

Final Results of NKTR-102, a Topoisomerase I Inhibitor-Polymer Conjugate, in Patients with Pretreated Metastatic Breast Cancer Demonstrating Significant Antitumor Activity

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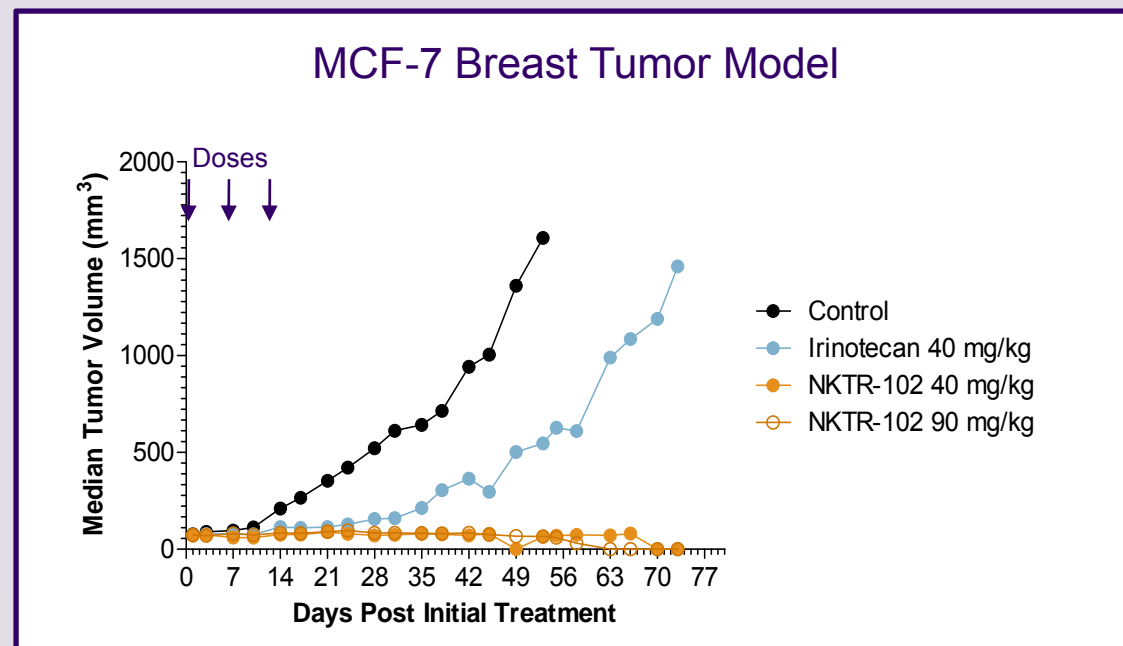
USC Norris Comprehensive Cancer Center, Los Angeles, CA; Institut Jules Bordet, Brussels, Belgium; Nottingham City Hospital, Nottingham, UK; Domaine Universitaire du Sart Tilman, Liege, Belgium; Weston Park Hospital, Sheffield, UK; UZ Antwerpen, Antwerp, Belgium; Stockton Hematology/Oncology, Stockton, CA; Clatterbridge Centre for Oncology, Bebington, UK; Louisville Oncology Research, Louisville, KY; Velindre NHS Trust Cardiff, Cardiff, UK; Gent University Hospital, Gent, Belgium; Mayo Clinic, Rochester, MN; Desert Hematology/Oncology, Rancho Mirage, CA; Nektar Therapeutics, San Francisco, CA; Mayo Clinic, Jacksonville, FL

