

# **BEACON: A Phase 3 Open-label, Randomized, Multicenter Study of Etirinotecan Pegol (EP) 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**

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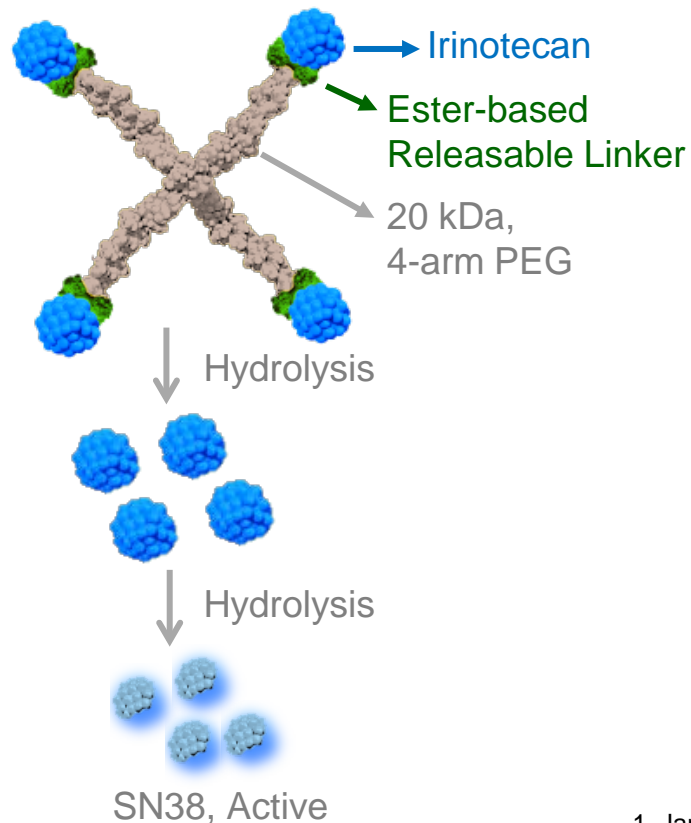
**BEACON**

BREAST CANCER OUTCOMES WITH NKTR-102

# Is a New Chemotherapy Option Needed?

- Chemotherapy remains mainstay of treatment for patients with advanced breast cancer
- Additional options are needed for patients after treatment with an anthracycline, taxane and capecitabine
  - Anti-tumor activity
  - No neuropathy
  - No cardiac toxicity

# Novel Pharmacology of Etirinotecan Pegol



- Compared to irinotecan, Etirinotecan Pegol prolongs elimination half-life of SN38 from 2 days to 50 days in patients<sup>1</sup>
- Given its size, Etirinotecan Pegol escapes from leaky tumor vasculature, concentrating the active metabolite in tumor<sup>2</sup>
- In a murine model of brain metastases, Etirinotecan Pegol results in 100-fold greater concentration of SN38 in brain lesions compared to irinotecan, prolonging survival<sup>3</sup>

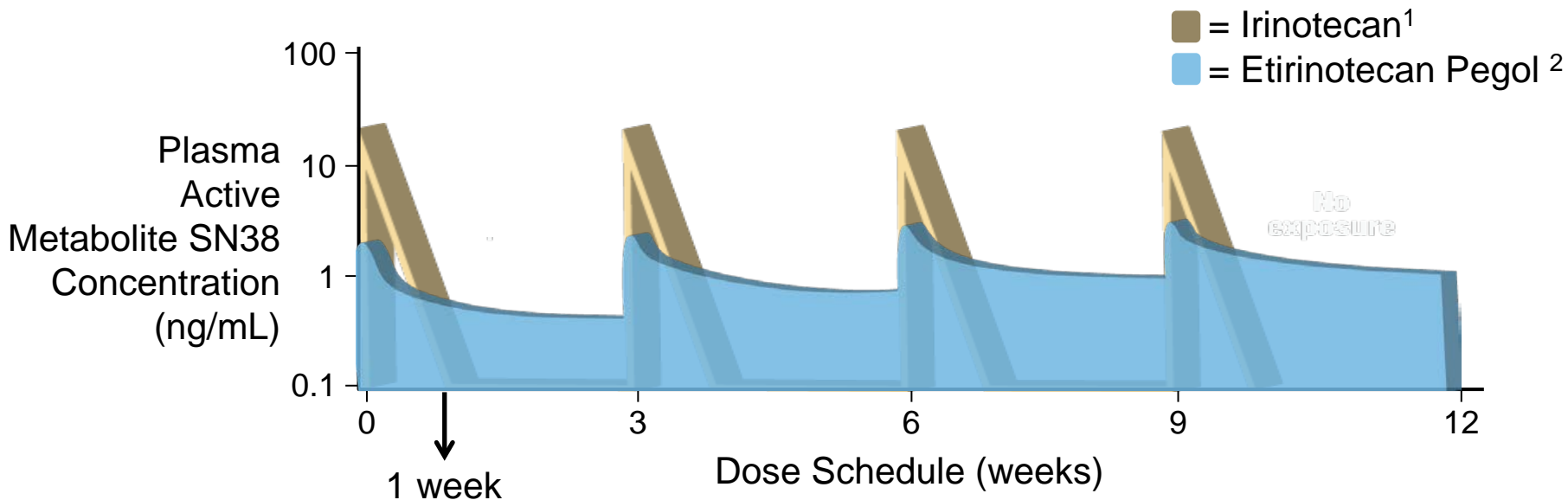
1. Jameson et al. *Clin Cancer Res.* 2013;19:268-78

