

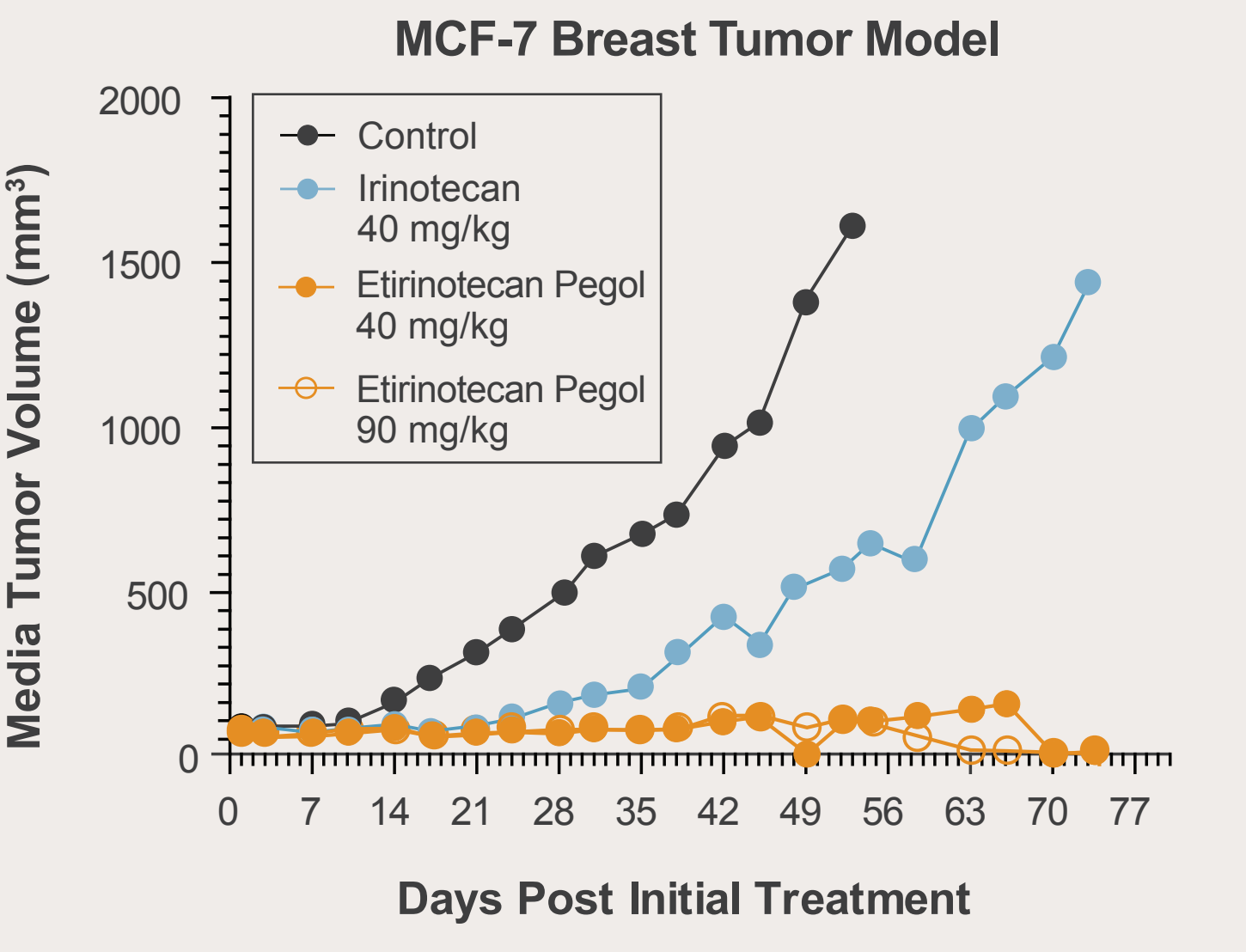
# Significant Antitumor Activity in a Randomized Phase 2 Study Comparing Two Schedules of Etririnotecan Pegol (NKTR-102)