Presented at the Breast Cancer Symposium

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Background

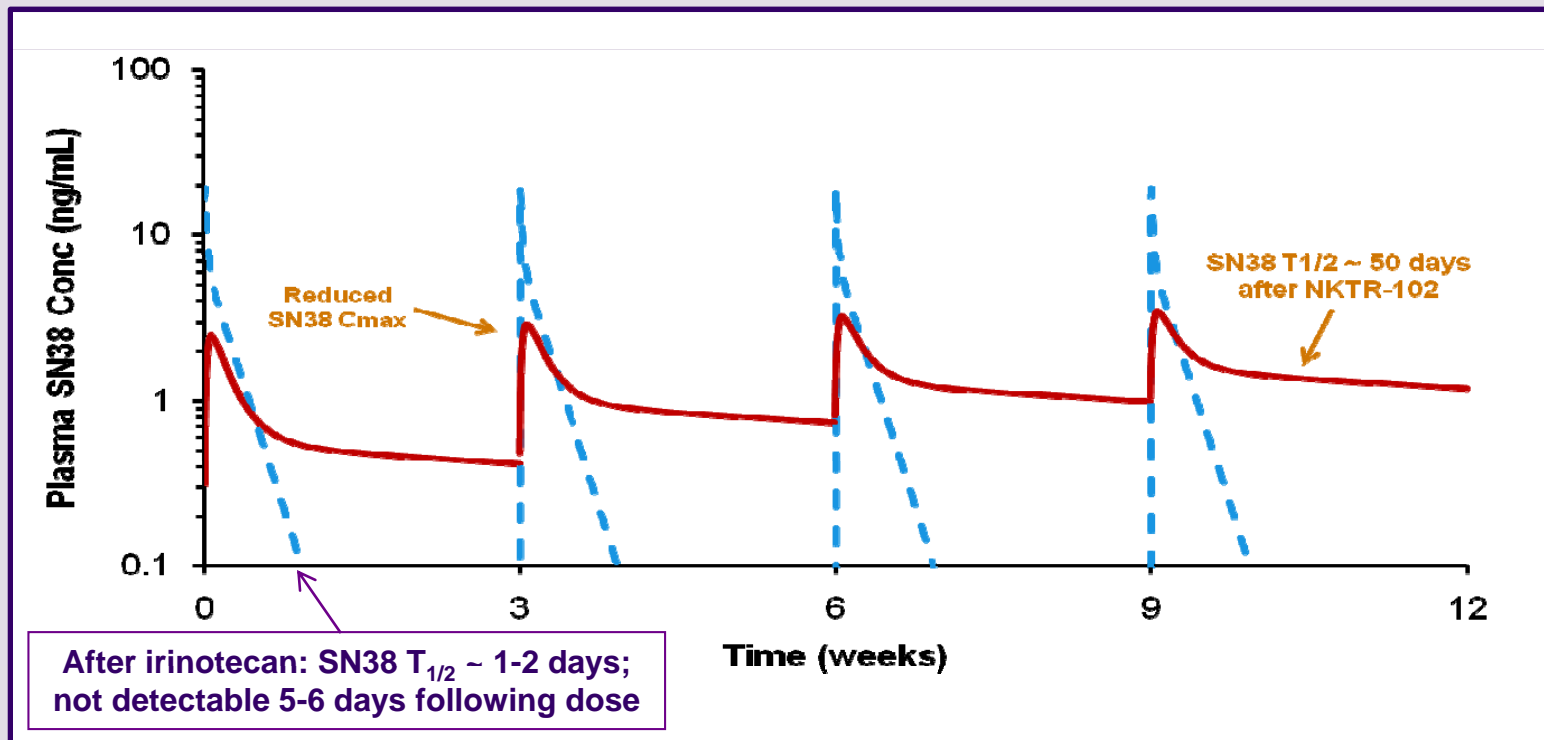
- NKTR-102 is a topoisomerase 1 inhibitor-polymer conjugate with reduced SN38 peak concentrations and a continuous exposure profile
- Topoisomerase 1 inhibition in MBC: Perez JCO 2004: q3w and weekly irinotecan
 - Mixed population: median 1 prior regimen for MBC (adjuvant only 13%, adjuvant + 1 MBC regimen 57%, 2 MBC regimens 33%)
 - ORR 14 and 23% (mPFS 1.9 and 2.8 months; mOS 8.6 and 9.7 months)
- NKTR-102 has superior efficacy (measured both by tumor growth delay and regression rate) compared to irinotecan against a wide range of human xenograft tumors.