2. Hoch et al. *Cancer Chemother Pharmacol.* 2014;74:1125-1137

3. Nounou et al. AACR Proceedings 2014 Abstract 35

# Comparative Pharmacokinetics of SN38: Irinotecan vs Etirinotecan Pegol

Etirinotecan Pegol's design results in low initial peak and sustained concentrations of active topoisomerase 1 inhibitor



1. Xie et al. *J Clin Oncol.* 2002;20:3293-3301

2. Jameson et al. *Clin Cancer Res.* 2013;19:268-78

# Etirinotecan Pegol Phase 1 and 2 Clinical Trials

- Phase 1 conducted in patients with advanced solid tumors<sup>1</sup>
  - Primary toxicity: Diarrhea with minimal myelosuppression
- Two schedules compared in MBC phase 2 (n=70), with a median of 2 prior regimens for MBC
  - 145 mg/m<sup>2</sup> every 2 or 3 weeks<sup>2</sup>
- Etirinotecan Pegol every 3 weeks chosen as the schedule for phase 3 trials due to numerically superior activity/better tolerability

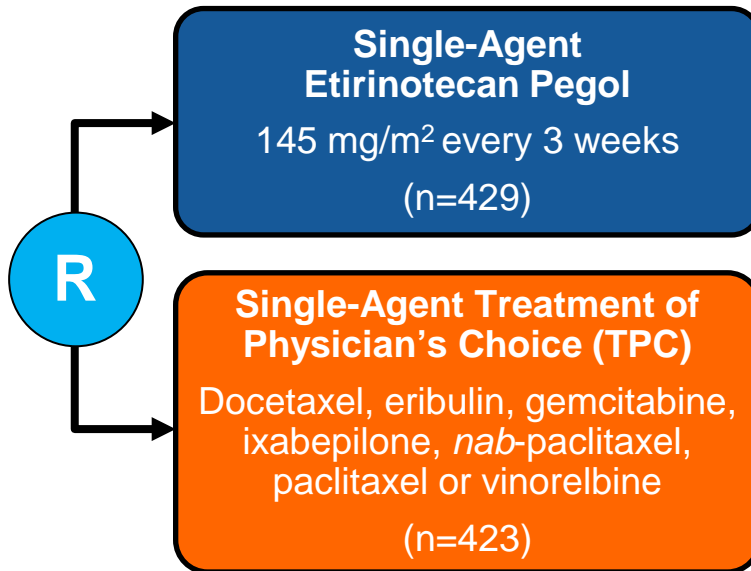
# BEACON Phase 3 Study Design

## Locally recurrent or metastatic breast cancer (n=852)

- Prior treatment with anthracycline, a taxane, and capecitabine
- ECOG PS 0-1
- 2-5 prior chemotherapies for advanced disease
- Stable brain mets allowed

### Stratification:

- Geographic region
- Prior eribulin use
- Receptor status



### Primary Endpoint

- Overall Survival

### Secondary Endpoints

- PFS, ORR, CBR, DoR, HRQoL

### Exploratory Endpoints

- PD Markers in CTC, others

135 centers in US, Canada, Belgium, France, Germany, Italy, Korea, Russia, Spain, The Netherlands, UK

Enrollment: Dec 2011 – Aug 2013  
Event cutoff: Dec 2014

# Statistical Considerations

- Overall Survival
  - Target enrollment = 840 patients (420 per treatment arm)
  - 90% power to detect a hazard ratio (HR) of 0.77 (two-sided alpha, 0.05); 10 months vs 13 months
  - 615 deaths required for the final analysis
  - Planned interim analysis by Lan-Demets method with O'Brien-Fleming guideline at 50% of events (two-sided significance level = 0.003)
- OS and PFS endpoints tested by two-sided stratified log-rank (ITT population)

# Baseline Characteristics

Characteristic, n (%)	Etirinotecan Pegol (n=429)	TPC (n=423)
Age, years, median (range)	55 (28-84)	55 (32-80)
ECOG PS		
0	175 (41%)	134 (32%)
1	252 (59%)	285 (67%)
≥ 2	2 (<1%)	4 (1%)
Median time since initial diagnosis of BC (yr)	5.8	5.4
Median time since diagnosis of ABC (yr)	2.5	2.5
Brain metastasis (history or stable)	36 (8%)	31 (7%)
Liver metastasis	229 (53%)	227 (54%)
Lung metastasis	155 (36%)	168 (40%)

ECOG PS, Eastern Cooperative Oncology Group performance status; ABC, advanced breast cancer; TPC, treatment of physicians' choice.

