed for the number of circulating tumour cells, the percentage of cells staining positive for a given biomarker, and the mean fluorescence intensity, reflecting the normalised intensity of the specific biomarker in the biomarker-positive circulating tumour cells (biomarkers included topoisomerase 1 and 2, markers of proliferation, apoptosis, and double stranded DNA breaks, circulating tumour cells, and efflux transporter). Analysis is ongoing and will be presented in a separate report.

	Etirinotecan pegol (n=429)	Treatment of physician's choice (n=423)
Age (years)	55 (28-84)	55 (32-80)
Sex		
Female	429 (100%)	423 (100%)
Male	0	0
Ethnic origin		
White	305 (71%)	292 (69%)
Black/African American	35 (8%)	34 (8%)
Asian	50 (12%)	55 (13%)
Native Hawaiian/Pacific Islander	1 (<1%)	0
Other/not reported	38 (9%)	42 (10%)
Geographical region		
North America	207 (48%)	195 (46%)
Western Europe	165 (39%)	177 (42%)
Eastern Europe	14 (3%)	9 (2%)
South Korea	43 (10%)	42 (10%)
ECOG performance status		
0	175 (41%)	134 (32%)
1	252 (59%)	285 (67%)
≥2	2 (<1%)	4 (<1%)
Time since initial breast cancer diagnosis (years)	5·8 (0·6-29·3)	5·4 (0·8-31·9)
Time since diagnosis of locally recurrent or metastatic disease (years)	2·5 (0·3-19·7)	2·5 (0·3-22·9)
Stage IV disease at diagnosis	70 (16%)	75 (18%)
Current breast cancer status		
Locally recurrent	4 (<1%)	8 (2%)
Metastatic	425 (99%)	415 (98%)
Visceral disease at enrolment	319 (74%)	324 (77%)
History of brain metastases	36 (8%)	31 (7%)
Metastatic sites at enrolment		
Brain	19 (4%)	18 (4%)
Liver	229 (53%)	227 (54%)
Lung	155 (36%)	168 (40%)
Bone	246 (57%)	243 (57%)
Hormone receptor status (ER or PR)		
Positive	295 (69%)	290 (69%)
Negative	133 (31%)	133 (31%)
Unknown	1 (<1%)	0
HER2 status*		
Positive	30 (7%)	37 (8%)
Negative	395 (92%)	387 (91%)
Unknown	4 (<1%)	4 (<1%)
Triple-negative disease	119 (28%)	117 (28%)
Previous anthracycline	410 (96%)	406 (96%)
Neoadjuvant or adjuvant setting	272 (63%)	276 (65%)
Anthracycline refractory†	58 (14%)	57 (13%)

(Table 1 continues on next page)

Outcomes

The primary endpoint of the study was overall survival, defined as the time from randomisation to death from any cause. Secondary endpoints included objective response, defined as the proportion of patients with measurable disease at baseline with a complete response or partial response per RECIST based on the best response as assessed by the investigator; progression-free survival, defined as the time from randomisation to the earliest evidence of documented disease progression (as assessed by the investigator) or death from any cause; clinical benefit, defined as the proportion of patients having a complete response, partial response, or stable disease for at least 6 months in the response-evaluable population; duration of response, defined as the time from first documented complete response or partial response until the earliest evidence of disease progression or death from any cause; patient-reported outcomes, assessed using the EORTC QLQ-C30 (version 3.0) and breast cancer-specific QLQ-BR23; and safety. Adverse events were assessed immediately after the first dose of treatment until 30 days after the final dose and were classified and graded according to the CTCAE version 4.0.

Statistical analysis

Based on a planned sample size of 840 patients (420 patients per treatment group), the trial had 90% power to detect a hazard ratio (HR) of 0·77 for overall survival based on death from any cause, with a two-sided alpha level of 0·05. This HR correlates to an increase in median survival from 10 months in the control group to 13 months in the etirinotecan pegol group. One interim analysis was planned when 50% of expected deaths (307 of 615) had occurred, based on stopping rules for superiority or absence of efficacy determined by the Lan-DeMets implementation of the O'Brien-Fleming guideline for boundaries.[9] The two-sided significance level for the single interim test was 0·003, and the two-sided significance level for the final analysis was 0·049.

The overall survival and progression-free survival endpoints were tested in the intention-to-treat population, which included all randomised patients, with a two-sided log-rank test stratified by geographical region, previous eribulin use, and receptor status. Because of little enrolment in one region (Eastern Europe), the strata for North America/Western Europe and Eastern Europe were combined in the final analysis. Patients who were alive at the time of analysis or lost-to-follow-up were censored at the time they were last

[redacted]

known to be alive. Kaplan-Meier median survival, 95% CIs, and survival curves were generated to summarise overall and progression-free survival data. A sensitivity analysis for overall survival was done with a Cox regression model to compare hazard rates between the two treatment groups with adjustment for geographical region, previous eribulin, and receptor status. Prespecified subgroup analyses for overall survival examined the effect of previous eribulin (yes or no), receptor status (triple negative, HER2-positive, *vs* hormone-receptor positive HER2-negative), number of previous regimens (≤3, 4, or ≥5), metastases to liver, lung, or brain at baseline, number of sites of disease (≤2 or >2), age (<40, 40≤ 65, and ≥65), ethnic origin (Caucasian *vs* other), ECOG performance status (0 *vs* 1), and geographical region (North America/Western Europe/Eastern Europe *vs* Asia). Secondary endpoints of overall response and duration of response were assessed in the response-evaluable population, which included randomised patients with investigator-assessed measurable disease by RECIST at baseline. The analysis of overall response was done with Fischer's exact test and clinical benefit with the Cochran Mantel-Haenszel test, with Clopper-Pearson exact two-sided 95% CI calculated for each group accordingly. Duration of response was assessed with a two-sided log-rank test stratified for geographical region, previous eribulin use, and receptor status.

Patient-reported outcomes were assessed before randomisation and every 8 weeks until progression, death, or withdrawal of consent from the study treatment. For all analyses of patient-reported outcomes, all randomised patients with data were included. Scoring of questionnaires followed the EORTC published scoring manual BR-23 scales. For each scale, raw scores were standardised via a linear transformation to a range from 0 to 100 (high scores represent a high or healthy level of functioning or high or severe level of symptomatology). Absolute scores and changes from baseline and categorical change (as improved, stable, or worsened) from baseline with a 5-point change for both were calculated by treatment group. Preplanned analysis methods included analysis of variance, mixed model repeated measure, and proportional odds model.

Summary statistics for adverse events were prepared for the safety population, which included all randomised patients who received at least one full or partial dose of their assigned treatment. Odds ratios summarising the extent of benefit of etirinotecan pegol versus treatment of physician's choice were calculated for selected incidence occurring in 10% or more of the safety population. An independent data monitoring committee reviewed interim safety results and the interim efficacy analysis.

Data were analysed with SAS (version 9.1 or higher). This study is registered with ClinicalTrials.gov, number NCT01492101.

	Etirinotecan pegol (n=429)	Treatment of physician's choice (n=423)
(Continued from previous page)		
Previous taxane	429 (100%)	423 (100%)
Taxane refractory†	178 (42%)	157 (37%)
Previous capecitabine	429 (100%)	423 (100%)
Capecitabine refractory†	306 (71%)	315 (74%)
Previous eribulin	71 (17%)	72 (17%)
Number of previous regimens for locally recurrent or metastatic disease	3 (1-6)	3 (1-6)
1‡	1 (<1%)	2 (<1%)
2	122 (28%)	120 (28%)
3	147 (34%)	161 (38%)
4	114 (27%)	118 (28%)
5	40 (9%)	20 (5%)
6+‡	5 (1%)	2 (<1%)

Data are n (%) or median (range). ECOG=Eastern Cooperative Oncology Group performance status. ER=oestrogen receptor. PR=progesterone receptor. *HER2 status was determined regardless of hormone receptor status. †Refractory disease was defined as disease progression while receiving therapy in the metastatic setting within 8 weeks of the last dose of the last regimen. ‡These patients were entered into the protocol in violation of the entry criteria which stipulated that patients must have received between two and five regimens for locally recurrent or metastatic disease.

Table 1: Baseline patient characteristics

	Etirinotecan pegol (n=425)	Treatment of physician's choice (n=406)
Study drug received		
Etirinotecan pegol	425 (100%)	–
Eribulin	–	164 (40%)
Vinorelbine	–	94 (23%)
Gemcitabine	–	71 (17%)
Nab-paclitaxel	–	31 (8%)
Paclitaxel	–	18 (4%)
Ixabepilone	–	15 (4%)
Docetaxel	–	13 (3%)
Number of cycles completed		
Mean (SD)	5·5 (5·2)	5·0 (4·2)
Median (range)	3·0 (1-35)	3·0 (1-26)
Relative dose intensity (%)*		
Mean (SD)	92·6 (10·7)	89·1 (16·2)
Median (range)	98·3 (55·2-107·7)	92·8 (31·7-168·4)

*Relative dose intensity was calculated as actual dose intensity (mg/m² per week) divided by expected dose intensity (mg/m² per week).

Table 2: Treatment exposure (safety population)

Role of the funding source

The funder was involved in the study design, data collection, data analysis, and interpretation of the results. The primary data were obtained and managed by the funder and an independent CRO (Quintiles), analysed by statisticians employed by the CRO, and verified by the funder. The first draft of this report was developed by an independent medical communications company with financial support from the funder.

Subsequent drafts were developed and revised by the corresponding author and reviewed and amended by all authors. The funder and corresponding author had full access to all raw data in the study, and all authors had final responsibility for the decision to submit for publication.

Results

Between Dec 19, 2011, and Aug 20, 2013, 852 patients (comprising the intention-to-treat population) were enrolled at 135 centres in North America, Europe, and Asia. Of these, 429 patients were randomly assigned to etirinotecan pegol and 423 to treatment of physician's choice (figure 1). Four patients in the etirinotecan pegol group and 17 in the treatment of physician's choice group did not receive the allocated intervention because the patient's condition deteriorated between randomisation and first dose of study drug or the patient elected to withdraw consent to proceed to treatment. Thus, 831 patients (comprising the safety population) ultimately received at least one dose of assigned treatment (425 assigned to etirinotecan pegol and 406 to treatment of physician's choice).

At the time of the final analysis, nearly 80% of patients either had died (635 [76%] of 831 patients) or withdrawn consent for survival follow-up (24 [3%] of 831 patients). The primary reason for study drug discontinuation based on the safety population was disease progression in both groups; other reasons included adverse events, physician's decision, patient withdrawal of consent, and death (figure 1).

Baseline demographic and disease characteristics were relatively well balanced between treatment groups (table 1). Most patients were treated in North America or Europe. Two-thirds (554 [65%]) had hormone-receptor positive and HER2-negative disease, while 236 (28%) were triple-negative and 62 (7%) were HER2-positive. The median age of both groups was 55 years, and most patients had a good performance status (ECOG 0–1). Performance status deteriorated to 2 or worse between randomisation and first dose in a few patients. Median time since diagnosis of locally recurrent or metastatic disease was the same in both groups. The most common metastatic sites were bone, followed by liver and then lung. 67 patients (8%) had a history of brain metastases. Per protocol, nearly all patients had received a previous anthracycline, and all patients had been previously treated with a taxane and capecitabine. More than two-thirds in each group had disease that had progressed on or within 8 weeks of terminating treatment with a taxane or capecitabine therapy or both. The median number of previous regimens for metastatic breast cancer was three in each treatment group. Slightly more patients in the etirinotecan pegol group than in the treatment of physician's choice had received five or more previous regimens for metastatic breast cancer (table 1).