A. Awada<sup>1</sup>, S. Chan<sup>2</sup>, G.H.M. Jerusalem<sup>3</sup>, R.E. Coleman<sup>4</sup>, M.T. Huizing<sup>5</sup>, A. Mehdi<sup>6</sup>, S.M. O'Reilly<sup>7</sup>, J.T. Hamm<sup>8</sup>, P.A. Garcia<sup>9</sup>, E.A. Perez<sup>10</sup>

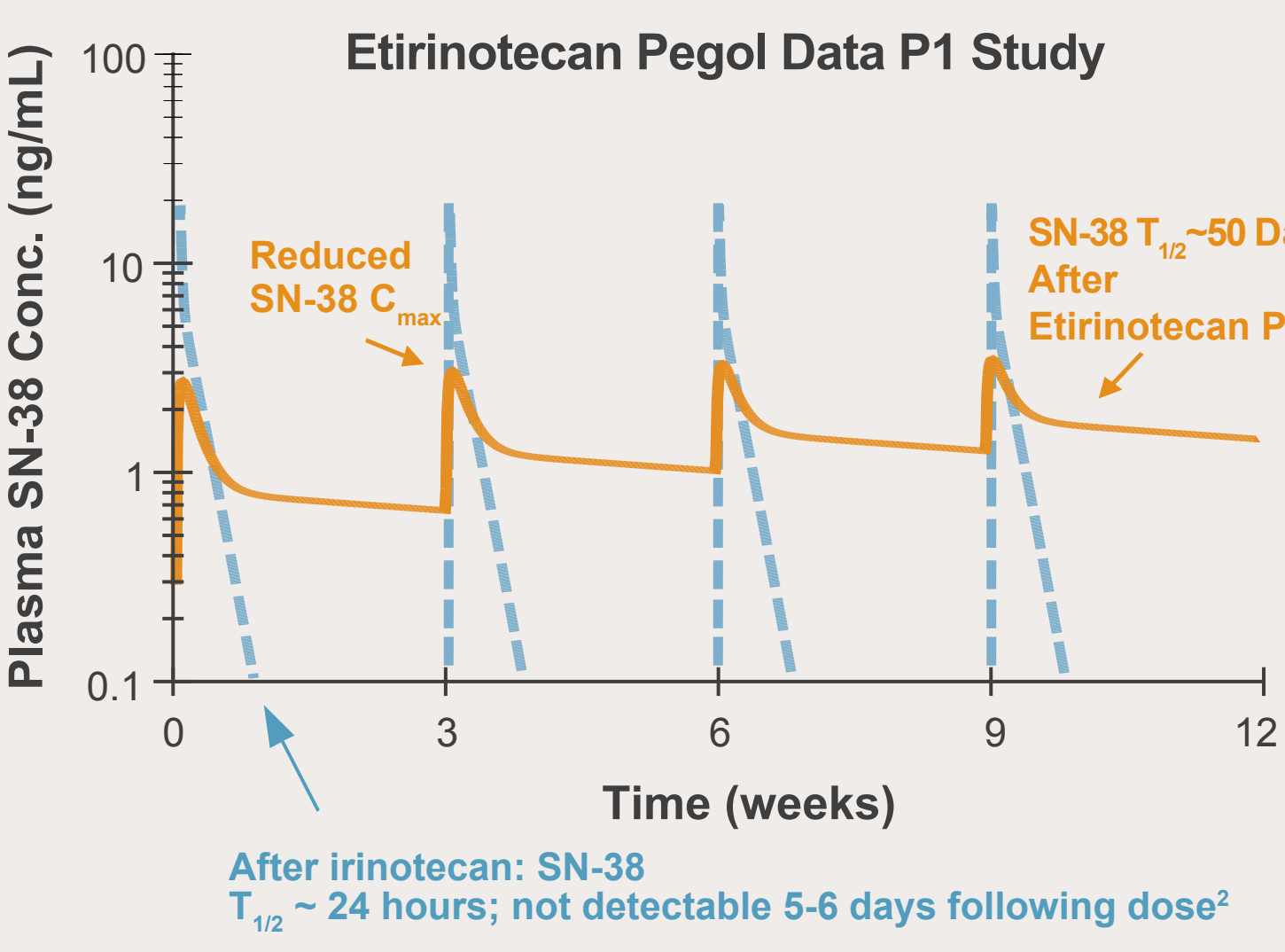
<sup>1</sup>Institut Jules Bordet, Brussels, Belgium; <sup>2</sup>Nottingham University Hospital, Nottingham, United Kingdom; <sup>3</sup>CHU Sart Tilman, Liege, Belgium; <sup>4</sup>Cancer Research Center, Sheffield, United Kingdom; <sup>5</sup>UZA, Edegem, Belgium; <sup>6</sup>Stockton Hematology/Oncology, Stockton, CA; <sup>7</sup>Clatterbridge Center for Oncology, Merseyside, United Kingdom; <sup>8</sup>Norton Health Care, Louisville, KY; <sup>9</sup>University of Southern California, Los Angeles, CA; <sup>10</sup>Mayo Clinic, Jacksonville, FL