Hoch et al; ENA 2007 abstract C10

Polymer Conjugation Improves SN38 PK

- Comparison of SN38 PK upon NKTR-102 or irinotecan administration:
 - Reduced Cmax (infusional-related toxicities are not seen with NKTR-102)
 - Greatly prolonged elimination half-life (50 days compared to 2 days)
- The large NKTR-102 molecule does not freely pass out of intact vasculature, which may account for higher SN38 levels in tumor tissues, where the local vasculature may be relatively more permeable

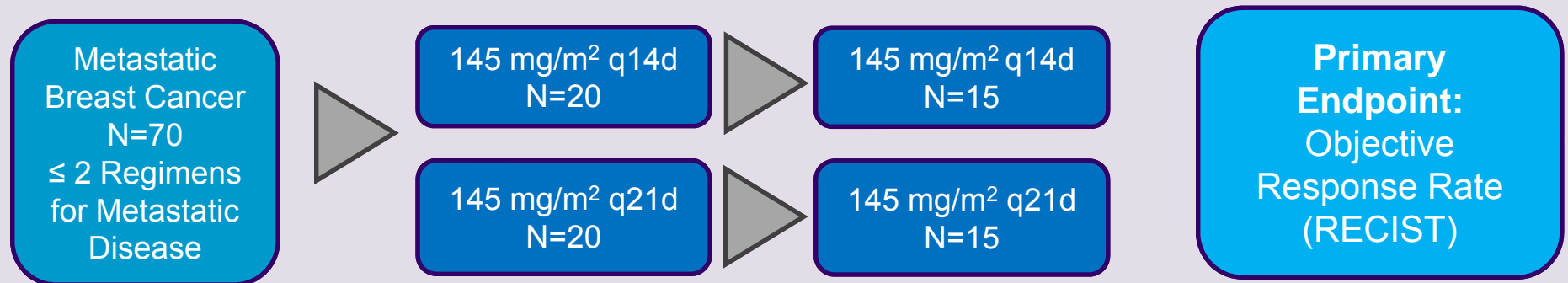


Study Design: Randomized to Two Schedules

Primary Efficacy Objective:

- Determine the objective response rate (ORR) by RECIST v 1.0
- Determine the optimal schedule of NKTR-102 in breast cancer

Secondary Objectives PFS, OS and safety



Statistical Hypotheses: H_0 ORR (RECIST version 1.0) \leq 5% and H_a ORR \geq 20%.
(Type 1 error = 0.029; type 2 error = 0.145)

Stage 1: If \geq 1 patient responds, that treatment regimen proceeds to the next stage.

Stage 2: An additional 15 are patients enrolled

If $>$ 4 patients respond out of 35 patients (Stage 1 + Stage 2 combined), the drug has met the efficacy threshold.

Key Eligibility Criteria

- Male or female patients with advanced breast cancer following taxane therapy (adjuvant or metastatic)
- Patients may also have received prior anthracycline or capecitabine
- No prior camptothecin therapy
- No more than two prior chemotherapy regimens given in the metastatic setting
- Measurable disease as defined by RECIST version 1.0
- ECOG PS: 0-1
- Adequate renal, hepatic and marrow function
- No known or suspected CNS metastases
- No significant pre-existing acute/chronic GI disorder

Demographics

		NKTR-102 145 mg/m ² Q14 days N=35	NKTR-102 145 mg/m ² Q21 days N=35
Age (years)	Median (Range)	53 (33-83)	56 (37-77)
ECOG PS	0 1	15 (43%) 20 (57%)	13 (37%) 22 (63%)
Receptor Status*	ER+ or PR+ ER-/PR-/Her2- (triple negative) Her2+	22 (63%) 11 (31%) 5 (14%)	21 (60%) 10 (29%) 1 (3%)
Prior Systemic Treatments*	Neoadjuvant and/or Adjuvant therapy Taxane based regimen in metastatic setting Prior AT only (anthracycline/taxane) Prior AT only for metastatic disease Prior ATC (anthracycline/taxane/capecitabine) Median cytotoxic regimens (metastatic disease) Visceral (at least one lesion)	28 (80%) 32 (91%) 23 (66%) 7 (20%) 8 (23%) 2 28 (80%)	24(69%) 33 (94%) 21 (60%) 9 (26%) 10 (29%) 2 32 (91%)
Time from Primary Dx to MBC	Median (years) (Range)	1.5 (0-7)	2 (0-12)
Time from Last Chemo to Entry	Median (months) (Range)	1.1 (0-22.6)	1.5 (0-84.7)