Patients in both treatment groups received a median of three treatment cycles (table 2). Eribulin was the most frequent treatment of physician's choice, followed by vinorelbine, gemcitabine, nab-paclitaxel, paclitaxel, ixabepilone, and docetaxel. Mean and median relative dose intensity were high (≥90%), but were higher with etirinotecan pegol than with treatment of physician's choice, and slightly fewer patients in the etirinotecan pegol group required one or more dose delays (178 patients [42%] of 425 patients in the etirinotecan pegol group *vs* 190 patients [47%] of 406 patients in the treatment of physician's choice group). The proportion of patients who had dose reductions was very similar in each group (117 patients [28%] in the etirinotecan pegol group and 115 patients [28%] in treatment of physician's choice group).

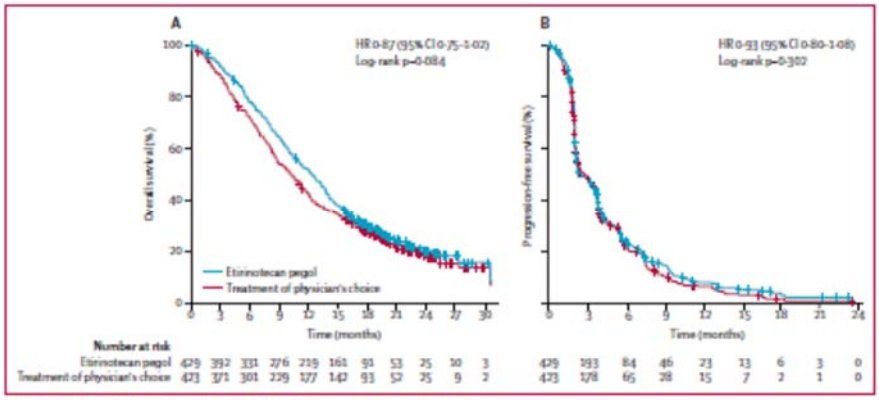


Figure 2: Kaplan-Meier plot of overall survival (A) and progression-free survival (B)
HR=hazard ratio.

[redacted]

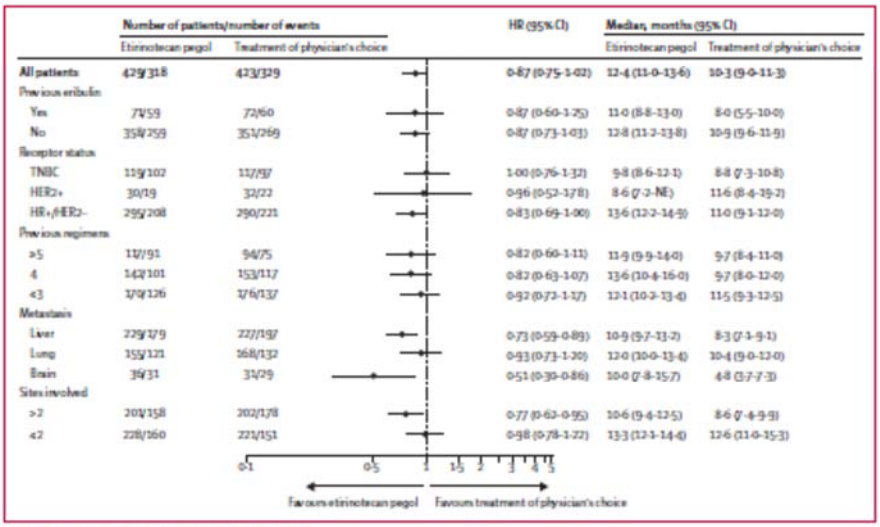


Figure 3: Planned subgroup analysis of overall survival
HR=hazard ratio. TNBC=triple-negative breast cancer. NE=not estimable.

The event cutoff for the primary overall survival analysis was Dec 8, 2014. With a median follow-up of 21·1 months (IQR 17·6–25·0) in the etirinotecan pegol group and 21·7 months (18·9–24·9) in the treatment of physician's choice group, a total of 647 deaths had occurred: 318 (74%) in the etirinotecan pegol group and 329 (78%) in the treatment of physician's choice group. Median overall survival was 12·4 months (95% CI 11·0–13·6) for etirinotecan pegol and 10·3 months (95% CI 9·0–11·3) for treatment of physician's choice (HR 0·87 [95% CI 0·75–1·02]; p=0·084; figure 2A). Survival at 6 months was 78·3% (95% CI 74·0–81·9) in the etirinotecan pegol group and 72·1% (67·5–76·1) in the treatment of physician's choice group. The corresponding 12-month rates were 52·0% (95% CI 47·1–56·7) in the etirinotecan pegol group and 42·8% (38·0–47·5) in the treatment of physician's choice group. Planned subgroup analyses showed a significant reduction in the risk of death with etirinotecan pegol relative to treatment of physician's choice in patients with a history of brain metastases, in those with liver metastasis, and in those with more than two sites of disease (figure 3). No significant difference was noted between groups for those patients who had previously received eribulin (figure 3).

Median follow-up was 16·6 months (IQR 8·4–21·3) in the etirinotecan pegol group and 16·4 months (5·7–17·7) in the treatment of physician's choice group. Median progression-free survival was 2·4 months (95% CI 2·1–3·5) with etirinotecan pegol and 2·8 months (2·1–3·5) with treatment of physician's choice (HR 0·93 [95% CI 0·80–1·08]; p=0·30; figure 2B). Approximately half of patients randomised to either treatment group had progressed at the time of first post-treatment tumour assessment. Progression-free survival was similar at 3 months (48·5% [95% CI 43·6–53·3] for etirinotecan pegol and 48·3% [43·2–53·2] for treatment of physician's choice) and at 6 months (23·4% [95% CI 19·3–27·7] and 21·8% [17·7–26·3]). In the 143 patients who had received previous eribulin (in addition to previous anthracycline, taxane, and capecitabine), median progression-free survival was 3·3 months (95% CI 1·9–4·0) for etirinotecan pegol and 2·0 months (1·8–3·4) for treatment of physician's choice (HR 0·74 [95% CI 0·51–1·07]; p=0·302).

	Etirinotecan pegol (n=354)	Treatment of physician's choice (n=358)
Complete response	2 (<1%)	1 (<1%)
Partial response	56 (16%)	60 (17%)
Stable disease	114 (32%)	107 (30%)
Progressive disease	157 (44%)	144 (40%)
Not evaluable	25 (7%)	46 (13%)

Table 3: Tumour responses for patients with measurable disease at baseline

712 patients had measurable disease at baseline (354 assigned to etirinotecan pegol and 358 assigned to

[redacted]

treatment of physician's choice; table 3). Objective responses were recorded for 58 (16%) patients in the etirinotecan pegol group and 61 (17%) in the treatment of physician's choice group (p=0·84). Median duration of response was 3·9 months (95% CI 3·5–5·1) in the etirinotecan pegol group and 3·7 months (2·1–3·9) in the treatment of physician's choice group (p=0·27). In the per-protocol population, a clinical benefit was noted in 76 (22%) of patients in the experimental group and in 75 (21%) of those in the control group (p=0·81); in the intention-to-treat population, clinical benefit was noted in 88 (21%) patients in the etirinotecan pegol group and 83 (20%) in the treatment of physician's choice group (p=0·73). Of the 143 patients who had received previous eribulin (in addition to previous anthracycline, taxane, and capecitabine), objective responses were noted in eight (14%) patients in the etirinotecan pegol group and four (7%) in the treatment of physician's choice group.

Comparison of subsequent chemotherapy between the two groups showed roughly equivalent use of at least one drug in 324 (76%) patients in the etirinotecan pegol group and 304 (72%) patients in the treatment of physician's choice group. Eribulin, the most common drug in the treatment of physician's choice group, was subsequently used more in the etirinotecan pegol group than in the treatment of physician's choice group (160 [37%] *vs* 74 [18%]). Other commonly used drugs included gemcitabine (103 [24%] and 78 [18%], respectively), vinorelbine (99 [23%] and 72 [17%]), and paclitaxel (87 [20%] and 62 [15%]). A small number of patients received five or more subsequent regimens (19 [4%] and 19 [4%], respectively).

Treatment-emergent adverse events were recorded for 417 (98%) of the 425 patients treated with etirinotecan pegol and 405 (100%) of the 406 treated with treatment of physician's choice, and led to treatment discontinuation in 47 (11%) patients in the etirinotecan pegol group and 27 (7%) patients in the treatment of physician's choice group (table 4). Drug-related adverse events leading to discontinuation occurred in 38 (9%) patients in the experimental group and 16 (4%) in the control group. The most common drug-related reasons for discontinuation in the etirinotecan pegol group were diarrhoea (13 [3%]) and neutropenia (ten [2%]); for the treatment of physician's choice group, this was peripheral neuropathy (seven [2%]). Drug-related fatalities were rare in both groups, with three deaths in

	Etirinotecan pegol (n=425)				Treatment of physician's choice (n=406)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Number of patients who reported at least one treatment-emergent adverse event	213 (50%)	160 (38%)	28 (7%)	16 (4%)	149 (37%)	169 (42%)	62 (15%)	25 (6%)
Nausea	240 (56%)	15 (4%)	0	0	148 (36%)	8 (2%)	0	0
Diarrhoea	240 (56%)	41 (10%)	0	0	75 (18%)	5 (1%)	0	0
Neutropenia-related events	70 (16%)	32 (8%)	9 (2%)	0	50 (12%)	79 (19%)	45 (11%)	1 (<1%)
Fatigue	127 (30%)	19 (4%)	0	0	114 (28%)	16 (4%)	0	0
Vomiting	161 (38%)	12 (3%)	0	0	68 (17%)	7 (2%)	0	0
Constipation	111 (26%)	1 (<1%)	0	0	123 (30%)	3 (<1%)	0	0
Decreased appetite	126 (30%)	5 (1%)	0	0	93 (23%)	5 (1%)	0	0
Asthenia	84 (20%)	8 (2%)	0	0	102 (25%)	15 (4%)	0	0
Headache	90 (21%)	5 (1%)	0	0	67 (17%)	4 (<1%)	0	0
Anaemia	46 (11%)	20 (5%)	0	0	63 (16%)	18 (4%)	1 (<1%)	0
Abdominal pain	86 (20%)	5 (1%)	0	0	47 (12%)	1 (<1%)	0	0
Alopecia	44 (10%)	0	0	0	95 (23%)	0	0	0
Neuropathy-related events	31 (7%)	1 (<1%)	1 (<1%)	0	89 (22%)	15 (4%)	0	0
Dyspnoea	52 (12%)	8 (2%)	0	0	58 (14%)	13 (3%)	4 (<1%)	1 (<1%)
Cough	59 (14%)	0	0	0	52 (13%)	0	0	0
Pyrexia	33 (8%)	0	0	0	62 (15%)	3 (<1%)	0	0
Dizziness	52 (12%)	4 (<1%)	0	0	39 (10%)	2 (<1%)	0	0
Abdominal pain upper	53 (12%)	3 (<1%)	0	0	36 (9%)	2 (<1%)	0	0
Myalgia	26 (6%)	0	0	0	58 (14%)	1 (<1%)	0	0
Decreased weight	56 (13%)	1 (<1%)	0	0	24 (6%)	0	0	0
Blurred vision	67 (16%)	1 (<1%)	0	0	11 (3%)	1 (<1%)	0	0
Back pain	36 (8%)	3 (<1%)	0	0	38 (9%)	2 (<1%)	0	0
Arthralgia	28 (7%)	0	0	0	39 (10%)	3 (<1%)	0	0
Dehydration	24 (6%)	17 (4%)	0	0	15 (4%)	6 (1%)	0	2 (<1%)
Peripheral oedema	19 (4%)	0	0	0	38 (9%)	5 (1%)	0	0

Table 4: Treatment-emergent adverse events occurring in 10% or more of patients

[redacted]

the etirinotecan pegol group (causes of death being pneumonia, myelodysplastic syndrome, and acute renal failure) and two in the treatment of physician's choice group (causes of death neutropenic sepsis and septic shock). Adverse events that were more common in the etirinotecan pegol group included diarrhoea, gastrointestinal toxicities, and cholinergic toxicities (eg, blurry vision); adverse events that were more common with treatment of physician's choice included neutropenia, infections, asthenia, and alopecia (table 4; appendix). In both groups, most of these events were CTCAE grade 1 or 2.