## Background

- Etririnotecan pegol is a unique, long acting topoisomerase I inhibitor that provides prolonged systemic exposure to SN-38, the active metabolite of irinotecan.
- Etririnotecan pegol has superior efficacy (measured both by tumor growth delay and regression rate) compared to irinotecan against a wide range of human xenograft tumors.<sup>1</sup>



## Polymer Conjugation Improves Pharmacokinetics of Irinotecan

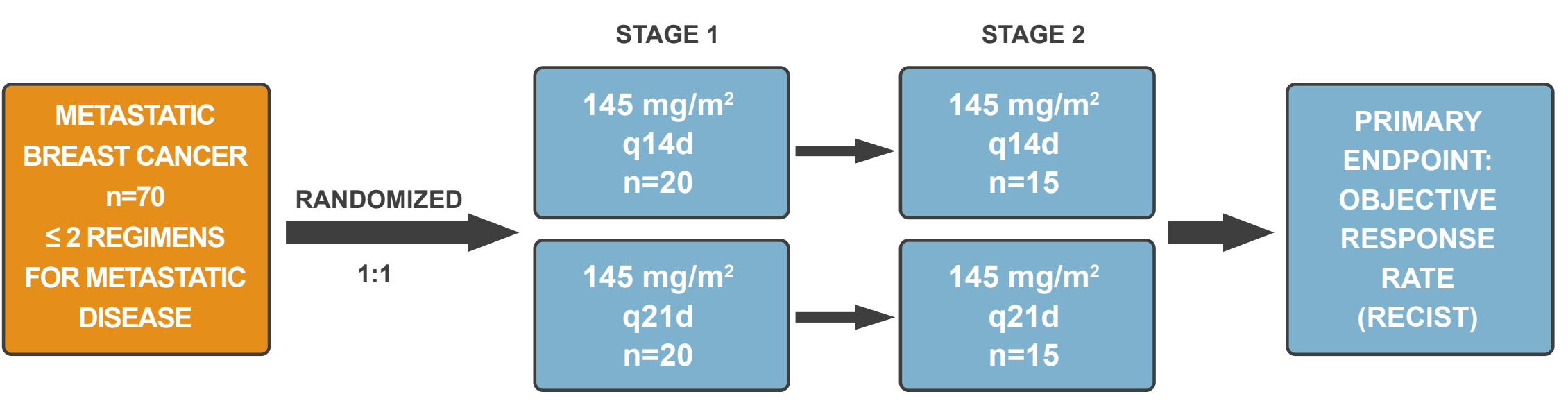


- Etririnotecan pegol demonstrated high antitumor activity in a range of tumors in Phase 1 (11% confirmed PRs)<sup>3</sup>
  - Of interest, 3 patients in the Phase 1 study with triple-negative breast cancer (TNBC) showed significant response to single-agent etirinotecan pegol<sup>2</sup>
- Etririnotecan pegol showed a 22% confirmed response rate per RECIST in heavily pre-treated women with platinum resistant/refractory ovarian cancer (Vergote IB, et. al. Proc. Am. Soc. Clin. Oncol. 2010; 28: Abstract 5013)<sup>4</sup>