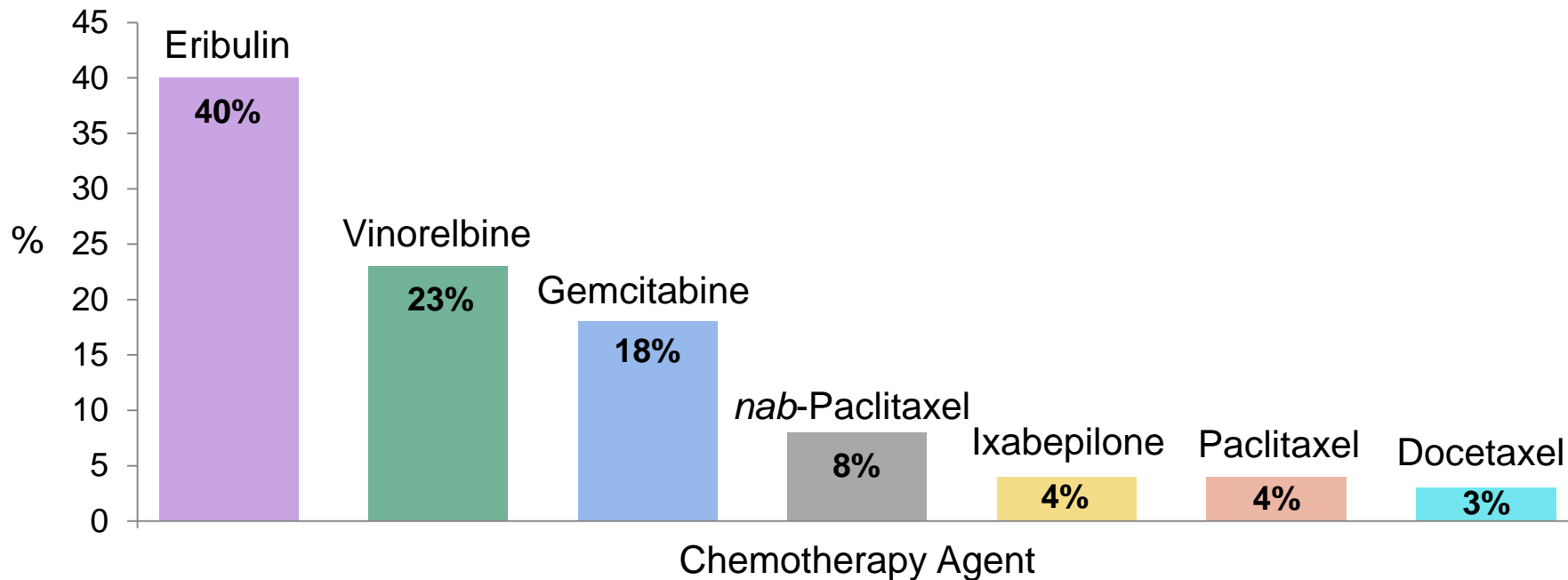


# Baseline Characteristics (cont'd)

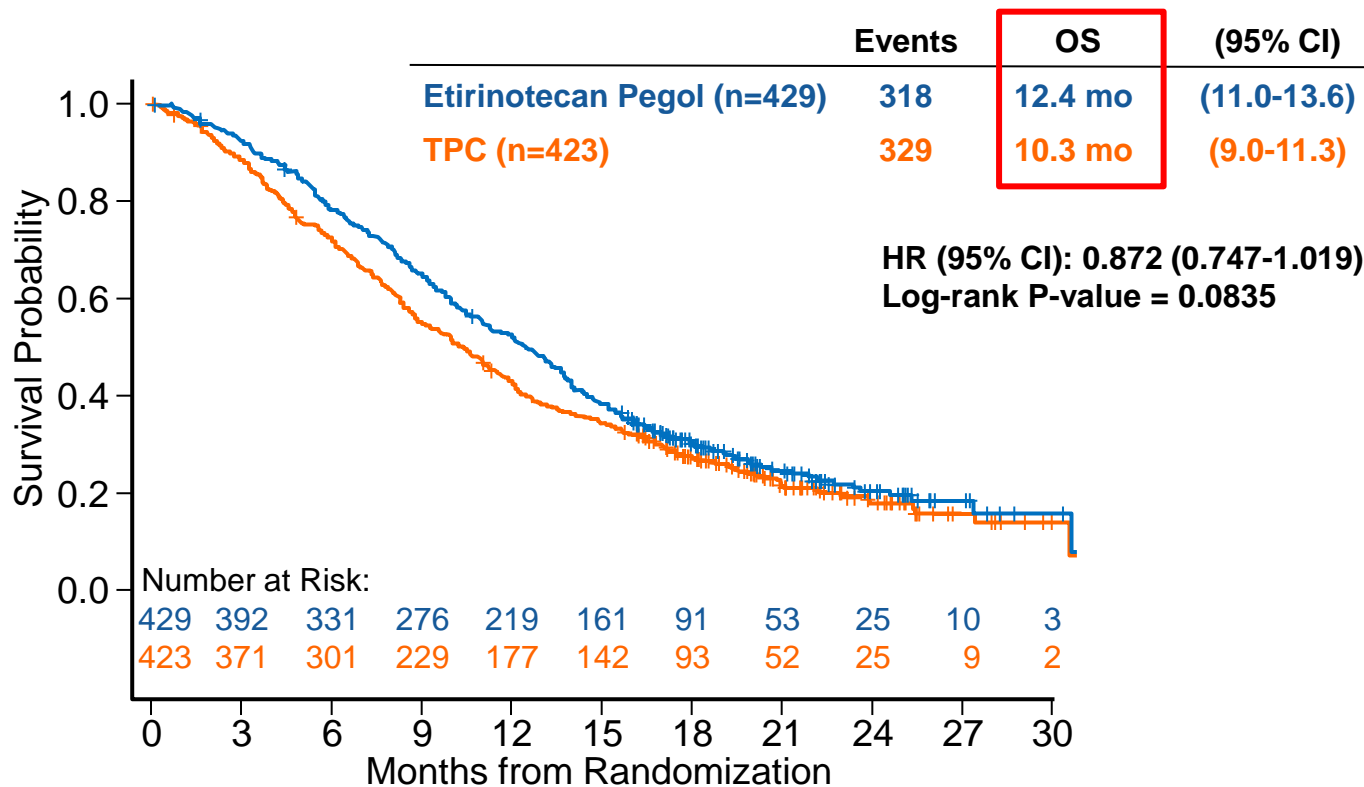
Characteristic	Etirinotecan Pegol (n=429)	TPC (n=423)
Receptor status (n, %)		
Hormone receptor positive	295 (69%)	290 (69%)
Triple negative	119 (28%)	117 (28%)
HER2 positive	30 (7%)	32 (8%)
Stage IV disease at initial diagnosis (n, %)	70 (16%)	75 (18%)
Visceral disease at enrollment (n, %)	319 (74%)	324 (77%)
Prior regimens for metastatic disease (median, range)	3 (1-6)	3 (1-6)
Prior chemotherapy exposure (n, %)		
Prior anthracycline	410 (96%)	406 (96%)
Prior taxane	429 (100%)	423 (100%)
Prior capecitabine	429 (100%)	423 (100%)
Prior eribulin	71 (17%)	72 (17%)