The incidence of grade 3 or worse events was significantly lower among patients treated with etirinotecan pegol (204 [48%] *vs* 256 [63%], respectively; odds ratio 0·54 [95% CI 0·41–0·71]; p<0·0001). Median time to onset of any grade 3 adverse events was slightly longer with etirinotecan pegol compared with treatment of physician's choice (34 days [IQR 1–488] and 21 days [1–344], respectively). Grade 3 or higher peripheral neuropathy was lower with etirinotecan pegol than with treatment of physician's choice (2 [<1%] *vs* 15 [4%]), but incidences of grade 3 or worse febrile neutropenia (3 [<1%] in etirinotecan pegol *vs* 8 [2%] in treatment of physician's choice) or neutropenia sepsis were low in both groups (none (0%) in etirinotecan pegol *vs* one (<1%) neutropenic sepsis in treatment of physician's choice). Serious adverse events were recorded for 128 (30%) patients treated with etirinotecan pegol and 129 (32%) treated with treatment of physician's choice. Adverse events leading to death occurred in five (1%) patients treated with etirinotecan pegol and eight (2%) treated with treatment of physician's choice. These events in the etirinotecan pegol group included one case each of pleural effusion, respiratory failure, myelodysplastic syndrome, pneumonia, and acute renal failure. Fatal events within the treatment of physician's choice group included two cases of pleural effusion and one case each of respiratory failure, hepatic failure, fluid overload, lung infection, neutropenic sepsis, and septic shock.

Grade 3 diarrhoea was more common with etirinotecan pegol (41 [10%] patients) than with treatment of physician's choice (5 (1%) patients), but grade 4 diarrhoea was not observed (table 4). Median time to onset of grade 3 diarrhoea was 43 days (IQR 3–488) in the etirinotecan pegol group versus 7 days (1–79) in the treatment of physician's choice group and the median time to resolution was 6 days (1–31) in the etirinotecan pegol group and 4 days (1–21) in the treatment of physician's choice group. Loperamide was used to treat diarrhoea in 274 (64%) of patients given etirinotecan pegol group and 27 (6%) given treatment of physician's choice. Octreotide was used in seven patients in the etirinotecan pegol group, and no patients in the treatment of physician's choice group. Diarrhoea leading to patient discontinuation occurred in 13 (3%) patients in the etirinotecan pegol group versus none in the treatment of physician's choice group.

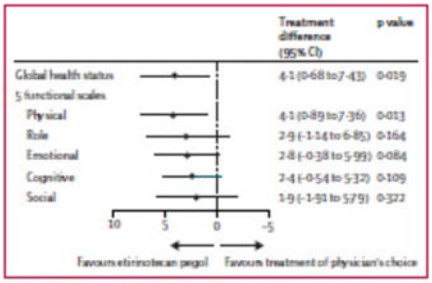


Figure 4: Mean change in EORTC global health status and functional scales over 32 weeks

Myelosuppression was more pronounced in the treatment of physician's choice group than in the etirinotecan pegol group. Grade 3 or worse neutropenia was more common with treatment of physician's choice (table 4), but rates of grade 3 or greater febrile neutropenia or neutropenia sepsis were low in both groups (three patients in the etirinotecan pegol group and eight in the treatment of physician's choice group). Grade 4 neutropenia occurred in nine (2%) patients in the etirinotecan pegol group and 45 (11%) in the treatment of physician's choice group. Growth factor support was more commonly used in the treatment of physician's choice group (110 [26%]) than in the etirinotecan pegol group (51 [12%]). Median onset of neutropenia was earlier with treatment of physician's choice (17 days [IQR 1–614]) compared with etirinotecan pegol (62 days [1–225]). Grade 3–4 anaemia and thrombocytopenia were relatively rare in both groups (20 [5%] in the etirinotecan pegol group *vs* 19 [5%] in the treatment of physician's choice group and 6 [1%] in the etirinotecan pegol group *vs* 8 [2%] in the treatment of physician's choice group for grade 3–4 thrombocytopenia). Infections and admissions to hospital for infections occurred more frequently in the treatment of physician's choice group (162 [40%] *vs* 131 [31%] and 29 [7%] *vs* 24 [6%], respectively).

For the analyses of patient-reported outcomes, most randomised patients completed at least one post-baseline visit (378 [88%] in etirinotecan pegol group and 355 [84%] in the treatment of physician's choice group). The primary assessment of health-related quality of life occurred up to 32 weeks after randomisation. Change and treatment effect after week 32 could not be reliably assessed because less than 10% of patients completed questionnaires after this timepoint. 421 (98%) patients in the etirinotecan pegol group and 405 (96%) in the treatment of physician's choice group completed the QLQ-C30 global health status questionnaire at baseline. By week 32, 69 (16%) patients in the etirinotecan pegol group and 59 (14%) patients in the treatment of physician's choice group completed the questionnaire.

[redacted]

Significant differences were noted in favour of etirinotecan pegol over 32 weeks for global health status (p=0·019) and physical functioning scales of the EORTC QLQ-C30 (p=0·013; figure 4). The differences were more profound over time with continued therapy (appendix pp 1–5). The differences between treatment groups in other functional scales were not significant. Analysis of the global health status and physical functionaling scales of the EORTC QLQ-C30 at time of disease progression showed a comparatively large decline in quality of life, with a mean overall change from baseline of −9·4 in global health status and of −10·8 and physical functioning.

Discussion

The BEACON study assessed whether etirinotecan pegol, a novel long-acting topoisomerase I inhibitor, is superior to currently available cytotoxic drugs used for the treatment of patients with advanced breast cancer who have already received an anthracycline, a taxane, and capecitabine. The study was designed to detect an HR of 0·77 for overall survival relative to the control group, a composite of seven different single drugs commonly used in this clinical setting. Although the difference between groups in overall survival was not statistically significant, the toxicity profiles were different.

Eribulin is the most recently approved anticancer agent in this population, and is approved as second-line (European Union and elsewhere) or third-line (USA) chemotherapy for advanced breast cancer. Unlike eribulin, other drugs (vinflunine, ixabepilone, sunitinib, and sorafenib) have failed to show a survival advantage, underscoring the need for more research in this area.[10–14] To date, we lack predictive biomarkers that can personalise chemotherapy and identify for an individual patient the drug from which they are most likely to benefit.

The HRs for progression-free survival for etirinotecan pegol and treatment of physician's choice were similar. As in many phase 3 trials in metastatic breast cancer, roughly half of our patients in both treatment groups had progressive disease at the first imaging timepoint (8 weeks), making any difference in progression-free survival difficult to detect. Apparently greater improvements in overall survival than in progression-free survival have also been reported in two other recent, large-scale, randomised, phase 3 clinical trials in a similar population to that studied in the BEACON trial.[15,16] Eribulin did not prolong progression-free survival compared with capecitabine (HR 1·08 [95% CI 0·93–1·25]; p=0·30), or overall survival (HR 0·88 [95% CI 0·77–1·00]; p=0·056).[15] Similarly, in the EMBRACE trial, eribulin failed to show a statistically significant benefit in progression-free survival compared with treatment of physician's choice (HR 0·87 [95% CI 0·71–1·05]; p=0·14), but did improve overall survival (HR 0·81 [95% CI 0·66–0·99]; p=0·041).[16] Outcomes for other efficacy parameters (clinical benefit and overall response) were similar between the two groups. Of note, a meta-analysis of 11 randomised clinical trials in metastatic breast cancer failed to show a clear association between other endpoints and overall survival.[17]

The proportion of patients with treatment-emergent adverse events was much the same with etirinotecan pegol and treatment of physician's choice, although the pattern of adverse events differed between groups, with fewer grade 3 or worse adverse events in the experimental group than in the control group; grade 3 or worse adverse events also tended to be of later onset in the experimental group than in the control group. Adverse event profiles also differed, in particular in terms of diarrhoea (higher with the experimental agent), neutropenia, and neuropathy (both higher with treatment of physician's choice). The incidence of infections and admissions to hospital for infection were higher in the treatment of physician's choice group than in the etirinotecan pegol group, which mirrored the substantially higher use of growth factor supportive care in the treatment of physician's choice group. Although etirinotecan pegol was associated with a lower incidence of asthenia, peripheral oedema, myalgia, and alopecia, its use was associated with higher rates of nausea, vomiting, and abdominal pain. The health-related quality of life analysis showed better results for both global health status and physical functioning in the etirinotecan pegol group compared with treatment of physician's choice.

Although diarrhoea was the most common grade 3 toxicity for patients receiving etirinotecan pegol, it led to discontinuation in only 13 (3%) patients. Strict diarrhoea management guidelines were in place, including temporary discontinuation of etirinotecan pegol after the third occurrence of grade 2 diarrhoea. As would be expected with the most commonly used drugs in the treatment of physician's choice group, grade 3 or higher neutropenia and peripheral neuropathy were more common with treatment of physician's choice. Less myelosuppression in the etirinotecan pegol group is likely to have resulted in fewer infections and hospitalisations for infections.

The results of the planned subgroup analyses are intriguing and consistent with the mechanism of action of etirinotecan pegol. Subgroup analyses suggest that etirinotecan pegol significantly prolonged overall survival in patients with a history of brain metastases, with liver metastases, and with two or more sites of disease. Results in patients with a history of brain metastases are supported by data from a murine model of brain metastases from breast cancer.[3] Etirinotecan pegol treatment of mice with established brain metastases resulted in a 50% survival, with surviving animals harbouring minimal residual CNS disease.

[redacted]

This recorded efficacy correlated with the ability of etirinotecan pegol to cross the blood–tumour barrier, leading to preferential accumulation and retention in brain tumours, followed by sustained exposure to the active metabolite SN38 at concentrations that lead to apoptosis of tumour cells. In addition to the ability to cross the blood–tumour barrier, etirinotecan pegol avoids P-glycoprotein and BCRP/ABCG2-mediated efflux, which probably provides an added benefit for uptake into the brain lesions. The preferential accumulation and retention in tumour tissue (in addition to brain lesions) that was noted in subcutaneously implanted tumours might also form the basis for the prolonged overall survival in patients with liver metastases, as highly vascular tumours are expected to promote extravasation of macromolecules like etirinotecan pegol.