References:  
 1. Persson H., et al. NKTR-102, a novel polyethylene glycol conjugate of irinotecan, has improved anti-tumor activity in three mouse xenograft models. Poster presented at the 2007 AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, Oct 22-26, 2007, San Francisco, CA USA. Poster no. C10  
 2. Xie R, Mathijssen RHJ, Sparreboom A, et al. Clinical pharmacokinetics of irinotecan and its metabolites: A population analysis. J Clin Oncol 20 (15): 3293-3301, 2002  
 3. Von Hoff DD, Jameson GS, Borad MJ et al. First Phase 1 trial of NKTR-102 (Peg-Irinotecan) reveals early evidence of broad anti-tumor activity in three different schedules. Presented at the 20th EORTC-NCI-AACR Symposium on "Molecular Targets and Cancer Therapeutics" Meeting, Oct 21-24, 2008, Geneva, Switzerland. Poster no. 595  
 4. Vergote IB, Michal JP, Pignatelli B, et al. Phase II study of NKTR-102 in women with platinum-resistant/refractory ovarian cancer. J Clin Oncol 28:15s, 2010 suppl; abstr 5013.

## Study Design & Objectives

### Study Design: Randomized Simon Two-Stage



**Statistical Hypotheses:** H<sub>0</sub> ORR (RECIST version 1.0) ≤ 5% and H<sub>a</sub> ORR ≥ 20%. (Type 1 error = 0.029; type 2 error = 0.145)

Stage 1: If ≥ 1 patient responds, that treatment regimen proceeds to the next stage. Stage 2: An additional 15 patients are enrolled.

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

### Etririnotecan Pegol Breast Cancer Study: Objectives

- Primary Efficacy Objective:**
- Determine the objective response rate (ORR) by RECIST v 1.0
  - Determine the optimal schedule of etirinotecan pegol in breast cancer
- Secondary Objectives:**
- Estimate progression-free survival (PFS)
  - Evaluate overall survival (OS) rates
  - Characterize the safety profile

## 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

## Study Demographics

- 70 patients (35 per schedule) randomized from February 2009 through May 2010 (median follow-up: 8 months)

		Etririnotecan Pegol 145 mg/m <sup>2</sup> q14d N=35	Etririnotecan Pegol 145 mg/m <sup>2</sup> q21d 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-/HER-2 (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 diag. to metastatic	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  
 Source: Data as of May 9, 2011

## Results

### Objective Tumor Response Rate by RECIST (Investigator Assessment)

Response by RECIST v 1.0	Etririnotecan Pegol 145 mg/m <sup>2</sup> q14d	Etririnotecan Pegol 145 mg/m <sup>2</sup> q21d	TOTAL
N	31*	35	66
ORR (confirmed + unconfirmed)	11(35%)	11(31%)	22 (33%)
ORR (confirmed)	10(32%)	9 (26%)	19 (29%)
CR (confirmed)	2 (7%)	0	2 (3%)
PR (confirmed)	8 (26%)	9 (26%)	17 (26%)
SD	12 (39%)	16 (46%)	28 (42%)
PD	9 (29%)	10 (29%)	19 (29%)
Duration of ORR (months)	8.3	4.4	5.8
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.  
 Source: Data as of May 9, 2011