# Patients on TPC Received Chemotherapy

## Breakdown of Agents Used



# Primary Efficacy Endpoint: Overall Survival



# Secondary Efficacy Endpoints

Endpoint	Etirinotecan Pegol (n=429)	TPC (n=423)
<b>Progression-free survival, median mo</b> (95% CI)	<b>2.4</b> (2.1-3.5)	<b>2.8</b> (2.1-3.5)
<b>Objective response rate, n (%)<sup>1</sup></b> (95% CI)	<b>58 (16%)</b> (12.7-20.7)	<b>61 (17%)</b> (13.3-21.3)
<b>Duration of response, median mo<sup>1</sup></b> (95% CI)	<b>3.9</b> (3.5-5.1)	<b>3.7</b> (2.1-3.9)
<b>Clinical benefit rate, n (%)<sup>2</sup></b> (95% CI)	<b>88 (21%)</b> (16.8-24.6)	<b>83 (20%)</b> (15.9-23.7)

Analyzed for patients with measurable disease by RECIST v1.1 at baseline

<sup>1</sup>In patients with measurable disease at baseline (n=354 [EP]; n=358 [TPC])

<sup>2</sup>CR+PR+SD ≥ 6 months

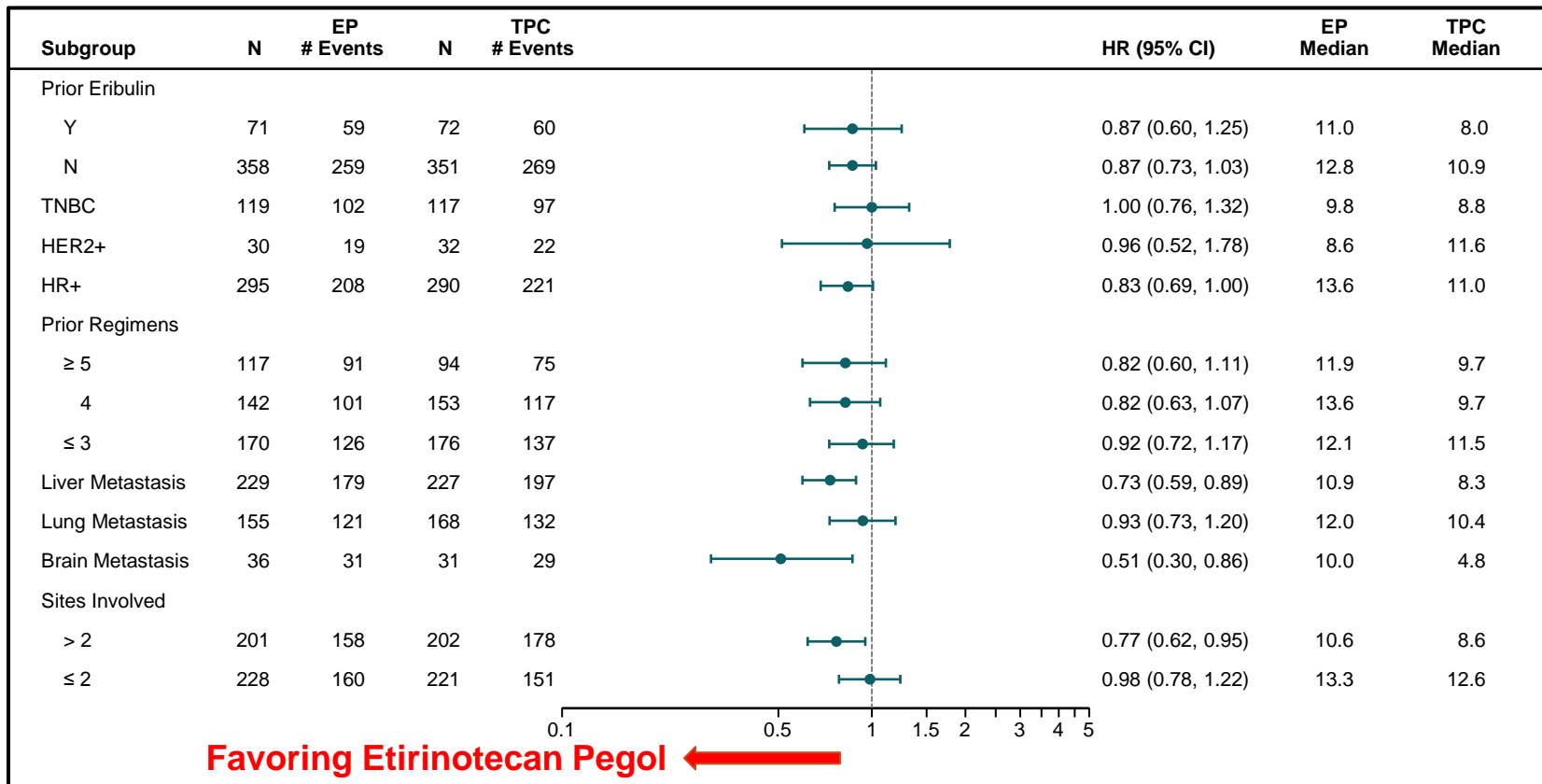
CI, confidence interval; CR, complete response; HR, hazard ratio; PR, partial response; SD, stable disease; TPC, treatment of physicians' choice.