A potential weakness to this study lay in the heterogeneity of the patient population: the requirement for between two and five previous regimens for locally advanced or metastatic disease allowed both patients with relatively indolent disease and relatively more aggressive disease to participate. The requirement for progression within 6 months of randomisation was intended to identify those patients who required therapy with a cytotoxic drug and actively progressing disease; however, a treatment effect in patients with less chemo-refractory disease could have been masked by the patients with extensive previous therapy. A more homogeneous patient population might have been better able to show a treatment effect.

In summary, findings of this large phase 3 trial showed clinical activity and reasonable tolerability with etirinotecan pegol in patients with heavily pretreated advanced breast cancer. In view of the frequency of cross-resistance and overlapping toxicities noted with many available drugs and the need for effective drugs in highly refractory disease, etirinotecan pegol could offer an enhanced mechanism of action of particular interest in patients with breast cancer with brain and liver metastases. Further clinical studies in patients with brain and liver metastases, as well as exploration of etirinotecan pegol target-specific predictive biomarkers measured in circulating tumour cells isolated from participating patients as part of the trial design, are ongoing.

Contributors

EAP, AA, JO'S, HSR, CT, S-AI, and JC served on the steering committee. EAP conceived and designed the trial. AA, JO'S, HSR, CT, S-AI, LSS, UH, ALH, and JC designed the trial. ALH and CT were involved in trial oversight. JO'S and HSR were involved in trial execution. EAP, AA, JO'S, HSR, CT, S-AI, PG-P, LSS, VD, DAY, DAP, AM, AM-A, J-SA, and JC recruited patients. EAP, CZ, UH, MT, and JC were involved in data interpretation. All authors participated in data review and analysis and preparation and review of the manuscript. JC made critical revisions to the manuscript for important intellectual content, and EAP gave final approval of the manuscript.

Declaration of interests

AA has participated in an advisory board for Nektar. HSR reports Nektar advisory board (uncompensated) and research funding to UCSF from Eisai. CT reports an advisory role for Eisai, AstraZeneca, and Pfizer, and speakers' bureau for Eisai. S-AI reports research funding from AstraZeneca and advisory role from AstraZeneca, Novartis, and Roche. LSS reports an advisory role with Genentech, Novartis, and Eisai. VD reports an advisory role for Nektar, Roche Genentech, Pfizer, Novartis, and Eisai. ALH is a consultant to Nektar. CZ, UH, and MT report employment at Nektar Therapeutics. JC reports consulting fees from Roche/Genentech and Celgene; honoraria for lectures from Roche/Genentech, Celgene, Novartis, and Eisai; and stockholder from MedSIR. EAP, JO'S, PG-P, DAY, DAP, AM, AMA, and J-SA declare no competing interests.

Acknowledgments

We thank the independent data monitoring committee (Kathy Miller, Hanu Arun, and James Boyce) for their study oversight. We thank the patients, their caregivers and families, and the investigators who participated in this study. We also thank Phillips Gilmore Oncology Communications (PA, USA) for providing medical writing support, funded by Nektar Therapeutics.

References

1 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, version 2, 2015. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf. (accessed May 15, 2015).

2 Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Ann Oncol* 2014; 25: 1871–88.

3 Hoch U, Staschen C-M, Johnson R, Eldon MA. Nonclinical pharmacokinetics and activity of etirinotecan pegol (NKTR-102), a long-acting topoisomerase 1 inhibitor, in multiple cancer models. *Cancer Chemother Pharmacol* 2014; 74: 1125–37.

4 Bai J, Zhou Z, Tang H, et al. Impact of PEGylation on biodistribution and tumor accumulation of Lipid-Mu peptide-DNA. *J Liposome Res* 2013; 23: 1–10.

5 Rothenberg ML, Kuhn JG, Rodriguez FI, et al. Phase 1 dose-finding and pharmacokinetic trial of irinotecan (CPT-11) administered every two weeks. *Ann Oncol* 2001; 12: 1631–41.

6 Jameson GS, Hamm JT, Weiss GJ, et al. Multicenter, phase I, dose-escalation study to assess the safety, tolerability, and pharmacokinetics of etirinotecan pegol in patients with refractory solid tumors. *Clin Cancer Res* 2013; 19: 268–78.

7 Von Hoff DD, Jameson GS, Borad MJ, et al. First phase I trial of NKTR-102 (PEG irinotecan) reveals early evidence of broad antitumor activity in three schedules. *Eur J Cancer* 2008; 6: 595.

8 Awada A, Garcia AA, Chan S, et al. Two schedules of etirinotecan pegol (NKTR-102) in patients with previously treated metastatic breast cancer: a randomised phase 2 study. *Lancet Oncol* 2013; 14: 1216–25.

9 DeMets DL, Lan KKG. Interim analysis: the alpha spending function approach. *Stat Med* 1994; 13: 1341–52.

10 Cortes J, Lovy C, Demidchik Y, et al. A randomised phase III study of vinflunine versus an alkylating agent of physician's choice in metastatic breast cancer (MBC) previously treated with or resistant to an anthracycline, a taxane, an antimetabolite and a vinca-alkaloid. *J Clin Oncol* 2015; 33: 1031.

11 Spurano JA, Vrodoljak E, Rhee O, et al. Randomised phase III trial of ixabepilone plus capecitabine versus capecitabine in patients with metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol* 2010; 28: 3256–63.

12 Hortobagyi GN, Gomez HL, Li RK, et al. Analysis of overall survival from a phase III study of ixabepilone plus capecitabine versus capecitabine in patients with MBC resistant to anthracyclines and taxanes. *Breast Cancer Res Treat* 2010; 122: 409–18.

13 Barrios CH, Liu MC, Lee SC, et al. Phase III randomised trial of sunitinib versus capecitabine in patients with previously treated HER2-negative advanced breast cancer. *Breast Cancer Res Treat* 2010; 121: 123–31.

14 Baselga J, Costa F, Gomez H, et al. A phase 3 trial comparing capecitabine in combination with sorafenib or placebo for treatment of locally advanced or metastatic HER2-Negative breast CancEr (the RESILIENCE study): study protocol for a randomised controlled trial. *Trials* 2013; 14: 228.

15 Kaufman PA, Awada A, Twelves C, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. *J Clin Oncol* 2015; 33: 594–601.

16 Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet* 2011; 377: 914–23.

17 Bunnykowski T, Bayse M, Piccart-Gebhart MJ, et al. Evaluation of tumor response, disease control, progression-free survival, and time to progression as potential surrogate end points in metastatic breast cancer. *J Clin Oncol* 2008; 26: 1987–92.

[redacted]

APPENDIX 3: LANCET ONCOLOGY ARTICLE, LIN, ET AL.

Review

Response assessment criteria for brain metastases: proposal from the RANO group

Nancy U Lin, Eudocia Q Lee*, Hidefumi Aoyama, Igor J Barani, Daniel P Barboriak, Brigitta G Baumert, Martin Bendszus, Paul D Brown, D Ross Camidge, Susan M Chang, Janet Dancey, Elisabeth G E de Vries, Laurie E Gaspar, Gordon J Harris, F Stephen Hodi, Steven N Kalkanis, Mark E Linskey, David R Macdonald, Kim Margolin, Minesh P Mehta, David Schiff, Riccardo Soffietti, John H Suh, Martin J van den Bent, Michael A Vogelbaum, Patrick Y Wen, for the Response Assessment in Neuro-Oncology (RANO) group*

Lancet Oncology 2015; 16: e270–78

See Online for interview with Nancy Lin

*Contributed equally

Department of Medical Oncology (N U Lin MD, F S Hodi MD) **and Center for Neuro-Oncology** (E Q Lee MD, Prof P Y Wen MD), **Dana-Farber Cancer Institute, Boston, MA, USA; Department of Radiology, Niigata University Graduate School of Medical and Dental Sciences, Chuo-ku, Niigata, Japan** (Prof H Aoyama MD); **Department of Radiation Oncology, University of California, San Francisco, CA, USA** (I J Barani MD); **Department of Radiology, Duke University Medical Center, Durham, NC, USA** (Prof D P Barboriak MD); **Department of Radiation-Oncology, MediClin Robert Janker Clinic & University of Bonn Medical Centre, Cooperation Unit Neuro-oncology, Bonn, Germany** (B G Baumert MD); **Department of Neuroradiology, University of Heidelberg, Heidelberg, Germany** (Prof M Bendszus MD); **Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA** (Prof P D Brown MD); **Division of Medical Oncology, School of Medicine, University of Colorado Denver, Denver, CO, USA** (D R Camidge MD); **Department of Neurosurgery, University of California, San Francisco, CA, USA** (Prof S M Chang MD); **NCIC Clinical Trials Group, Ontario Institute for Cancer Research, Queen's University, Kingston, ON, Canada** (Prof J Dancey MD); **Department of Medical Oncology, University Medical Center Groningen, University of Groningen, RB Groningen, Netherlands** (Prof E G E de Vries MD); **Department of Radiation Oncology, The Anschutz**

CNS metastases are the most common cause of malignant brain tumours in adults. Historically, patients with brain metastases have been excluded from most clinical trials, but their inclusion is now becoming more common. The medical literature is difficult to interpret because of substantial variation in the response and progression criteria used across clinical trials. The Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group is an international, multidisciplinary effort to develop standard response and progression criteria for use in clinical trials of treatment for brain metastases. Previous efforts have focused on aspects of trial design, such as patient population, variations in existing response and progression criteria, and challenges when incorporating neurological, neuro-cognitive, and quality-of-life endpoints into trials of patients with brain metastases. Here, we present our recommendations for standard response and progression criteria for the assessment of brain metastases in clinical trials. The proposed criteria will hopefully facilitate the development of novel approaches to this difficult problem by providing more uniformity in the assessment of CNS metastases across trials.

Introduction

Brain metastases are the most common cause of malignant brain tumours in adults. Of the nearly 1·5 million patients in the USA who received a primary diagnosis of cancer in 2007, about 70 000 of these primary diagnoses are estimated to eventually relapse in the brain.[1,2] Despite the frequency of brain metastases, prospective trials in this patient population are limited, and the criteria used to assess response and progression in the CNS are heterogeneous.[3] This heterogeneity largely stems from the recognition that existing criteria sets, such as RECIST,[4,5] WHO,[6] or Macdonald Criteria,[7] are themselves distinct and have gaps and limitations in their ability to address issues specific to the assessment of patients with brain metastases (table 1).[5] Key issues in the imaging of CNS metastases include the modality and frequency of assessment, the method of measurement (linear, bidimensional, volumetric), the magnitude of change that defines response or progression, differentiation between tumour-related and treatment-related changes, the inclusion (or exclusion) of corticosteroid use and clinical signs and symptoms with imaging definitions of progression and response, and the inclusion (or exclusion) of systemic disease status into the definition of CNS response and progression.