### Response Rate By Prior Therapy

Prior Therapy Subgroup	Response by RECIST v 1.0 n/N (%) Evaluable Patients		
	Etririnotecan Pegol 145 mg/m <sup>2</sup> q14d	Etririnotecan Pegol 145 mg/m <sup>2</sup> q21d	TOTAL
Prior A/T only ORR (confirmed)	7/22 (32%)	5/21 (24%)	12/43(28%)
Prior A/T in MBC ORR (confirmed)	3/7 (43%)	2/9 (22%)	5/16 (31%)
Prior A/T/C ORR (confirmed)	2/6 (33%)	3/10 (30%)	5/16 (31%)

Source: Data as of May 9, 2011

### Response Rate By Tumor Characteristics

Disease Subgroup	Response by RECIST v 1.0 n/N (%) Evaluable Patients		
	Etririnotecan Pegol 145 mg/m <sup>2</sup> q14d	Etririnotecan Pegol 145 mg/m <sup>2</sup> q21d	TOTAL
ER+ and/or PR+ ORR (confirmed)	8/21 (38%)	4/21 (19%)	12/42 (29%)
TNBC ORR (confirmed)	2/8 (25%)	5/10 (50%)	7/18 (39%)
Visceral Disease ORR (confirmed)	8/25 (32%)	9/32 (28%)	17/57 (30%)