* Numbers may add up to more than 100% due to patients included in multiple rows

Objective Tumor Response Rate by RECIST (Investigator Assessment)

Response by RECIST v 1.0	NKTR-102 145 mg/m ² Q14 days	NKTR-102 145 mg/m ² Q21 days	TOTAL
N	31*	35	66
ORR	10 (32%)	9 (26%)	19 (29%)
CR	2 (7%)	0	2 (3%)
PR	8 (26%)	9 (26%)	17 (26%)
SD	12 (39%)	16 (46%)	28 (42%)
PD	9 (29%)	10 (29%)	19 (29%)
Clinical benefit (CR+PR+SD≥6 months)	13 (42%)	17 (49%)	30 (46%)

*4 patients in the Q14 day arm with no post-baseline scans and no other evidence of progression were excluded from the evaluable population.

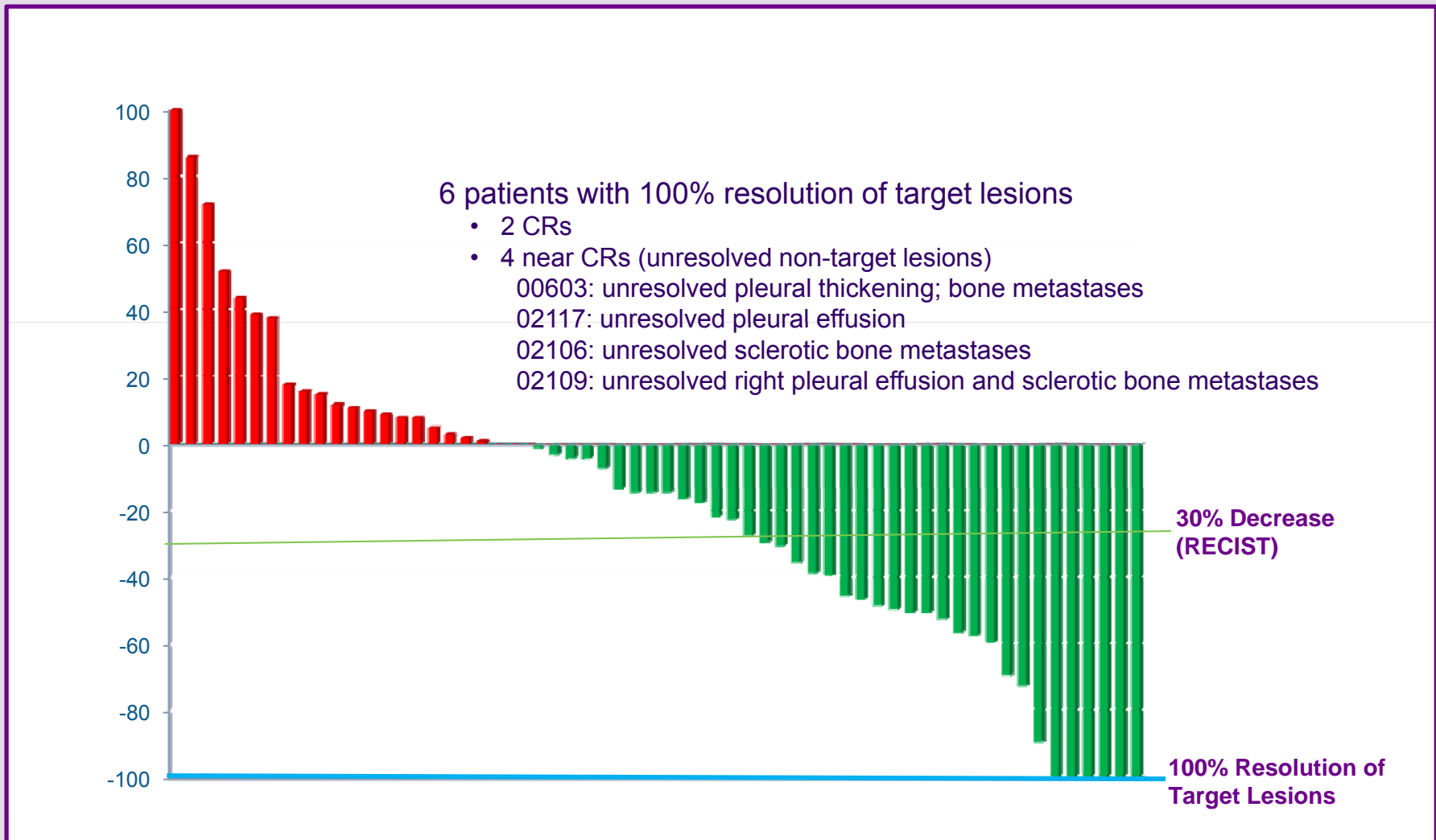
Response Rate by Prior Therapy

Prior Therapy Subgroup	Response by RECIST v 1.0 n/N (%) Evaluable Patients		
	NKTR-102 145 mg/m ² Q14 days	NKTR-102 145 mg/m ² Q21 days	TOTAL
Prior A/T only	7/22 (32%)	5/21 (24%)	12/43 (28%)
Prior A/T in MBC	3/7 (43%)	2/9 (22%)	5/16 (31%)
Prior A/T/C	2/6 (33%)	3/10 (30%)	5/16 (31%)