Scope and purpose of the proposed RANO-BM criteria

Prospective clinical trials to assess new treatments for patients with active brain metastases are becoming increasingly common. Additionally, we welcome the trend away from automatic exclusion of patients with brain metastases from clinical trials of novel therapies. The concurrent proliferation of response criteria for assessment of CNS metastases has made interpretation of trial results challenging. The Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group first convened in 2011 to review the medical literature and propose new standard criteria for the radiological assessment of brain metastases in clinical trials. As reported in a previous review,[5] the group acknowledges that objective response or progression-free survival, or both, might not always be the most relevant primary study endpoints, depending on the patient population, the treatment being assessed, and question being asked and that neuro-cognition and quality-of-life might be of greater importance in some settings. However, if an investigator chooses to include objective response or progression as key endpoints, we believe the trial community would be best served if the endpoints are assessed and defined more uniformly than they are at present. The criteria we propose are relevant for the assessment of parenchymal brain metastases only and do not cover leptomeningeal metastases, which are generally not radiographically measurable in a reliable and reproducible manner. Response criteria for leptomeningeal metastases will be assessed by a different RANO group. The proposed criteria for brain metastases also do not cover dural metastases or skull metastases invading the brain.

Process of RANO-BM criteria development

The RANO-BM is an international group of experts in medical oncology, neuro-oncology, radiation oncology, neurosurgery, neuroradiology, neuropsychology, biostatistics, and drug development who, in collaboration with government and industry partners, are working towards the development of more streamlined and broadly acceptable criteria for assessment of brain metastases. After completion of a literature review and critique, the group convened a series of meetings and regular teleconferences to formulate the following proposal for

[redacted]

	Imaging modality	Target lesion	Maximum number of CNS target lesions	Measurement technique	Shrinkage required for partial response	Confirmatory scans	Steroids	Neurological symptoms	Extracranial disease
RECIST 1.0[3]	CT or MRI	Longest diameter ≥10 mm	Five	Unidimensional	≥30%	Required in non-randomised trials where response in the primary endpoint	Not included	Not included	Included
RECIST 1.1[4]	CT or MRI	Longest diameter ≥10 mm	Two	Unidimensional	≥30%	Required in non-randomised trials where response in the primary endpoint	Not included	Not included	Included
Macdonald[7]	CT or MRI	Minimum size not specified	Not specified	Bidimensional	≥50%	Required at least 1 month apart	Stable or decreased	Stable to improved	Not applicable
WHO[6]	Not specified	Minimum size not specified	All lesions	Bidimensional	≥50%	Required at least 4 weeks apart	Not included	Not included	Included
RANO (high-grade glioma)[8]	CT or MRI	Contrast-enhancing lesions with two perpendicular diameters ≥10 mm	At least two lesions, and up to five lesions in patients with multiple lesions*	Bidimensional	≥50%	Required at least 4 weeks apart	Stable or decreased compared with time of baseline scan	Stable to improved clinically	Not applicable

*For patients with multiple lesions, of which only one or two are increasing in size, the enlarging lesions should be considered the target lesions and other lesions will be considered non-target lesions.

Table 1: Comparison of standard response criteria

Medical Campus, University of Colorado Denver, Aurora, CO, USA (Prof L E Gaspar MD); MGH 3D Imaging Lab, Massachusetts General Hospital, Boston, MA, USA (Prof G J Harris PhD); Department of Neurosurgery, Henry Ford Health System, Detroit, MI, USA (S N Kalkanis MD); Department of Neurological Surgery, University of California, San Francisco, CA, USA (Prof M E Linskey MD); UC Irvine Medical Center, Orange, CA, USA (Prof M E Linskey); Department of Oncology, London Regional Cancer Program, London Health Sciences Centre, University of Western Ontario, London, ON, Canada (D R Macdonald MD); Division of Oncology, Stanford University, Stanford, CA, USA (Prof K Margolin MD); Maryland Proton Treatment Center, University of Maryland School of Medicine, Baltimore, MA, USA (Prof M P Mehta MD); Division of Neuro-Oncology, University of Virginia, Charlottesville, VA, USA (Prof D Schiff MD); Department of Neurology/Neuro-Oncology, University of Turin, Turin, Italy (Prof R Soffietti MD); Department of Radiation Oncology/T28 (Prof J H Suh MD) and Department of Neurosurgery/ND40 (Prof M A Vogelbaum MD), Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH,

response criteria in brain metastases from solid tumours. We selected RECIST 1.1[4] and the RANO response assessment criteria for high-grade gliomas (HGG)[8] as the starting point. We identified gaps in the existing RECIST and RANO-HGG criteria applicable to patients with solid tumour brain metastasis and, when possible, resolved areas of controversy with an evidence-based approach and through expert opinion and consensus. We have presented our proposed criteria to the US Food and Drug Administration (FDA) and the RECIST group for feedback. We fully recognise that this is a work in progress and that the criteria are subject to revision on the basis of new data.

Proposed RANO-BM criteria

Similar to RECIST 1.1, definitions for radiographical response will be based on unidimensional measurements.

Definitions

Measurable disease is defined as a contrast-enhancing lesion that can be accurately measured in at least one dimension, with a minimum size of 10 mm, and is visible on two or more axial slices that are preferably 5 mm or less apart with 0 mm skip (and ideally ≤1·5 mm apart with 0 mm skip). Additionally, although the longest diameter in the plane of measurement is to be recorded, the diameter perpendicular to the longest diameter in the plane of measurement should be at least 5 mm for the lesion to be considered measurable. If the MRI is performed with thicker slices, the size of the measurable lesion at baseline should be at least double the slice thickness. Interslice gaps, if present, should also be considered in the determination of the minimum size of measurable lesions at baseline. Measurement of a tumour around a cyst or surgical cavity is a particularly difficult challenge. Generally, such lesions should be considered non-measurable unless there is a nodular component that measures 10 mm or more in longest diameter and 5 mm or more in the perpendicular plane. The cystic or surgical cavity should not be measured for the determination of a response (figure 1).

Non-measurable disease includes all other lesions, including lesions with longest dimension less than 10 mm, lesions with borders that cannot be reproducibly measured, dural metastases, bony skull metastases, cystic-only lesions, and leptomeningeal disease.

We recognise that many patients with brain metastases present with small sub-centimetre lesions and that some centres routinely perform MRI imaging with 3 mm slice thickness or less. We have discussed whether the lower size limit of a measurable lesion could be reduced to 5 mm or even less. However, in view of concerns about reproducibility and interpretation of changes in small lesions, the overall consensus was to maintain consistency with RECIST 1.1. Patients with non-measurable disease can still be included in trials where response is not the primary endpoint (eg, in trials with progression-free survival, overall survival, or other primary endpoints). For studies in which CNS objective response is the primary endpoint, we generally recommend a cutoff of 10 mm to limit the study to measurable disease.

For investigators who choose to lower the minimum size limit of measurable disease to 5 mm, we strongly recommend MRI imaging with 1·5 mm slice thickness or less. Complete response and unequivocal progressive disease can probably be interpreted even with lesions as small as 5 mm. However, measurement of small changes, such as the minimum 20% increase in longest diameter to determine progressive disease or the minimum 30% decrease in longest diameter to determine partial response, might not be robust or reproducible. With the intrinsic uncertainty of measurements of small lesions, any lesion less than 10 mm in longest diameter should be

[redacted]

regarded as unchanged from baseline unless there is a minimum 3 mm change in the measured longest diameter.

The decision to include patients with multiple lesions with a sum diameter of 10 mm or more but of which the largest lesion measures less than 10 mm should be taken with caution if objective response is the primary endpoint. If such patients are included, response should be assessed using the sum of the longest diameters of the lesions, and the response criteria should be clearly delineated in the protocol. Thin-section MRI imaging with 1·5 mm or thinner slice thickness would be necessary in this setting (appendix).

Methods of measurement

The same method of assessment and the same technique should be used to characterise each identified and reported lesion at baseline and during follow-up. Consistent use of imaging techniques across all imaging timepoints is important to ensure that the assessment of interval appearance, disappearance of lesions, or change in size is not affected by scan parameters such as slice thickness. Use of thin section imaging (appendix) is particularly important for the assessment of lesions less than 10 mm in longest diameter or small changes in lesion size, or both.

Gadolinium-enhanced MRI is the most sensitive and reproducible method available to measure CNS lesions selected for response assessment.[10,11] Suggested brain MRI specifications are detailed in the appendix. MRI is strongly encouraged as the default standard imaging technique, although CT with and without contrast could be considered in specific circumstances (eg, countries with limited medical resources or contraindication for MRI).

Tumour-response assessment

Only patients with measurable CNS disease at baseline should be included in protocols where objective CNS tumour response is the primary endpoint. For studies in which objective response is not the primary endpoint, the protocol must specify prospectively whether entry is restricted to those with measurable disease or if patients with non-measurable disease are also eligible. Assignment of CNS response is independent of systemic disease response. CNS lesions are to be assessed according to RANO-BM criteria, whereas non-CNS lesions would most typically be assessed according to RECIST 1.1 criteria. Generally, CNS lesions should initially be re-assessed by MRI at protocol-specified intervals 6–12 weeks apart, although there might be specific circumstances in which longer (or shorter) intervals are desirable. For patients who remain stable for extended periods of time, a longer interval between scans might be appropriate.

All baseline assessments should be done as close as possible to the treatment start and no more than 4 weeks before the beginning of treatment. For previously treated lesions, we recommend documentation of how each lesion was previously treated (eg, stereotactic radiosurgery, whole brain radiotherapy, surgical resection). When more than one measurable lesion in the CNS is present at baseline, all lesions up to a maximum of five CNS lesions should be identified as target lesions and will be recorded and measured at baseline. All measurements should be recorded in metric notation. Target lesions should be selected on the basis of their size (longest diameter) and as those that can be measured reproducibly. For patients with recurrent disease who have multiple lesions, of which only one or two are increasing in size, the enlarging lesions should be prioritised as target lesions for the response assessment. Lesions with prior local treatment (ie, stereotactic radiosurgery or surgical resection) can be considered measurable if progression has occurred since the time of local treatment. However, careful consideration should be given to lesions previously treated with stereotactic radiosurgery, in view of the possibility of treatment effect, which we discuss below. Whether such lesions can be considered measurable should be specified prospectively in the clinical protocol. 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. All other CNS lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be classified as present, absent, or unequivocal progression, and followed up.

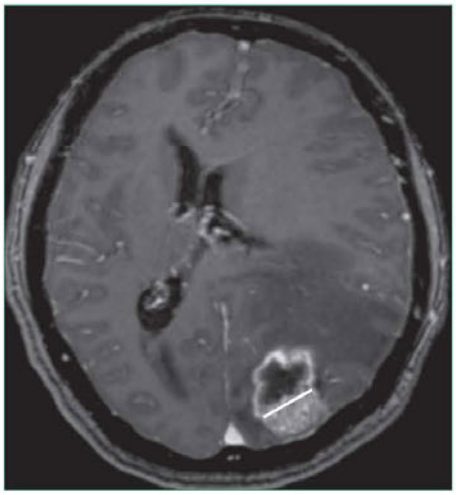


Figure 1: **Axial contrast-enhanced T1-weighted MRI of a brain metastasis from breast carcinoma with a partial solid and cystic component**
Only the solid component is used for measurement of the longest diameter.

USA; and Neuro-Oncology Unit, Daniel den Hoed Cancer Center, Erasmus University Medical Center, Rotterdam, Netherlands
(Prof M J van den Bent MD)
Correspondence to:
Dr Nancy U Lin, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA 02215, USA
nlin@partners.org

See Online for appendix

Review

Panel 1: Response assessment of target and non-target lesions

Target lesions

Complete response
Disappearance of all CNS target lesions sustained for at least 4 weeks; with no new lesions, no use of corticosteroids, and patient is stable or improved clinically.