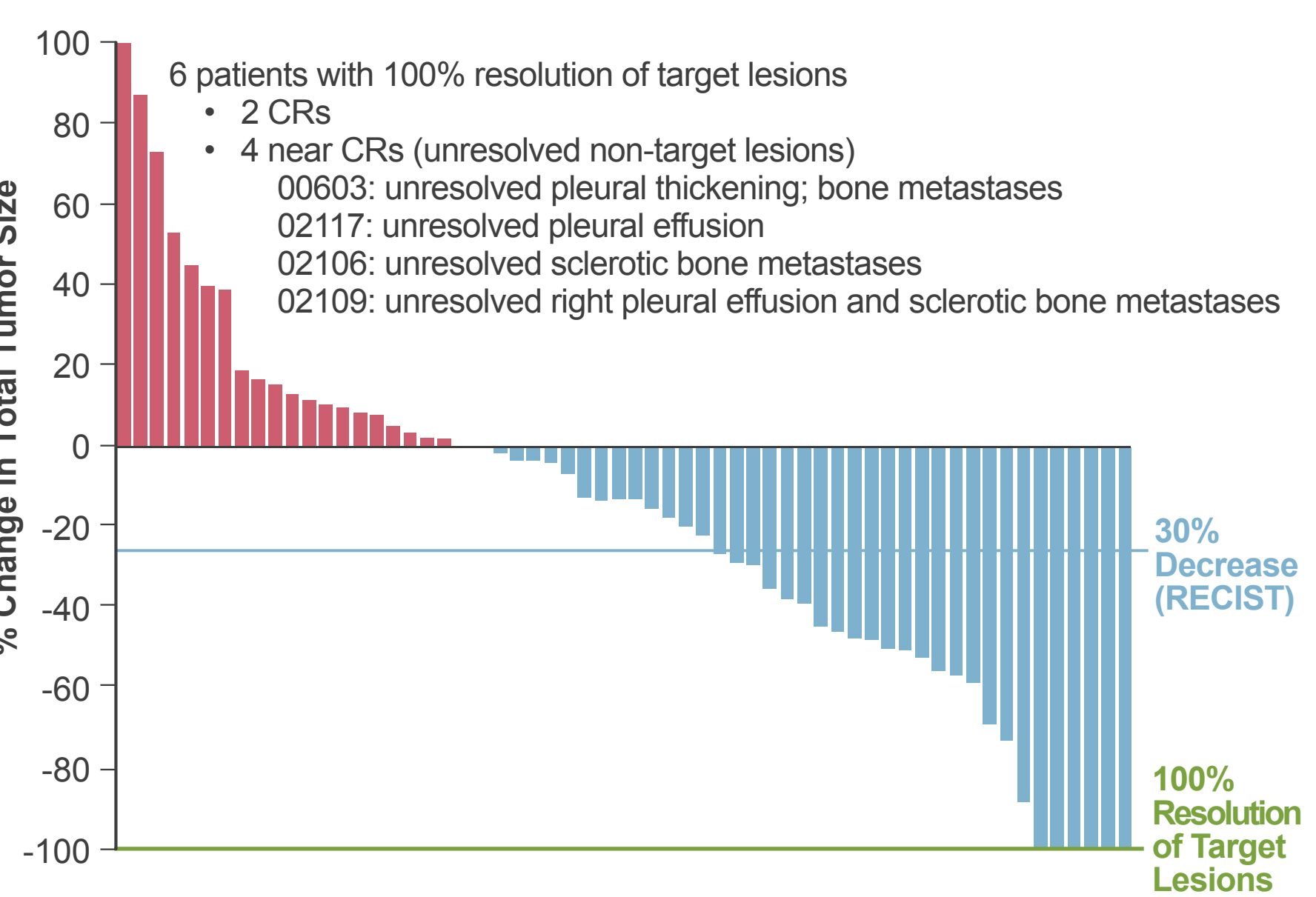
Source: Data as of May 9, 2011

### Study Drug Administration and Discontinuation Due to AE

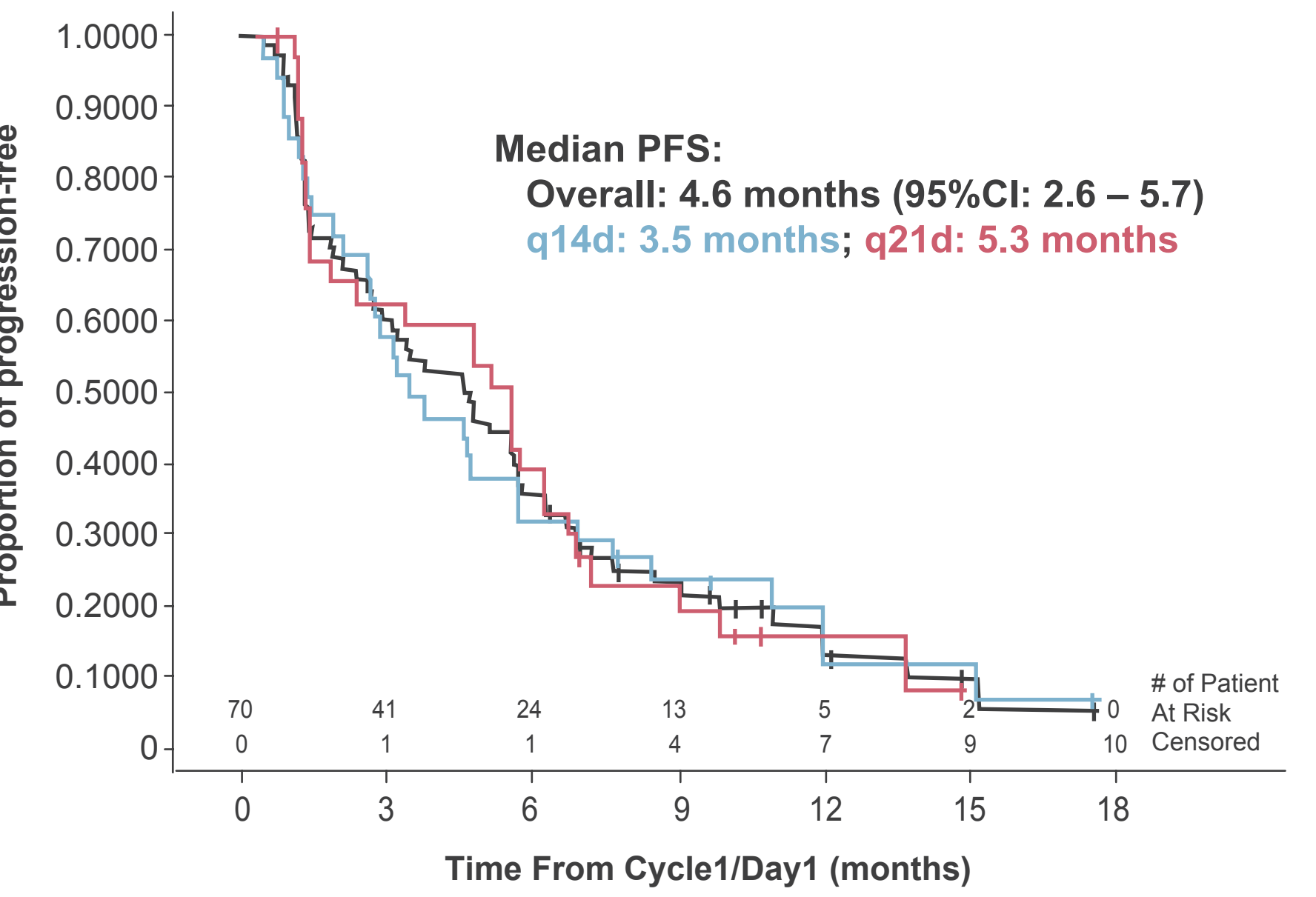
	Etririnotecan Pegol 145 mg/m <sup>2</sup>		
	q14d (N=35)	q21d (N=35)	TOTAL (N=70)
Discontinuation from Study Drug Due to AE	7 (20.0%)	5 (14.3%)	12 (17.1%)
Total Exposure Duration (days)	85 (1-393)	113.5 (1-420)	85 (1-420)
Median (Range)			
Total No. of Cycles Received	6.0 (1-29)	6.0 (1-21)	6.0 (1-29)
Median (Range)			