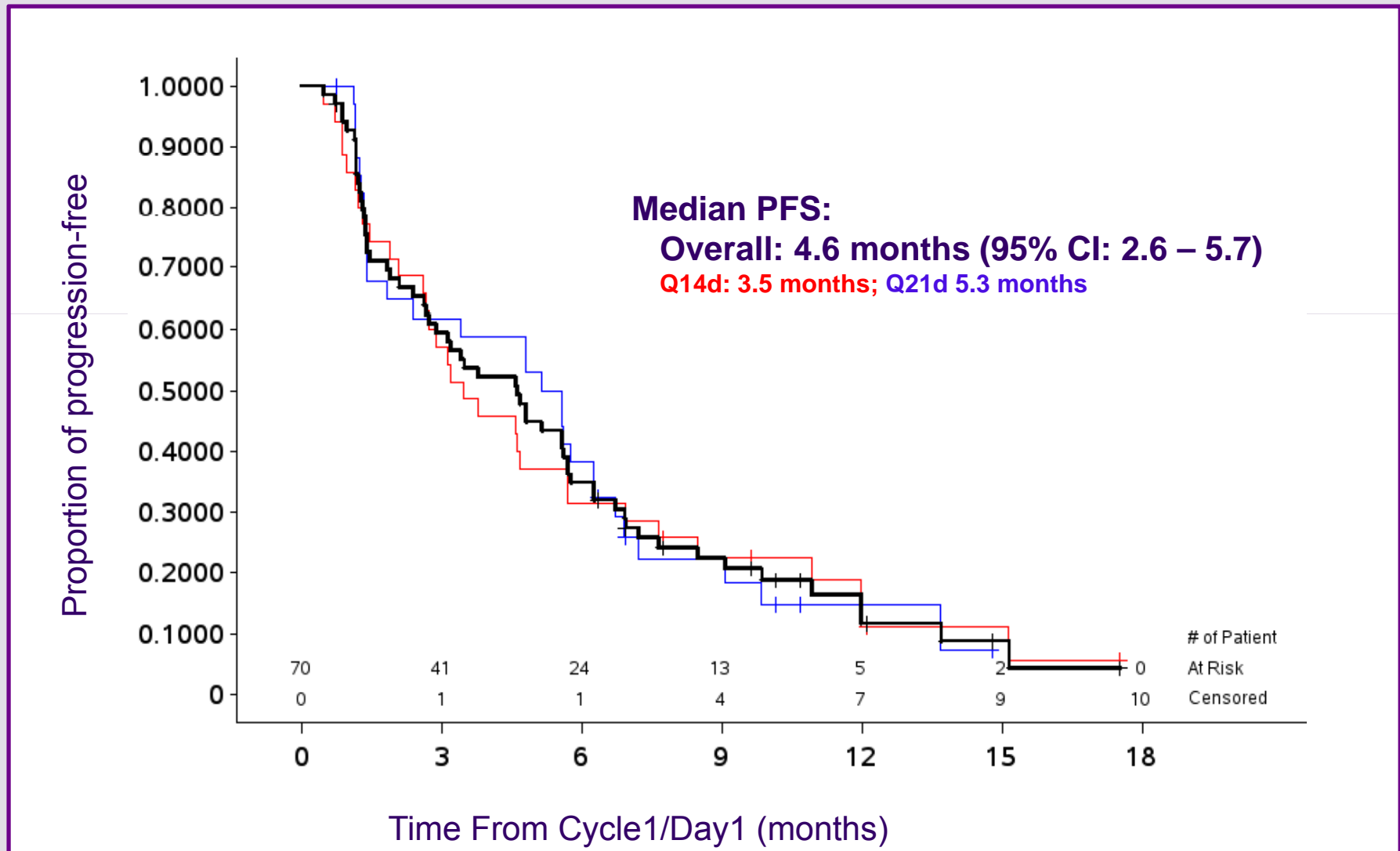
Response Rate by Tumor Characteristics

Disease Subgroup	Response by RECIST v 1.0 n/N (%) Evaluable Patients		
	NKTR-102 145 mg/m ² Q14 days	NKTR-102 145 mg/m ² Q21 days	TOTAL
ER+ and/or PR+	8/21 (38%)	4/21 (19%)	12/42 (29%)
TNBC	2/8 (25%)	5/10 (50%)	7/18 (39%)
Visceral Disease	8/25 (32%)	9/32 (28%)	17/57 (30%)

