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

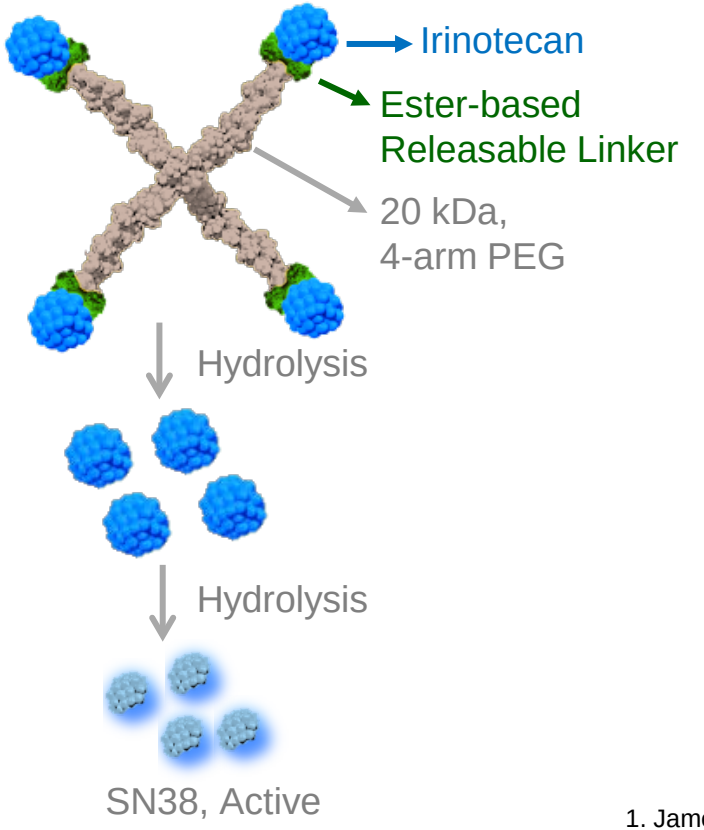
BREAST CANCER OUTCOMES WITH NKTR-102

PRESENTED AT: ASCO Annual '15 Meeting

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

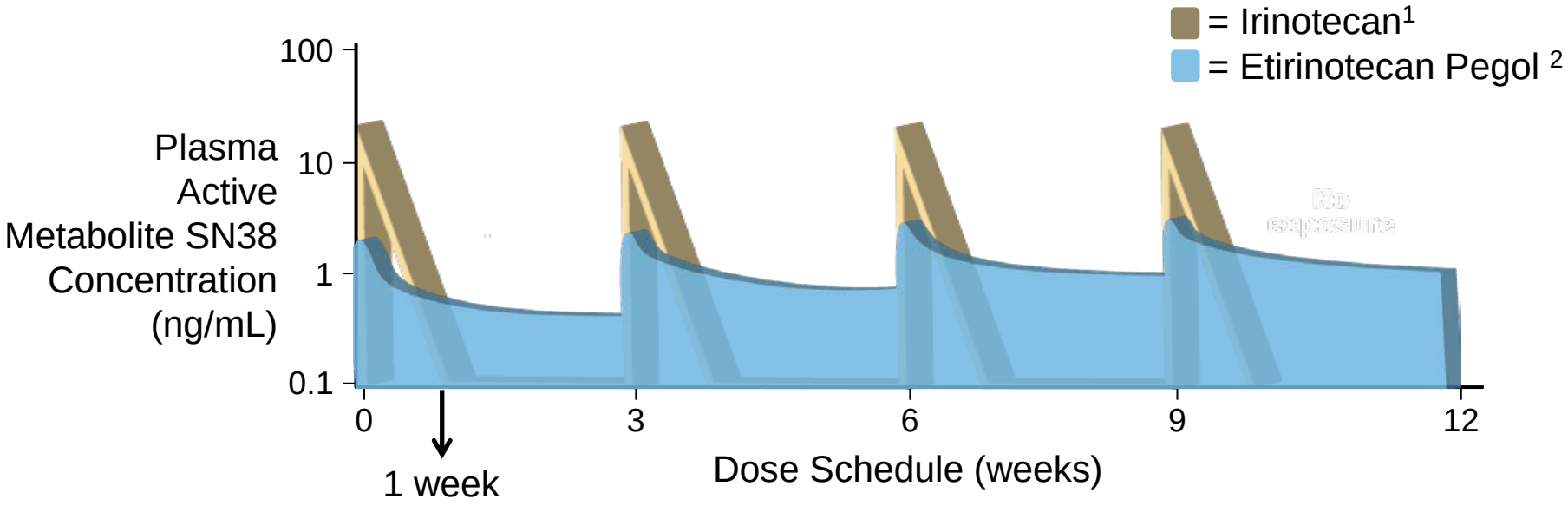


- Compared to irinotecan, Etirinotecan Pegol prolongs elimination half-life of SN38 from 2 days to 50 days in patients[1]
- Given its size, Etirinotecan Pegol escapes from leaky tumor vasculature, concentrating the active metabolite in tumor[2]
- In a murine model of brain metastases, Etirinotecan Pegol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