Source: Data as of May 9, 2011

### Maximum Decline in Tumor Measurements

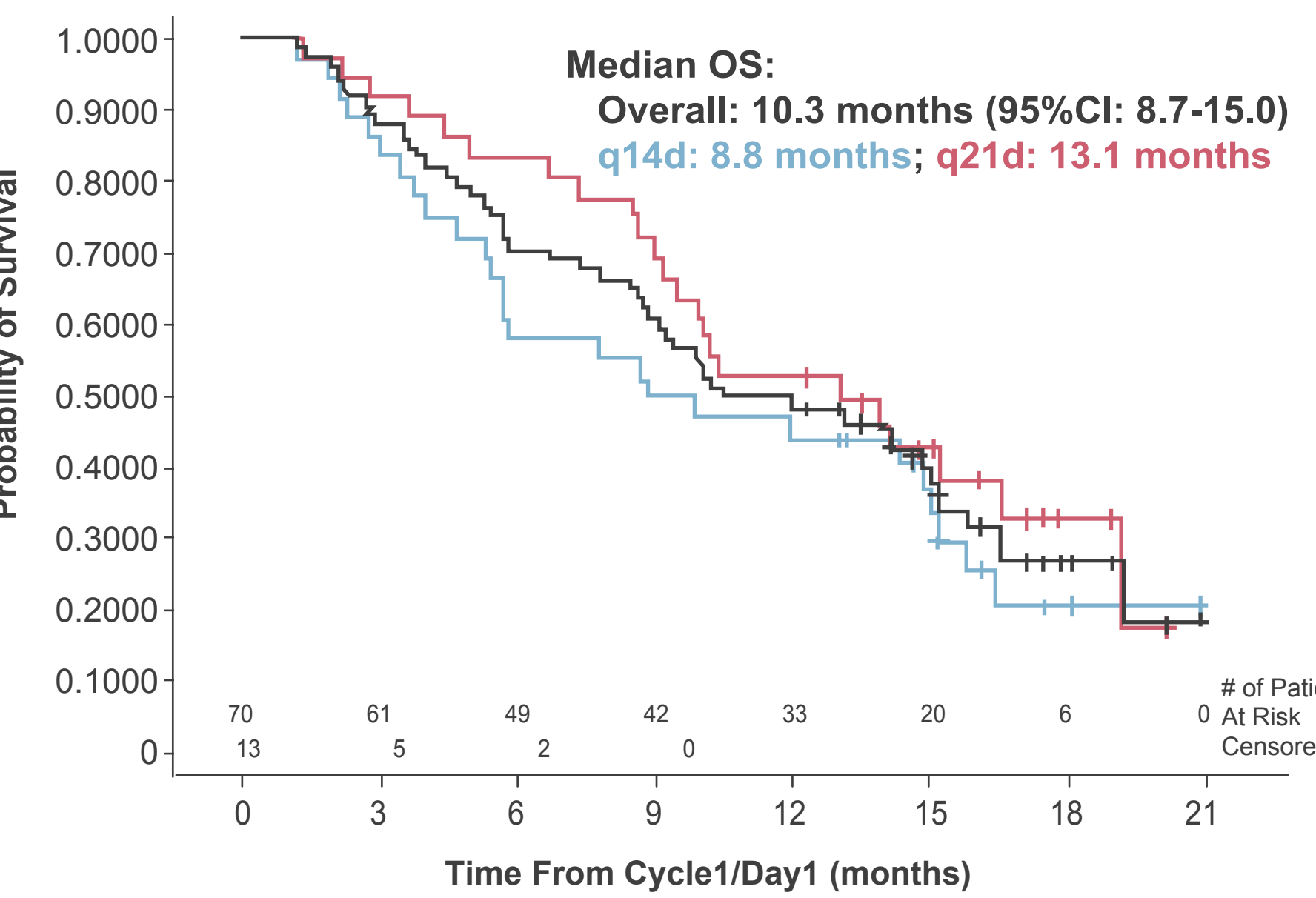


### Progression-Free Survival (All Patients)



Kaplan-Meier graph of progression-free survival. Analysis includes the intent-to-treat population. Tickmarks show censored data. Source: Data as of May 9, 2011

### Overall Survival (All Patients)



Kaplan-Meier graph of overall survival. Analysis includes the intent-to-treat population. Tickmarks show censored data. Source: Data as of May 9, 2011

## Conclusions

- High confirmed objective response rate observed with single-agent etirinotecan pegol in patients with advanced breast cancer previously treated with taxane +/- capecitabine (89% with prior anthracycline):
  - 29% confirmed objective response rate
  - 32% ORR on 14-day schedule; 26% on 21-day schedule
  - PFS: 4.6 months in 2<sup>nd</sup>/3<sup>rd</sup> line
  - Preliminary estimate for median survival: 10.3 months
- Similar antitumor activity for both schedules; 21-day schedule appears better tolerated in a setting of improved survival.
- 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.
- Etririnotecan pegol is being evaluated in multiple cancer indications as a single agent and combination therapy.
- A Phase 3 global pivotal study (BEACON) utilizing the q21 day dosing schedule is underway in patients with advanced breast cancer.

## Safety

### 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 <sup>2</sup> q14d* N=35		145 mg/m <sup>2</sup> q21d 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
N (%)	q14d N=35		q21d N=35	
	Grade 1	Grade 2	Grade 1	Grade 2
Alopecia	7 (20%)	0	3 (9%)	1 (3%)

\*2 possible treatment-related deaths occurred (both in q21d): sepsis and acute renal failure following diarrhea  
 Source: Data as of May 9, 2011

### Safety: Time Course of Diarrhea and Neutropenia

	Etririnotecan Pegol 145 mg/m <sup>2</sup> q14d N=35	Etririnotecan Pegol 145 mg/m <sup>2</sup> q21d N=35
Diarrhea (≥Grade 3)		
Cycle 1 and/or 2	9%	3% (G3 only)
Cycle 3 and/or 4	0%	8% (G3 only)
Cycle 4*	11%	14% (G3 only)
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 (28-203) [3]
Duration, Median (Range) days	12 (6-15)	8 (6-14)

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