Partial response
At least a 30% decrease in the sum longest diameter of CNS target lesions, taking as reference the baseline sum longest diameter sustained for at least 4 weeks; no new lesions; stable to decreased corticosteroid dose; stable or improved clinically.

Progressive disease
At least a 20% increase in the sum longest diameter of CNS 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%, at least one lesion must increase by an absolute value of 5 mm or more to be considered progression.

Stable disease
Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter while on study.

Non-target lesions
Non-target lesions should be assessed qualitatively at each of the timepoints specified in the protocol.

Complete response
Requires all of the following: disappearance of all enhancing CNS non-target lesions, no new CNS lesions.

Non-complete response or non-progressive disease
Persistence of one or more non-target CNS lesion or lesions.

Progressive disease
Any of the following: unequivocal progression of existing enhancing non-target CNS lesions, new lesion(s) (except while on immunotherapy-based treatment), or unequivocal progression of existing tumour-related non-enhancing (T2/FLAIR) CNS lesions. In the case of immunotherapy-based treatment, new lesions alone may not constitute progressive disease.

Definition of best overall CNS response

Best overall CNS response is a composite of radiographical CNS target and non-target lesion responses (panel 1), corticosteroid use, and clinical status. For non-randomised trials in which CNS response is the primary endpoint, confirmation of partial response or complete response at least 4 weeks later is necessary to deem either one the best overall response.

At each protocol-specified timepoint, a response assessment should occur and CNS assessments should be coincident with extra-CNS assessment. Table 2 shows the additional corticosteroid and clinical status requirements to deem a partial response or complete response.

Assessment of target and non-target CNS lesions

While on study, all CNS target lesions should have their actual measurement recorded, even if very small (eg, 2 mm). If the lesion disappears, the value should be recorded as 0 mm. However, if the lesion is sufficiently small (but still present) to be assigned an exact measure, a default value of 5 mm should be recorded on the case report form.

Lesions might coalesce during treatment. As lesions coalesce, a plane between them may be maintained that would aid in obtaining maximum longest diameter of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

New lesions can appear during treatment. The finding of a new CNS lesion should be unequivocal and not due to technical or slice variation. A new lesion is one that was not present on prior scans. If the MRI is obtained with slice thickness of 1·5 mm or less, the new lesion should also be visible in axial, coronal, and sagittal reconstructions of 1·5 mm or thinner projections. If a new lesion is equivocal, for example because of its small size (ie, ≤5 mm), continued therapy can be considered, and a follow-up assessment will clarify if it really is new disease. If repeated scans confirm a new lesion, progression should be declared using the date of the initial scan showing the new lesion. In the case of immunotherapy, however, new lesions alone cannot constitute progressive disease.

Unequivocal progression of non-target lesions can merit discontinuation of therapy. When a patient also has measurable disease, to be deemed as having unequivocal progression on the basis of non-target disease alone there must also be an overall substantial worsening in non-target disease such that, even in the presence of stable disease or partial response in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. When the patient has only non-measurable disease, there must be an overall level of substantial worsening to merit discontinuation of therapy.

The RANO-BM group acknowledges the case of patients who have been treated with stereotactic radiosurgery[12] or immunotherapy-based approaches, for whom there has been radiographical evidence of enlargement of target and non-target lesions, which do not necessarily represent tumour progression. If radiographical evidence of progression exists, but clinical evidence indicates that the radiological changes are due to treatment effect (and not to progression of cancer), additional evidence is needed to distinguish between true progression and treatment effect, in which case standard MRI alone is insufficient. The methods used to distinguish between true progression and treatment effect should be specified prospectively in the clinical protocol. Patients can be continued on protocol therapy pending further investigation with one or more of the following options.

The scan can be repeated at the next protocol-scheduled assessment or sooner, and generally within about 6 weeks. An investigator can choose a shorter time interval if progressive symptoms or other clinical concerns arise. Continued tumour growth might be consistent with

[redacted]

	Complete response	Partial response	Stable disease	Progressive disease
Target lesions	None	≥30% decrease in sum longest distance relative to baseline	<30% decrease relative to baseline but <20% increase in sum longest distance relative to nadir	≥20% increase in sum longest distance relative to nadir*
Non-target lesions	None	Stable or improved	Stable or improved	Unequivocal progressive disease*
New lesion(s)†	None	None	None	Present*
Corticosteroids	None	Stable or decreased	Stable or decreased	Not applicable‡
Clinical status	Stable or improved	Stable or improved	Stable or improved	Worse*
Requirement for response	All	All	All	Any‡

*Progression occurs when this criterion is met. †A new lesion is one that not present on prior scans and is visible in minimum two projections. If a new lesion is equivocal, for example because of its small size, continued therapy can be considered, and follow-up assessment will clarify if the new lesion is new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan showing the new lesion. For immunotherapy-based approaches, new lesions alone to do not define progression. ‡Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

Table 2: **Summary of the response criteria for CNS metastases proposed by RANO-BM**

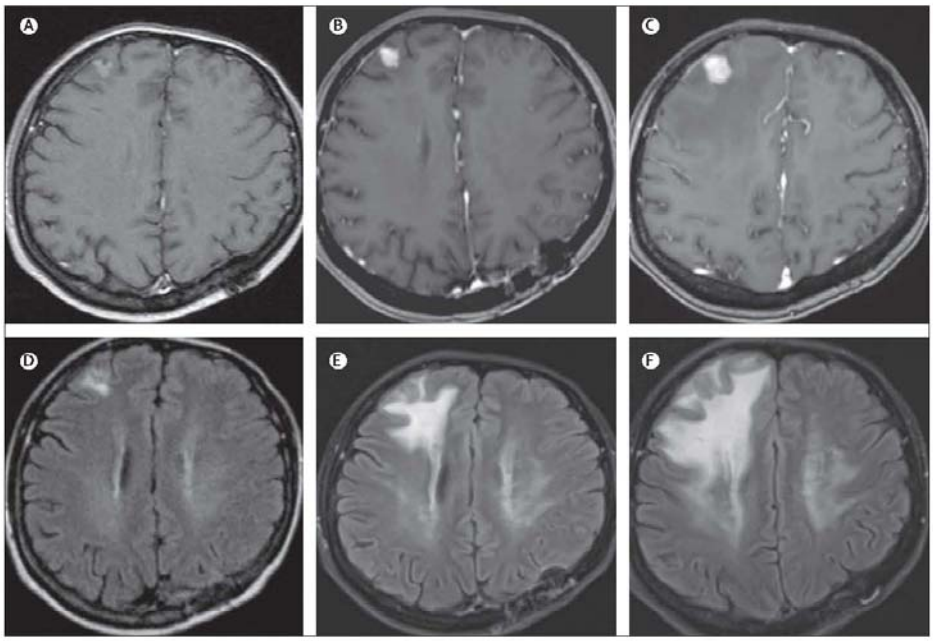


Figure 2: **True progression of brain metastasis**
Axial contrast-enhanced T1-w (A–C) and FLAIR images (D–F) of melanoma metastases before (A, D), during therapy with ipilimumab (B, E), and 3 months later (C, F). Note the constant increase in the extent of the contrast enhancing lesion and perifocal oedema.

radiographical progression, in which case the patient should leave the study (figure 2). Stabilisation and shrinkage of a lesion can be consistent with treatment effect, in which case the patient can stay in the study (figure 3). For patients with equivocal results even on the next restaging scan, the scan can be repeated again at a subsequent protocol-scheduled assessment or sooner, although surgery or use of an advanced imaging modality (in the case of stereotactic radiosurgery), or both, are strongly encouraged. Surgical pathology can be obtained via biopsy or resection.

For lesions treated by stereotactic radiosurgery, additional evidence of tumour progression or treatment effect (radionecrosis) can be acquired with an advanced imaging modality, such as perfusion MRI, magnetic resonance spectroscopy, or ^{18}FLT or ^{18}FDG PET.[13] On the basis of a literature review and extensive discussions, we found the literature insufficiently robust to conclude

[redacted]

that any one modality or approach can be recommended across all patients to distinguish between radiation necrosis and true progression. Instead, we recommend clinical judgment and involvement of a multidisciplinary team. We recognise this recommendation is less than satisfactory and agree that more sensitive and specific methods to distinguish between treatment effect and tumour progression are needed. Note that these advanced imaging modalities have not been extensively studied with regards to immunotherapy-based approaches and therefore cannot be recommended to distinguish between tumour progression and immune-related changes at present. Irrespective of the additional testing obtained, if subsequent testing shows that progression has occurred, the date of progression should be recorded as the date of the scan this issue was first raised. Patients can also have an equivocal finding on a scan (eg, a small lesion that is not clearly new). Continued treatment is permissible until the next protocol-scheduled assessment. If the subsequent assessment shows that progression has indeed occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected.

In patients receiving immunotherapy-based treatment, an initial increase in the number and size of metastases can be followed by radiographical stabilisation or regression.[34] This pattern might be related to the mechanism of action of immunotherapy, including immune infiltrates, and the time to mount an effective immune response. Thus, progressive disease should not be solely defined by the appearance of new lesions but rather as a minimum 20% increase in the sum longest diameter of CNS target and new lesions, as unequivocal progression of existing enhancing non-target CNS lesions, as unequivocal progression of existing non-enhancing (T2/FLAIR) CNS lesions, or as clinical decline related to the tumour. If immune response-related radiographical changes are suspected, we advise to not change treatment until a short interval scan is obtained. If the subsequent assessment confirms that progression has indeed

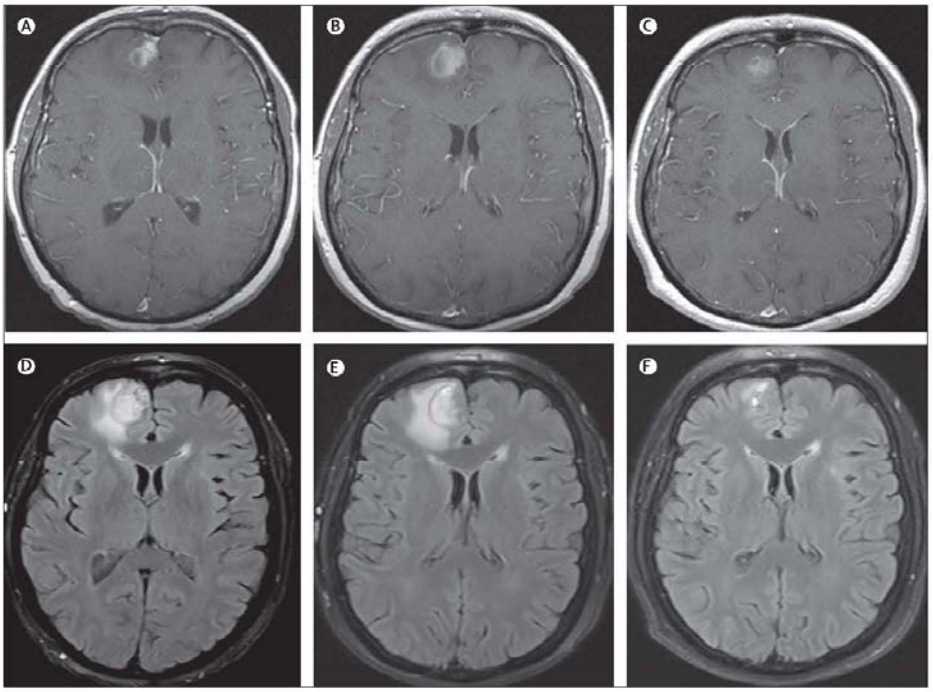


Figure 3: **Pseudoprogression of brain metastasis**
Axial contrast-enhanced T1-w (A–C) and FLAIR images (D–F) of melanoma metastases before (A, D), on ipilimumab (B, E), and 6 weeks after end of immunotherapy (C, F). Note the right frontal metastases with contrast enhancement and perifocal oedema (A, C), which increase under therapy (B, E) and resolve without change of therapy (C, F).