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[1]
  - 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^2 every 2 or 3 weeks[2]
- Etirinotecan Pegol every 3 weeks chosen as the schedule for phase 3 trials due to numerically superior activity/better tolerability

1. Jameson et al. *Clin Cancer Res.* 2013;19:268-78
2. Awada et al. *Lancet Oncol.* 14(12):1216-1225

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

R

Single-Agent Etirinotecan Pegol

145 mg/m^2 every 3 weeks

(n=429)

Single-Agent Treatment of Physician's Choice (TPC)

Docetaxel, eribulin, gemcitabine, ixabepilone, *nab*-paclitaxel, paclitaxel or vinorelbine

(n=423)

Primary Endpoint
- Overall Survival

Secondary Endpoints
- PFS, ORR, CBR, DoR, HRQoL

Exploratory Endpoints
- PD Markers in CTC, others

Stratification:
- Geographic region
- Prior eribulin use
- Receptor status

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%)

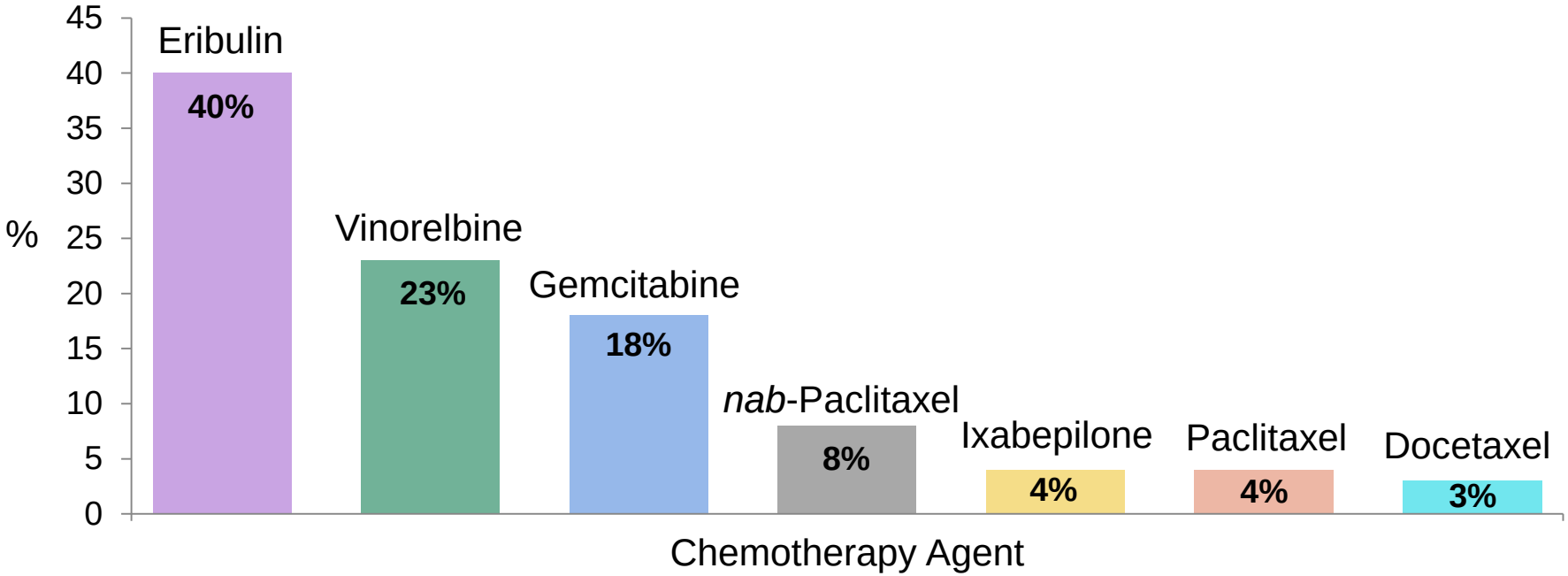
ECOG PS, Eastern Cooperative Oncology Group performance status; ABC, advanced breast cancer; TPC, treatment of physicians' choice.