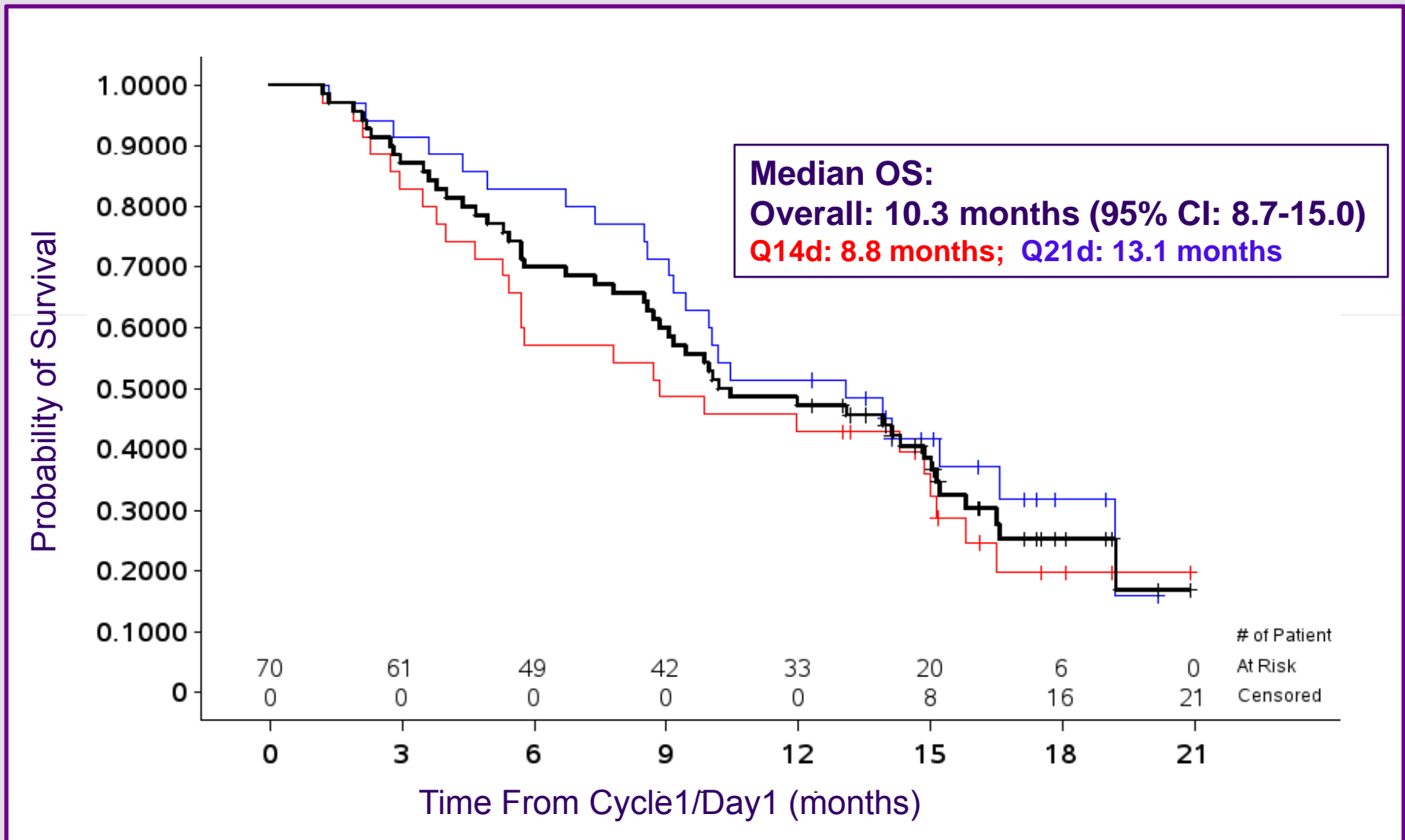
Maximum Decline in Tumor Measurements



Progression-Free Survival (All Patients)



Overall Survival (All Patients)



Safety-Summary of Drug Related AEs

Most Common Drug-related Grade 3 and 4 Adverse Events > 5% or Event of Interest N (%)	145 mg/m ² Q14 days* N=35		145 mg/m ² Q21 days N=35	
	Grade 3	Grade 4	Grade 3	Grade 4
Diarrhea	6 (17%)	1 (3%)	8 (23%)	0
Neutropenia	2 (6%)	2 (6%)	3 (9%)	1 (3%)
Dehydration	3 (9%)	0	4 (11%)	0
Fatigue	4 (11%)	0	3 (9%)	0
Vomiting	3 (9%)	0	0	0
Anaemia	1 (3%)	0	0	1 (3%)
Asthenia	2 (6%)	0	0	0
Lethargy	2 (6%)	0	0	0
Lymphopenia	1 (3%)	1 (3%)	0	0
Neutropenic sepsis	0	0	1 (3%)	0
Febrile neutropenia	0	0	1 (3%)	0
	Grade 1	Grade 2	Grade 1	Grade 2
Alopecia	7 (20%)	0	3 (9%)	1 (3%)

*2 possible treatment-related deaths (both on the Q14 day schedule): sepsis and acute renal failure following diarrhea

Time Course of Diarrhea and Neutropenia