[redacted]

CNS (RANO-BM)	Non-CNS (RECIST 1.1)	Response
Complete response, partial response, or stable disease	Complete response, partial response, or stable disease	Log as CNS and non-CNS complete response, partial response, or stable diseases
Complete response, partial response, or stable disease	Progressive disease	Log as CNS complete response, partial response, or stable disease; log as non-CNS progressive disease
Progressive disease	Complete response, partial response, or stable disease	Log as CNS progressive disease; log as non-CNS complete response, partial response, or stable disease
Progressive disease	Progressive disease	Log as both CNS and non-CNS progressive disease

Table 3: CNS and non-CNS response assessment

CNS (RANO-BM)	Non-CNS (RECIST 1-1)	Bi-compartmental PFS	Note
Complete response, partial response, or stable disease	Progressive disease	Log as a progression-free survival event	Log as non-CNS progressive disease
Progressive disease	Complete response, partial response, or stable disease	Log as a progression-free survival event	Log as CNS progressive disease
Progressive disease	Progressive disease	Log as a progression-free survival event	Log as both CNS and non-CNS progressive disease

Table 4: Bi-compartmental progression-free survival

occurred, the date of progression should be recorded as the date of the initial scan where progression was suspected.

Corticosteroid use and clinical deterioration

In the absence of clinical deterioration related to the tumour, an increase in corticosteroid dose alone should not be used as a sole determinant of progression. Patients with stable imaging results and whose corticosteroid dose has increased for reasons other than clinical deterioration related to the tumour do not qualify as having stable disease or progression. These patients should be observed closely, and if their corticosteroid dose can be reduced back to baseline, they will be considered as having stable disease, but if further clinical deterioration related to the tumour becomes apparent, they will be considered as having progression.

The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that patients who have a decrease in score on the Karnofsky performances scale from 100 or 90 to 70 points or less, a decrease of minimum 20 points from 80 or less, or a decrease from any baseline to 50 points or less, for at least 7 days, be considered as having neurological deterioration, unless this functional impairment is attributable to comorbid events, treatment-related toxicity, or changes in corticosteroid dose.

Volumetric criteria

Research of the value of volumetric versus unidimensional measurements for the assessment of CNS lesion response is ongoing.[15–18] Volumetric measurement was the topic of much discussion and debate within the RANO-BM group. The RANO-BM group judges that the existing data are not yet strong enough to justify the universal requirement of volumetric response criteria in clinical trials of patients with brain metastases. Volumetric analyses in real-time adds cost and complexity and is not available at all centres. Yet, RANO-BM also believes that the assessment and reporting of volumetric response in clinical trials (in addition to the unidimensional RANO-BM criteria) will add to the knowledge base, either justify or negate the need for volumetric measurements in future trials, and encourage its inclusion as a secondary endpoint when feasible.

The appropriate cutoff to define a partial response on the basis of volumetric measurements was another topic of debate. If a tumour forms a perfect sphere, a 30% unidimensional reduction corresponds to about a 65% volumetric reduction, and there are data showing concordance of response assessments with these cut-offs in patients with brain metastasis.[17] Also, volumetric changes of minimum 20% appear to be reproducible between readers,[19,20] and results of one study[21] showed that 20% or greater volumetric reduction was associated with improvements in neurological signs and symptoms.

The RANO-BM group believes that use of the same criteria and cutoffs across trials will allow trial results to be interpreted in their proper context. Thus, for investigators who choose to report volumetric response data, we propose the following. First, partial volumetric response should be defined as a 65% or greater decrease in the sum volume of CNS target lesions, in addition to the corticosteroid and clinical status criteria as outlined previously. Second, volumetric response should be reported as a waterfall plot to provide a global sense of potential efficacy. Third, in the absence of high quality data across multiple studies to show a clear correlation between lower volumetric thresholds and some measure of patient benefit, such as quality of life, neuro-cognitive function, or overall survival, it is premature to formally define a category of minor response or to lower the threshold at which to consider a volumetric response. However, we encourage digital archiving of trial images and accompanying linked clinical outcome data to allow

Review

for studies to be pooled to determine whether different cutpoints could be justified in the future.

Treatment of non-CNS (extracranial) disease

Preclinical and clinical data sometimes show a differential response in intracranial versus extracranial locations, which could be related to inadequate drug penetration, differences in tumour microenvironment, or tumour heterogeneity between organ sites, among other possibilities. Many systemic agents are not expected to have CNS activity, primarily because of poor drug penetration. Local CNS therapies, such as whole-brain radiotherapy, stereotactic radiosurgery, or surgery, are not expected to affect extracranial sites at all.

Traditionally, RECIST has used a summation of representative target lesions across all organ sites. Historically, patients with brain metastases have been excluded from systemic therapy trials. Even when included, patients with brain metastases often had to have stable, treated CNS lesions on study entry, and CNS lesions were rarely chosen as target lesions. The Macdonald and RANO-HGG criteria do not provide guidance about the treatment of extracranial disease, since extracranial disease is not relevant in most patients with primary brain tumours. The consequences have been an absence of flexibility to continue protocol therapy in the setting of discordant CNS versus non-CNS response or progression, a disincentive to image the brain as part of clinical trials, and the use of different definitions of response and progression endpoints in local therapy trials and systemic therapy trials.

We propose that CNS and non-CNS should be assessed as separate compartments (table 3). As such, CNS response will be scored irrespectively of extracranial response and vice versa. For progression, CNS and non-CNS will be scored according to RANO-BM and RECIST 1.1 criteria, respectively (table 4). If progression occurs in either or both compartments, the criteria for bi-compartmental progression-free survival will have been met. Protocols can also prospectively specify CNS progression-free survival and non-CNS progression-free survival as endpoints. Protocols should specify the plan for patients who progress in one compartment only. For example, a patient who develops isolated CNS progression in a systemic therapy trial can be given the option to have their CNS disease treated with whole-brain radiotherapy, stereotactic radiosurgery, or surgery and remain on protocol therapy until the time of non-CNS disease progression, unacceptable toxicity, or death. The date of non-CNS progressive disease should be recorded when it occurs.

Additional endpoints for localised therapy trials

Patients with brain metastases frequently undergo focal treatments such as surgical resection and stereotactic radiosurgery. With these modalities, the technical success of the treatment is appropriately measured by assessment of the site of localised therapy and not distant sites. For example, outcomes after stereotactic radiosurgery are commonly reported as local control (ie, control of the treated lesion) and distant brain failure (ie, the appearance of new or progressive lesions outside the treated field). This situation is analogous to breast cancer, in which trials of locoregional therapy will commonly report endpoints such as ipsilateral invasive breast cancer recurrence or regional invasive breast cancer recurrence.[22] Panel 2 outlines the RANO-BM-proposed definitions of bicompartmental progression-free survival, CNS progression-free survival, non-CNS progression-free survival, and local CNS progression-free survival, which account for the variety of trial endpoints that might be chosen depending on the clinical situation, treatment modality, and overall study goal.

Conclusion

We recognise that our proposal adds complexity to the assessment of patients with brain metastases enrolled in clinical trials. However, limitations of the existing response criteria have led to frequent, but inconsistent, modifications by investigators. Additionally, because brain metastases can be treated using multiple modalities, which might or might not have effects outside of the treated field or outside the brain, endpoints in trials have also been defined differently according to the modality. Whereas the choice of primary and secondary endpoints will naturally vary according to the treatment modality, overall study goal, and study type (eg, proof of concept, technical validation, phase 3 registration study), we believe the definition of the endpoints should ideally remain constant. Frequently asked questions are listed and answered in the appendix.

Panel 2: **Sites of inclusion for assessment of bi-compartmental progression-free survival, CNS progression-free survival, non-CNS progression-free survival, and CNS_{local} progression-free survival**

Bi-compartmental progression-free survival
Include local CNS lesions, distant CNS lesions, and non-CNS lesions

CNS progression-free survival
Include local CNS lesions and distant CNS lesions

Non-CNS progression-free survival
Include non-CNS lesions only

CNS_{local} progression-free survival
Include local CNS lesions only

Search strategy and selection criteria

We searched Medline, PubMed, and the references of relevant articles using the following search terms: "brain metastases", "breast cancer", "lung cancer", "melanoma", "whole brain radiotherapy", "stereotactic radiosurgery", and "radiation necrosis". Additional cross-referenced search terms were added for specific topics such as "volumetric", "perfusion MRI", "positron emission tomography", and "immunotherapy". We included only articles published in English between Jan 1, 1980, and Oct 1, 2014.

[redacted]

Future plans include collaborations with RECIST investigators to analyse historical datasets and to solicit feedback from other investigators to refine the proposed criteria in future iterations. However, we should note that any retrospective analysis of historical datasets will be limited by the quality and nature of the recorded data. For example, because very few studies simultaneously collect unidimensional, bidimensional, and volumetric measurements, retrospective studies of large datasets are unlikely to provide answers to all of the questions raised above unless there is a large-scale effort to collect archival images and conduct central radiology review. In addition, because information for corticosteroid use, functional status, neurological symptoms, neuro-cognitive functioning, and quality of life were also variably collected and assessed, associations between response and functional outcomes will be challenging to validate. We would encourage investigators interested in the specialty of brain metastasis to strategise together on how best to gather the necessary common data elements across trials to allow such analyses in the future.

Contributors

All authors contributed to the literature search and writing of the report. MB prepared the figures.

Declaration of interests

DPB has a leadership position in ECOG-ACRIN and declares non-financial support from GE Medical Systems, outside the submitted work. BGB declares personal fees and non-financial support from Roche Pharma AG, academic institutions, and Bayer Pharma AG, outside the submitted work. MB declares grants and personal fees from Guerbet, Codman, Bayer, personal fees from Novartis and Vascular Dynamics, grants from Siemens, personal fees from Roche, outside the submitted work. FSH declares grants and non-financial support from Bristol-Myers Squibb, personal fees from Merck, non-financial support from Genentech, personal fees and non-financial support from Novartis, outside the submitted work; in addition, FSH has a patent immune therapy target pending. NUL declares grants from Breast Cancer Research Foundation, during the conduct of the study, grants to support clinical trials from Array Biopharma, Genentech, GlaxoSmithKline, Novartis, and Kadmon. DRM declares personal fees from Roche Canada and personal fees and non-financial support from Merck Canada, outside the submitted work. MPM declares consulting relationships with AbbVie, BMS, Celldex, Electa, Genentech, Merck, Novelos, Novocure, and Philips and has served on the Board of Directors of Pharmacyclis with stock options, unrelated to the submitted work. MJvdB declares grants and personal fees from Roche and AbbVie, personal fees from Amgen, MSD, Actelion, and Merck, outside the submitted work. MAV declares personal fees and non-financial support from Merck, personal fees from Neuralstem and Pharmacokinesis, personal fees and other from Infuseon Therapeutics, and grants and non-financial support from National Cancer Institute, outside the submitted work. PYW declares research support from AbbVie, Agios, Anigochem, AstraZeneca, Exelixis, Genentech/Roche, GlaxoSmith Kline, Karyopham, Merck, Novartis, Sanofi-Aventis, Vascular Biogenics, Celldex, SigmaTau, Midatech, Momenta, outside the submitted work. HA, IJB, PDB, DRC, SMC, JD, EGEdV, LEG, GJH, SNK, EQL, MEL, KM, DS, RS, and JHS declare no competing interests.