# **Pre-planned Subgroup Analyses**

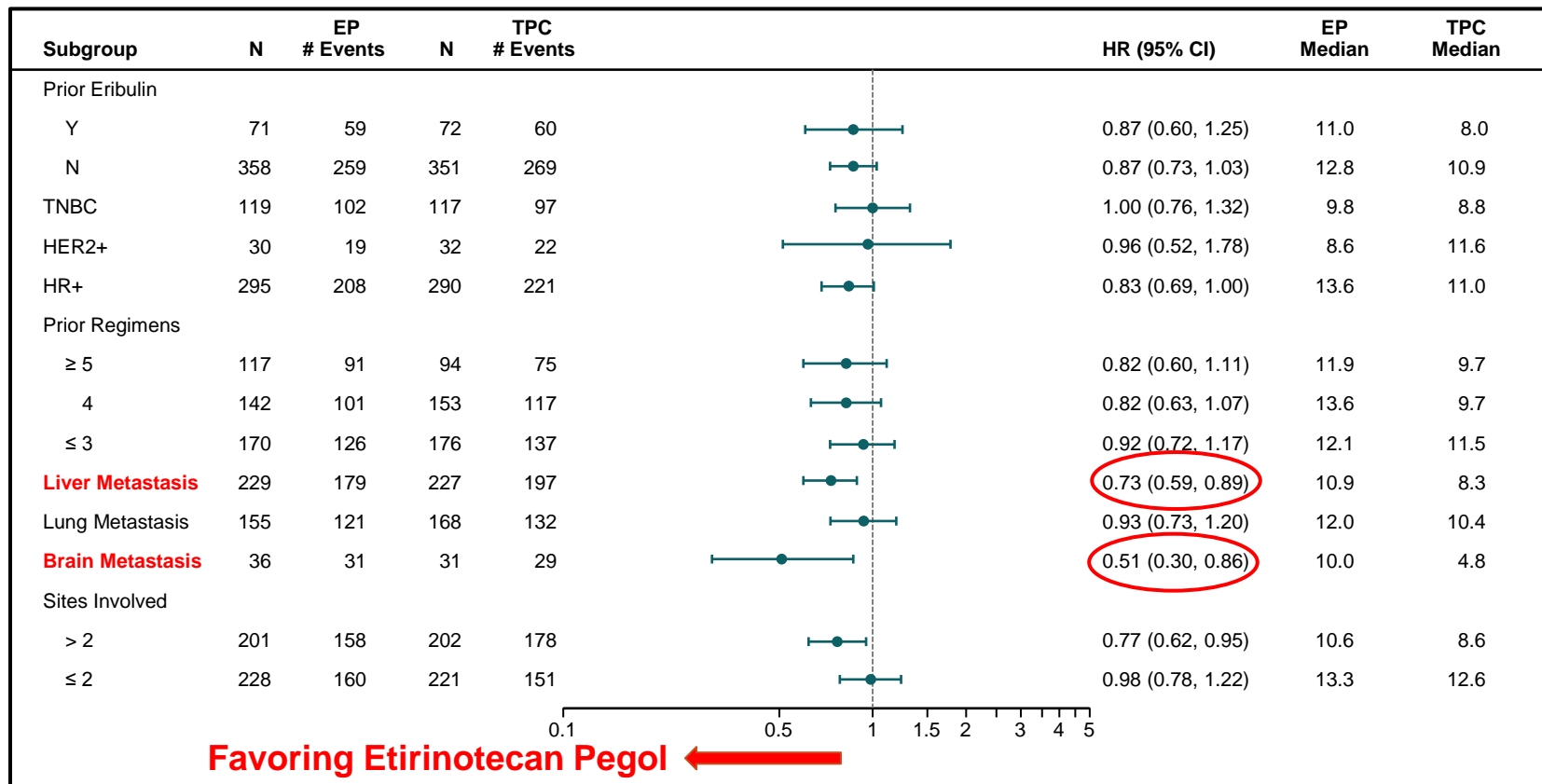
## **Safety and Quality of Life**

### **Circulating Tumor Cells Initial Results**

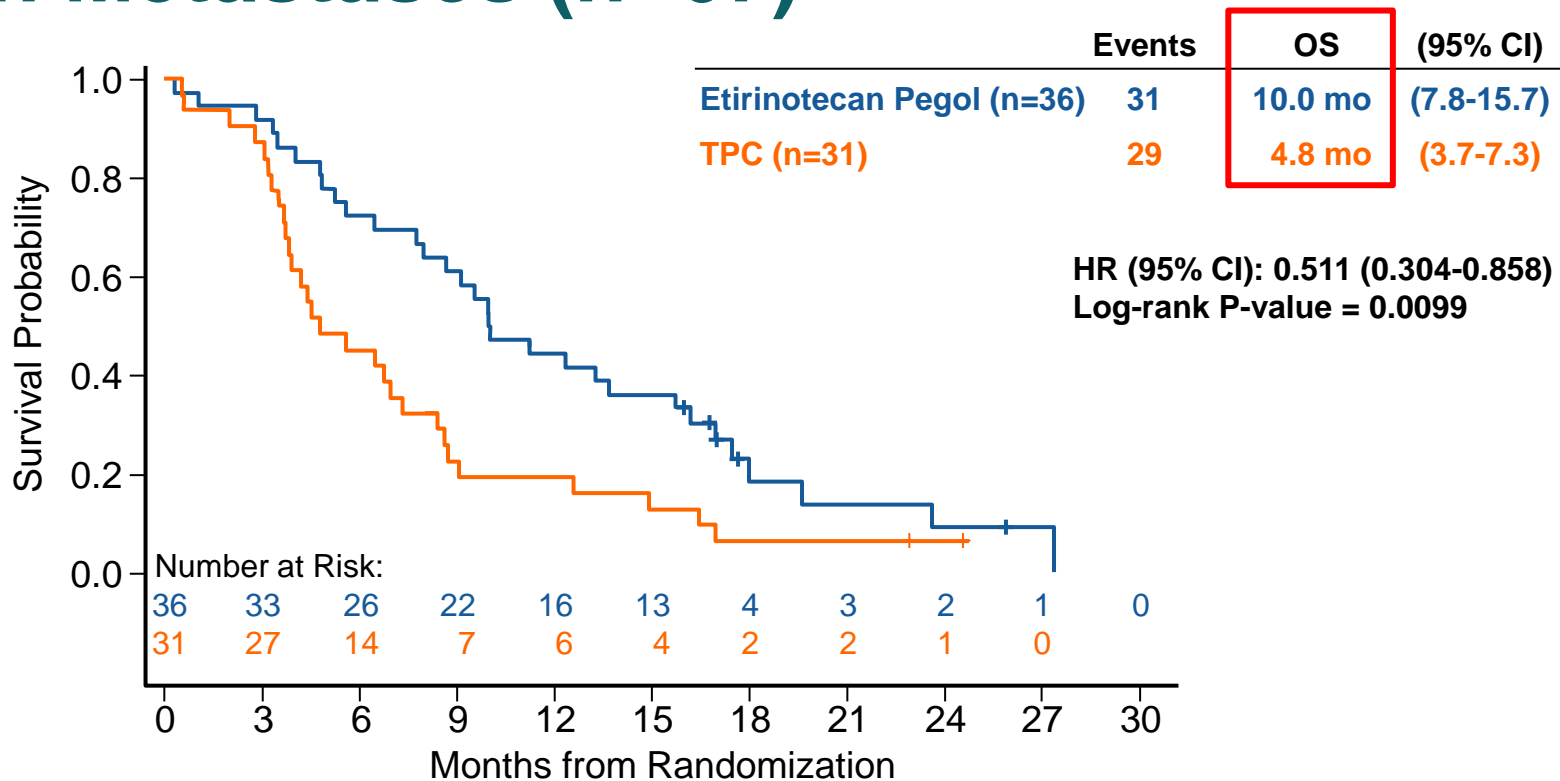
# Pre-planned OS Subgroup Analyses



# Pre-planned OS Subgroup Analyses

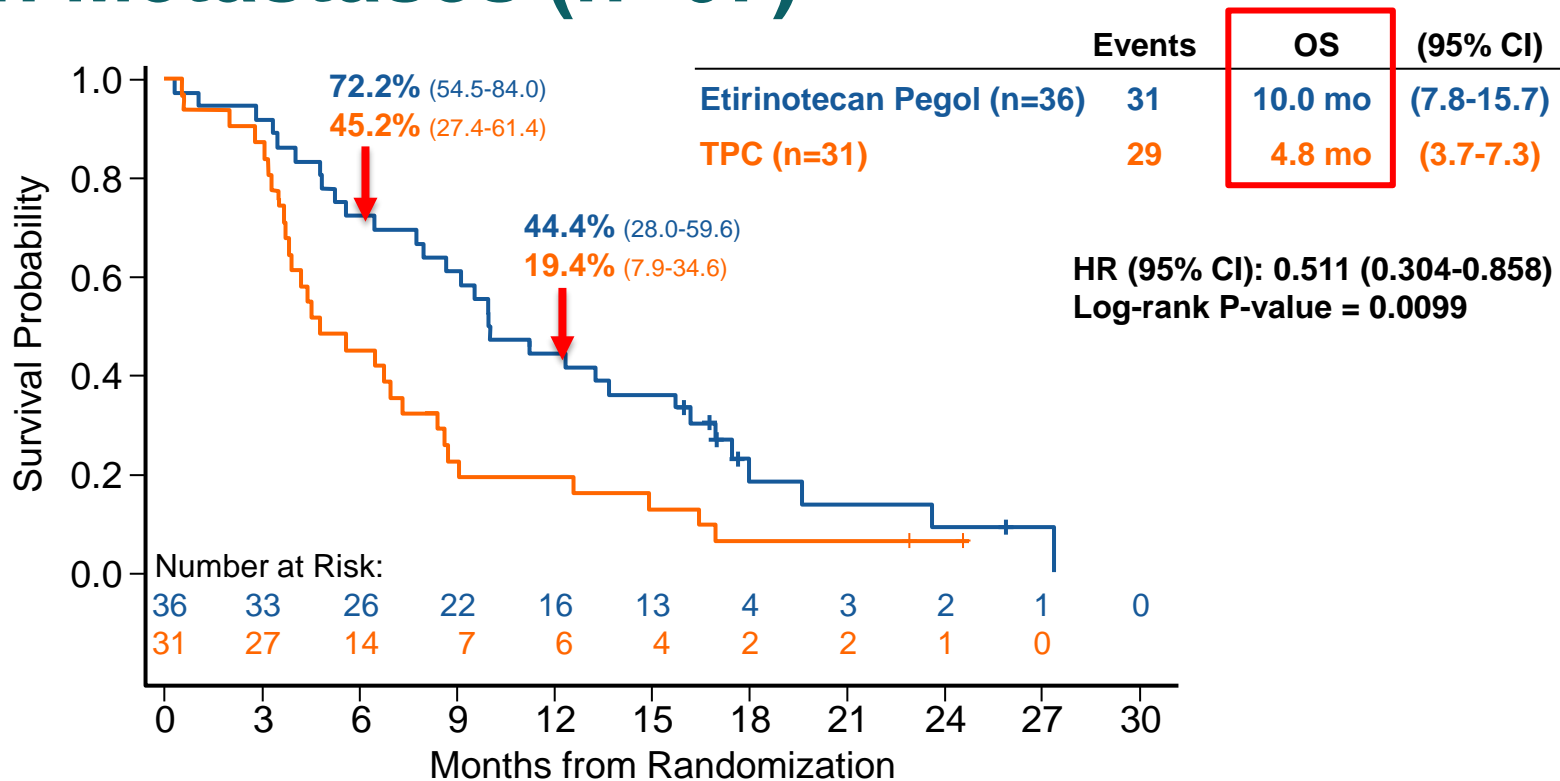


# Overall Survival in Patients With History of Brain Metastases (n=67)





# Overall Survival in Patients With History of Brain Metastases (n=67)



# Adverse Events: All Grades

All Grades (>5% Difference, Incidence > 20%)	Etirinotecan Pegol (n=425)	TPC (n=406)