	NKTR-102 145 mg/m ² q14d N=35	NKTR-102 145 mg/m ² q21d N=35
Diarrhea (≥ Grade 3)		
Cycle 1 and/or 2	9%	3%
Cycle 3 and/or 4	0%	6%
Cycle 4+	11%	14%
Onset Time, Median (Range) days [# cycle]	88 (1-121) [6]	93 (8-107) [5]
Duration, Median (Range) days	8.5 (1-16)	14 (2-39)
Neutropenia (≥ Grade 3)		
Cycle 1 and/or 2	3%	3%
Cycle 3 and/or 4	0%	6%
Cycle 4+	9%	3%
Onset Time, Median (Range) days [# cycle]	98 (15-188) [6.5]	60 (28-140) [3]
Duration, Median (Range) days	12 (6-15)	9.8 (6-14)

Anti-diarrheals given therapeutically; no prophylactic anti-diarrheals administered

Study Drug Administration and Discontinuation Due to AE

	NKTR-102 145 mg/m ²		
	Q14 days (N=35)	Q21 days (N=35)	TOTAL (N=70)
Discontinuation from Study Drug Due to AE	7 (20.0%)	5 (14.3%)	12 (17.1%)
Total Exposure Duration (days) Median (Range)	85 (1-393)	113.5 (1-420)	85 (1-420)
Total No. of Cycles Received Median (Range)	6.0 (1-29)	6.0 (1-21)	6.0 (1-29)