Acknowledgments

We thank Patricia Cortazar, Suzanne Demko, Ruthann Giusti, Patricia Keegan, and Richard Pazdur from the US Food and Drug Administration for their feedback regarding these proposed radiographic criteria. This work was supported in part by the Breast Cancer Research Foundation (grant to NUL), but this support did not directly influence the writing of this manuscript or the decision to submit it for publication.

References

1 Davis FG, Dolecek TA, McCarthy BJ, Villano JL. Toward determining the lifetime occurrence of metastatic brain tumors estimated from 2007 United States cancer incidence data. *Neuro Oncol* 2012; **14:** 1171–77.

2 American Cancer Society. Cancer Facts & Figures. Atlanta, GA: American Cancer Society; 2007.

3 Lin NU, Lee EQ, Aoyama H, et al. Challenges relating to solid tumour brain metastases in clinical trials, part 1: patient population, response, and progression. A report from the RANO group. *Lancet Oncol* 2013; **14:** e396–406.

4 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45:** 228–47.

5 Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92:** 205–16.

6 Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981; **47:** 207–14.

7 Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol* 1990; **8:** 1277–80.

8 Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol* 2010; **28:** 1963–72.

9 Lin NU, Wefel JS, Lee EQ, et al. Challenges relating to solid tumour brain metastases in clinical trials, part 2: neurocognitive, neurological, and quality-of-life outcomes. A report from the RANO group. *Lancet Oncol* 2013; **14:** e407–16.

10 Schellinger PD, Meinck HM, Thron A. Diagnostic accuracy of MRI compared to CCT in patients with brain metastases. *J Neurooncol* 1999; **44:** 275–81.

11 Sze G, Milano E, Johnson C, Heier L. Detection of brain metastases: comparison of contrast-enhanced MR with unenhanced MR and enhanced CT. *AJNR Am J Neuroradiol* 1990; **11:** 785–91.

12 Patel TR, McHugh BJ, Bi WL, Minja FJ, Knisely JP, Chiang VL. A comprehensive review of MR imaging changes following radiosurgery to 500 brain metastases. *AJNR Am J Neuroradiol* 2011; **32:** 1885–92.

13 Shah R, Vattoth S, Jacob R, et al. Radiation necrosis in the brain: imaging features and differentiation from tumor recurrence. *Radiographic* 2012; **32:** 1343–59.

14 Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res* 2009; **15:** 7412–20.

15 Bauknecht HC, Romano VC, Rogalla P, et al. Intra- and interobserver variability of linear and volumetric measurements of brain metastases using contrast-enhanced magnetic resonance imaging. *Invest Radiol* 2010; **45:** 49–56.

16 Harris GJ, Plotkin SR, Maccollin M, et al. Three-dimensional volumetrics for tracking vestibular schwannoma growth in neurofibromatosis type II. *Neurosurgery* 2008; **62:** 1314–20.

17 Sze G, Mehta M, Schultz C, et al. Radiologic response evaluation of brain metastases: uni-dimensional (1D), W.H.O. RECIST vs bi-dimensional (2D) or 3-dimensional (3D) criteria. *Proc Am Soc Clin Oncol* 2001; **20** (suppl): abstr 234.

18 van der Weide H, de Kunder S, Houben R, Bosmans G, Lambin P, Baumert BG. Influence of metastatic volume on local control and survival assessed by 3D volumetric measurements after radiosurgery in patients with brain metastases and planned observation. *Strahlenther Onkol* 2011; **187:** 523–24 (abstr).

19 Yang DY, Sheehan J, Liu YS, et al. Analysis of factors associated with volumetric data errors in gamma knife radiosurgery. *Stereotact Funct Neurosurg* 2009; **87:** 1–7.

20 Pan HC, Cheng FC, Sun MH, Chen CC, Sheehan J. Prediction of volumetric data errors in patients treated with gamma knife radiosurgery. *Stereotact Funct Neurosurg* 2007; **85:** 184–91.

21 Lin NU, Dieras V, Paul D, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. *Clin Cancer Res* 2009; **15:** 1452–59.

22 Hudis CA, Barlow WE, Costantino JP, et al. Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *J Clin Oncol* 2007; **25:** 2127–32.

[redacted]

THE LANCET Oncology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Lin NU, Lee EQ, Aoyama H, et al, for the Response Assessment in Neuro-Oncology (RANO) group. Response assessment criteria for brain metastases: proposal from the RANO group. *Lancet Oncol* 2015; **16**: e270–78.

[redacted]

APPENDIX

Proposed Response Assessment Criteria for Brain Metastases: Response Assessment in Neuro-Oncology (RANO) Working Group

Recommendations for Minimum Requirements for Brain Imaging

MR Scanners: 1.5T and 3T MR scanners only

- Localizer/Scout
- 3D T1w pre-contrast (MPRAGE, 3D IR SFPGR T1w)
  - minimum TE
  - TI, TR and flip angle according to manufacturer specific / field strength specific recommendations for optimum image quality
  - SENSE / SMASH / GRAPPA / ASSET allowed
  - Slice/3D slab orientation: sagittal or transverse
  - FOV: 256 mm x 256 mm
  - Matrix: 256x256
  - Slice thickness: ≤ 1.5 mm
  - Full brain coverage
- DWI
  - single shot EPI sequence
  - minimum TE
  - TR > 3000 ms
  - Spectral fat suppression
  - b: 0 and 1000 s/mm^2 (3 directions)
  - SENSE / SMASH / GRAPPA / ASSET: optional for 1.5 T, obligatory for 3 T.
  - Slice orientation: transverse
  - Slice thickness: 5mm
  - Slice gap: 0
  - Number of slices: Full brain coverage
  - FOV: 240 mm x 240 mm
  - Matrix: 128 x 128 or higher
  - Postprocessing: Calculation of ADC maps (diffusion trace maps)
- 2D FLAIR, transverse
  - Turbo Spin Echo (TSE) / Fast Spin Echo (FSE) sequence
  - TE: 90-140ms
  - TR: 6000-10000 ms
  - TI: 2000-2500 ms (use TI according to optimized protocol for specific inversion pulses and field strength)
  - SENSE / SMASH / GRAPPA / ASSET allowed
  - Slice orientation: transverse

  - Slice thickness: 5mm
  - Slice gap: 0
  - Number of slices: same as sequence 2
  - FOV: 240 mm x 240 mm
  - Matrix: 256 x 256 or higher
  - Slice positioning as in sequence 2
- 3D FLAIR (OPTIONAL)
  - 3D Turbo Spin Echo (TSE) / Fast Spin Echo (FSE) sequence
  - TE: 90-140ms
  - TR: 6000-10000 ms
  - TI: 2000-2500 ms (use TI according to optimized protocol for specific inversion pulses and field strength)
  - SENSE / SMASH / GRAPPA / ASSET / ARC allowed
  - Slice orientation: sagittal or transverse
  - Slice thickness: ⍰ 1.5 mm
  - Number of slices: Full brain coverage
  - FOV: 250 mm x 250 mm
  - Matrix: 224 x 224 or higher
  - Slice positioning as in sequence 1
- Contrast agent injection
  - 0.1 mmol/kg BW of a Gd-based contrast agent
- T2w-TSE
  - Turbo Spin Echo (TSE) / Fast Spin Echo (FSE) sequence
  - TE: 80-120ms
  - TR: ≥ 2500 ms
  - SENSE / SMASH / GRAPPA / ASSET allowed
  - Slice orientation: transverse
  - Slice thickness: 5mm
  - Slice gap: 0
  - Number of slices: same as sequence 2
  - FOV: 240 mm x 240 mm
  - Matrix: 256 x 256 or higher
  - Slice positioning as in sequence 2
- 3D T1w post-contrast (MPRAGE, 3D IR FSPGR T1w)
  - Sequence parameters and slice positioning as in sequence 1

Further sequences can be added to the protocol according to the preferences of the respective center. The order and timing of prescribed sequences after contrast administration should also be respected.

Frequently Asked Questions

How large does a new lesion have to be to count as progression?	Except in the case of immunotherapy-based treatments, a new lesion is defined by any enhancing lesion that was not present on prior imaging (performed with same technique) and that is now visible on axial, coronal, and sagittal reconstructions of ≤ 1.5 mm projections (when MRI is performed with ≤ 1.5 mm slice thickness). If there is any doubt, then treatment may continue until the next scheduled assessment. If the lesion has grown, then this would confirm progression and the date of progression will be backdated to when the lesion first appeared on imaging.
Are RANO criteria for brain metastases accepted by regulatory agencies such as the FDA?	The FDA was consulted during development of RANO-BM. The FDA notes the following: 1. The proposed bi-compartmental PFS assessment criteria could be acceptable in the context of a well designed randomized clinical trial either as an endpoint to support an application for accelerated approval or potentially to regular approval or to support a request for Breakthrough Therapy designation. 2. Use of the proposed bi-compartmental response criteria in a single arm trial is problematic because the natural history of progression using this model has not been established. 3. FDA would recommend that a sponsor proposing to use these response criteria meet with FDA to discuss the proposal and consider submitting the trial for a Special Protocol Assessment (SPA).
What is the definition of progression after SRS?	If there is evidence of radiographic progression but there is clinical evidence supporting the possibility that the radiological changes are due to treatment effect (and not to progression of cancer), additional evidence may be required to distinguish true progression versus treatment effect. The methods that may be used to distinguish between the two entities include: (1) repeating the scan to determine if the lesion has grown, which is suggestive of tumor progression, (2) surgical pathology, (3) an advanced imaging modality such as perfusion demonstrating findings consistent with progression.
Should lesions previously treated with SRS be included as target lesions?	Lesions previously treated with SRS are not ideal target lesions given the possibility of treatment effect. Instead,

[redacted]

	lesions not previously treated with local therapies are preferred as target lesions. However, the RANO-BM working group recognizes that restricting target lesions to those not previously treated with SRS may limit accrual in some cases. Whether a SRS-treated lesion can be considered measurable should be specified prospectively in the clinical protocol.
For systemic therapies, how is response determined for extracranial vs. intracranial locations?	We recommend using RECIST 1.1 for extracranial disease and RANO-BM for intracranial disease. Table 3 provides guidance with regards to an overall bi-compartmental response assessment.
Is leptomeningeal disease measurable?	For RANO-BM, leptomeningeal disease is not measurable. A separate RANO proposal for response assessment of leptomeningeal metastases is being developed.*

* Chamberlain M, Soffietti R, Raizer J, et al. Leptomeningeal metastasis: a Response Assessment in Neuro-Oncology critical review of endpoints and response criteria of published randomized clinical trials. *Neuro Oncol* 2014;**16**(9):1176-85.

[redacted]

[redacted]