<b>More Common on Etirinotecan Pegol</b>		
Diarrhea	66%	20%
Nausea	60%	38%
Vomiting	41%	19%
Decreased appetite	31%	24%
Abdominal pain	21%	12%
<b>More Common on TPC</b>		
Neutropenia <sup>1</sup>	26%	43%
Infections	31%	40%
Asthenia	22%	29%
Alopecia	10%	23%

<sup>1</sup>Neutropenia=neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic sepsis

# Adverse Events: Grade $\geq 3$

	Etirinotecan Pegol (n=425)		TPC (n=406)	
<b>Grade <math>\geq 3</math> Toxicity Regardless of Causality (<math>\geq 3\%</math> Difference)</b>	<b>48%</b>		<b>63%<sup>1</sup></b>	
<b>More Common on Etirinotecan Pegol</b>	<b>Grade 3</b>	<b>Grade 4</b>	<b>Grade 3</b>	<b>Grade 4</b>
Diarrhea	10%	0	1%	0
<b>More Common on TPC</b>				
Neutropenia <sup>2</sup>	8%	2%	20%	11%
Peripheral neuropathy <sup>3</sup>	<1%	<1%	4%	0

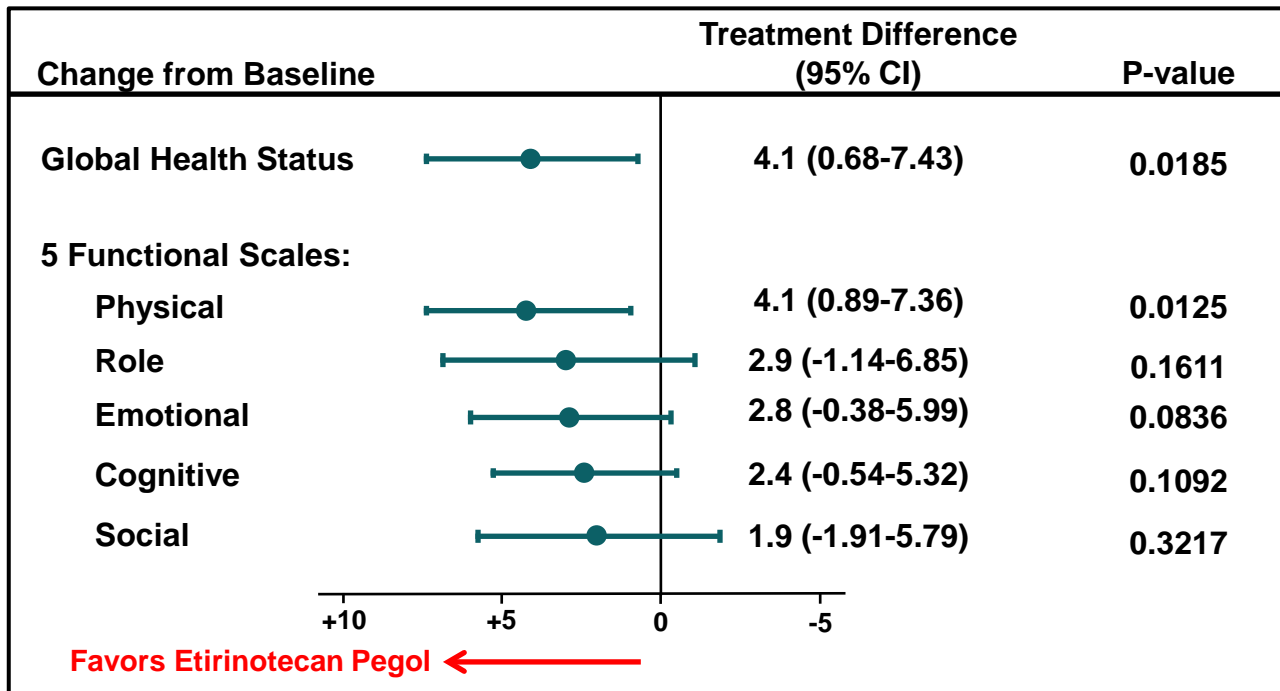
<sup>1</sup>P < 0.001

<sup>2</sup>Neutropenia=neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic sepsis