Baseline Characteristics (cont'd)

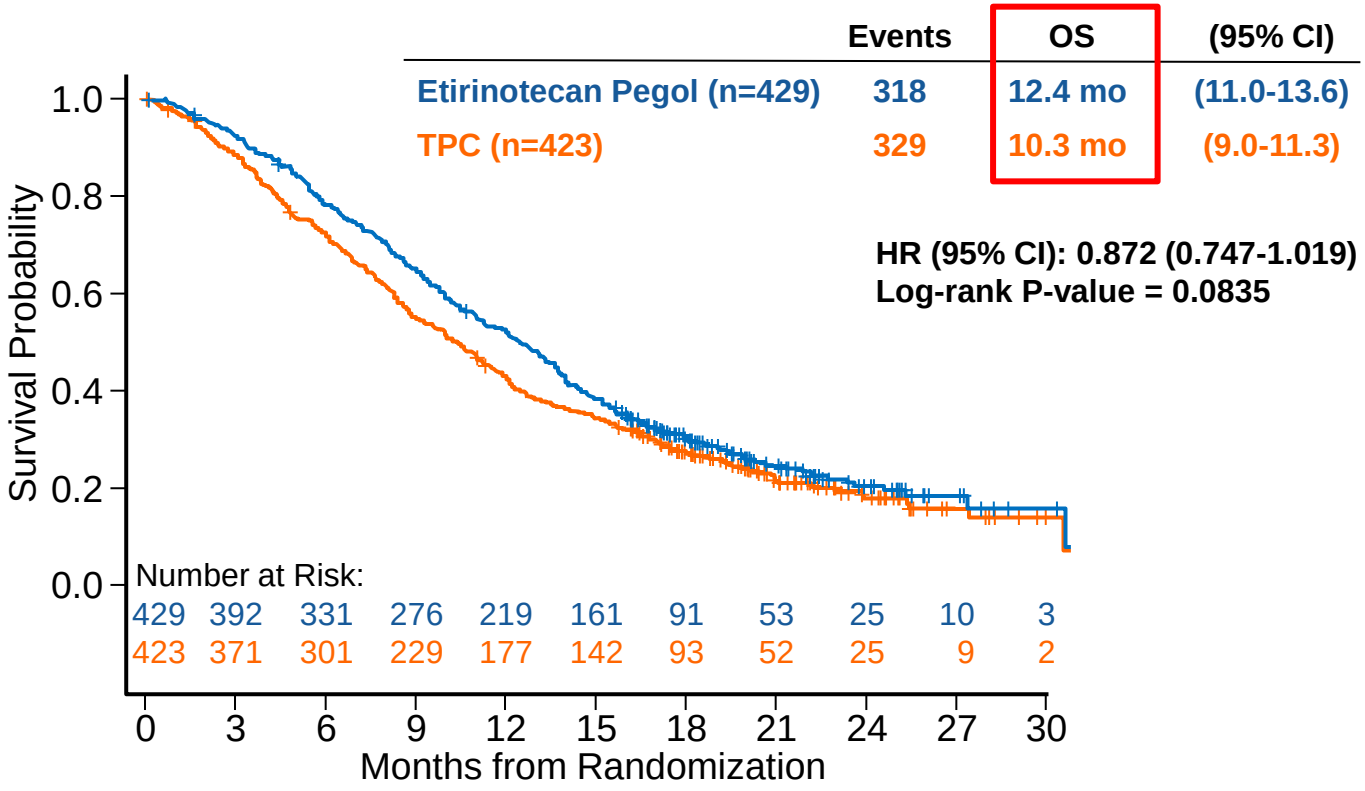
Characteristic	Etirinotecan Pegol (n=429)	TPC (n=423)
Receptor status (n, %)		
Hormone receptor positive	295 (69%)	290 (69%)
Triple negative	119 (28%)	117 (28%)
HER2 positive	30 (7%)	32 (8%)
Stage IV disease at initial diagnosis (n, %)	70 (16%)	75 (18%)
Visceral disease at enrollment (n, %)	319 (74%)	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)
Progression-free survival, median mo (95% CI)	**2.4** (2.1-3.5)	**2.8** (2.1-3.5)
Objective response rate, n (%)[1] (95% CI)	**58 (16%)** (12.7-20.7)	**61 (17%)** (13.3-21.3)
Duration of response, median mo[1] (95% CI)	**3.9** (3.5-5.1)	**3.7** (2.1-3.9)
Clinical benefit rate, n (%)[2] (95% CI)	**88 (21%)** (16.8-24.6)	**83 (20%)** (15.9-23.7)

Analyzed for patients with measurable disease by RECIST v1.1 at baseline
[1]In patients with measurable disease at baseline (n=354 [EP]; n=358 [TPC])
[2]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.