Conclusions

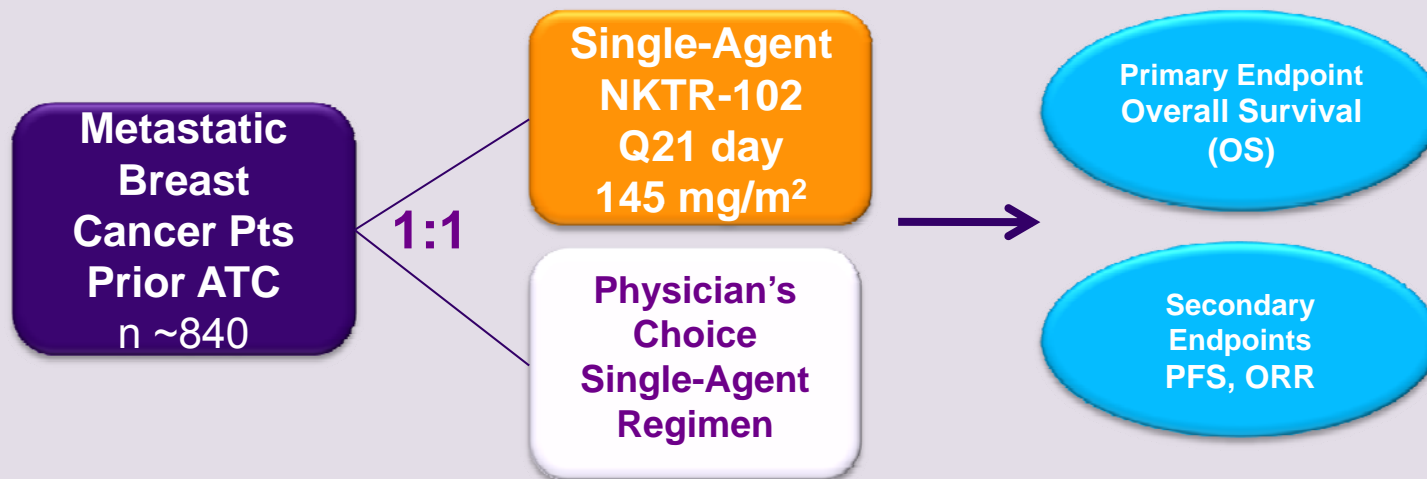
- 29% ORR observed with single-agent NKTR-102 in patients with advanced breast cancer previously treated with taxane (89% prior anthracycline; 23% prior capecitabine):
 - 32% ORR on 14-day schedule; 26% on 21-day schedule
 - PFS: 4.6 months
 - Preliminary estimate for median OS: 10.3 months
- 21-day schedule appears better tolerated (with PFS: 5.3m, OS 13.1m)
- ORR is maintained in heavily pre-treated and poor prognosis subsets
 - A/T/C Pre-treated: 31%
 - Triple negative: 39%
 - Visceral disease: 30%
- Side effects generally manageable; most common Grade 3/4 toxicity was diarrhea (20-23%) typically occurring after 3 months of therapy for both schedules
- NKTR-102 on the q21d schedule is being evaluated in multiple cancer indications as a single and combination agent. Phase 3 planning is underway in platinum-resistant ovarian cancer and advanced breast cancer

BEACON Phase 3 Study

NKTR-102 vs. Physician's Choice in Women with Metastatic Breast Cancer

BEACON

BrEAsT Cancer Outcomes with NKTR-102



- Study planned for Q4 2011 start

Acknowledgements

- Investigators and Study Staff at Participating Centers in the United States, Belgium and United Kingdom:

Institut Jules Bordet, Brussels, BE

Domaine Universitaire du Sart Tilman, Liege, BE

UZ Antwerpen, Antwerp, BE

University Hospital, Gent, BE

Clatterbridge Centre for Oncology, Bebington, UK

Nottingham City Hospital, Nottingham, UK

Weston Park Hospital, Sheffield, UK

Velindre NHS Trust Cardiff, Cardiff, UK

St James University Hosp, Leeds, UK

Mayo Clinic, Jacksonville, FL

Mayo Clinic, Rochester, MN

CF Research Resource, East Providence, RI

Stockton Hematology/Oncology, Stockton, CA

Louisville Oncology Research, Louisville, KY

Desert Hematology/Onc, Rancho Mirage, CA

USC Norris CCC, Los Angeles, CA

- Nektar Study Team

Biostatistician: Carol Zhao, M.S.

Study monitors and auditors

The Patients and Their Families