<sup>3</sup>Peripheral neuropathy is a combination of 12 Preferred Terms

# Health-Related Quality of Life (EORTC QLQ-C30<sup>1</sup>)

## Difference in Mean Scores Over 32 Weeks



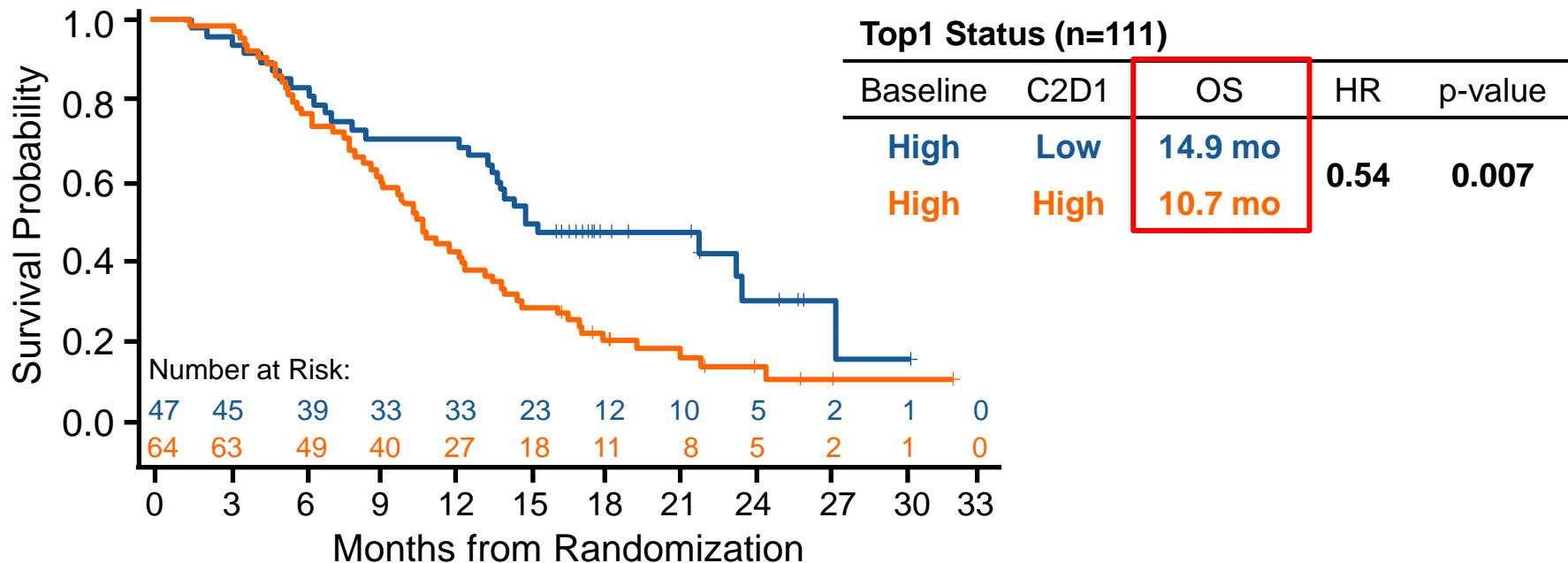
Estimated using a mixed-effects model repeated measures from baseline scores over 32 weeks

# Circulating Tumor Cells (CTCs)

- Biomarkers under evaluation include:
  - Topoisomerase 1 and 2
  - Marker of proliferation
  - Marker of apoptosis
  - Marker of double-stranded DNA breaks
  - Efflux transporter
- Analyzed at baseline and by change over time
- Most promising signal to date:
  - Change in number of topoisomerase 1 (Top1) positive CTCs (from high to low) over time

# Change in Top1 Positive CTCs Associated with Survival in Etirinotecan Pegol Arm

Classification of patients as Top1-high or Top1-low based on median number of Top1 positive CTCs at baseline



# Conclusions

- Etirinotecan Pegol is a novel topoisomerase 1 inhibitor with clinical activity and good tolerability in patients with heavily pretreated advanced breast cancer
- The 2.1 month improvement in median survival favoring Etirinotecan Pegol did not reach statistical significance
- Important survival results in pre-defined subgroups of patients deserve further study
  - History of brain metastases: 10.0 vs 4.8 months (HR=0.51;  $p<0.01$ )
  - History of liver metastases: 10.9 vs 8.3 months (HR=0.73;  $p=0.002$ )
- Etirinotecan Pegol has fewer grade  $\geq 3$  toxicities and improved quality of life compared to TPC
- Exploration of potential predictive biomarkers ongoing

# Acknowledgements

- All patients, their families and caregivers
- All co-investigators and research coordinators
- Data Monitoring Committee: Kathy Miller, Banu Arun, James Boyett