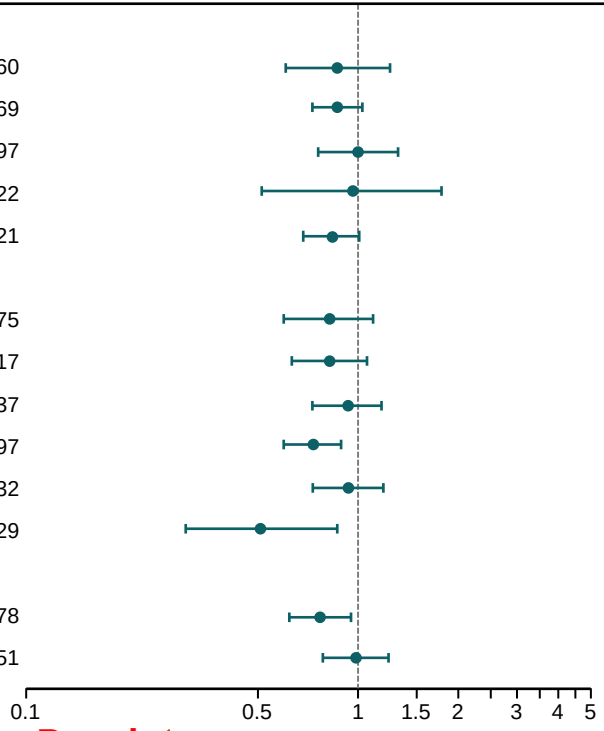
Pre-planned Subgroup Analyses

Safety and Quality of Life

Circulating Tumor Cells Initial Results

Pre-planned OS Subgroup Analyses

Subgroup	N	EP # Events	N	TPC # Events	HR (95% CI)	EP Median	TPC Median
Prior Eribulin							
Y	71	59	72	60	0.87 (0.60, 1.25)	11.0	8.0
N	358	259	351	269	0.87 (0.73, 1.03)	12.8	10.9
TNBC	119	102	117	97	1.00 (0.76, 1.32)	9.8	8.8
HER2+	30	19	32	22	0.96 (0.52, 1.78)	8.6	11.6
HR+	295	208	290	221	0.83 (0.69, 1.00)	13.6	11.0
Prior Regimens							
≥ 5	117	91	94	75	0.82 (0.60, 1.11)	11.9	9.7
4	142	101	153	117	0.82 (0.63, 1.07)	13.6	9.7
≤ 3	170	126	176	137	0.92 (0.72, 1.17)	12.1	11.5
Liver Metastasis	229	179	227	197	0.73 (0.59, 0.89)	10.9	8.3
Lung Metastasis	155	121	168	132	0.93 (0.73, 1.20)	12.0	10.4
Brain Metastasis	36	31	31	29	0.51 (0.30, 0.86)	10.0	4.8
Sites Involved							
> 2	201	158	202	178	0.77 (0.62, 0.95)	10.6	8.6
≤ 2	228	160	221	151	0.98 (0.78, 1.22)	13.3	12.6



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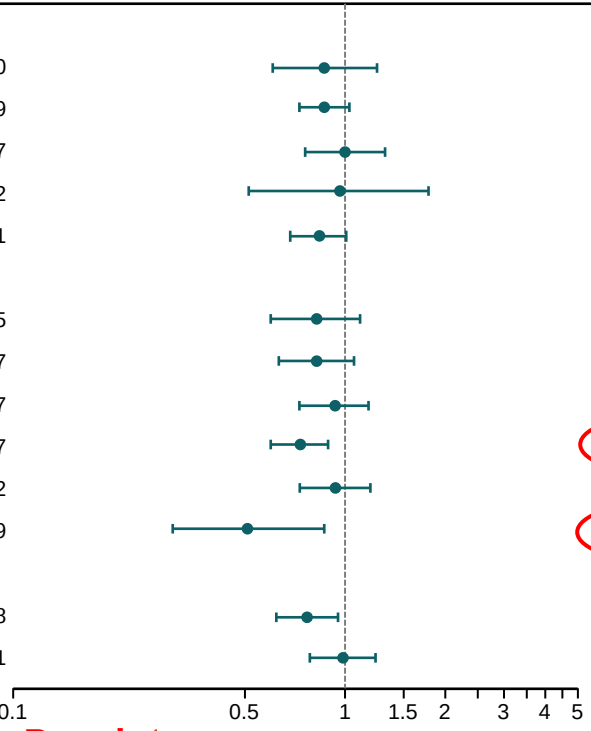
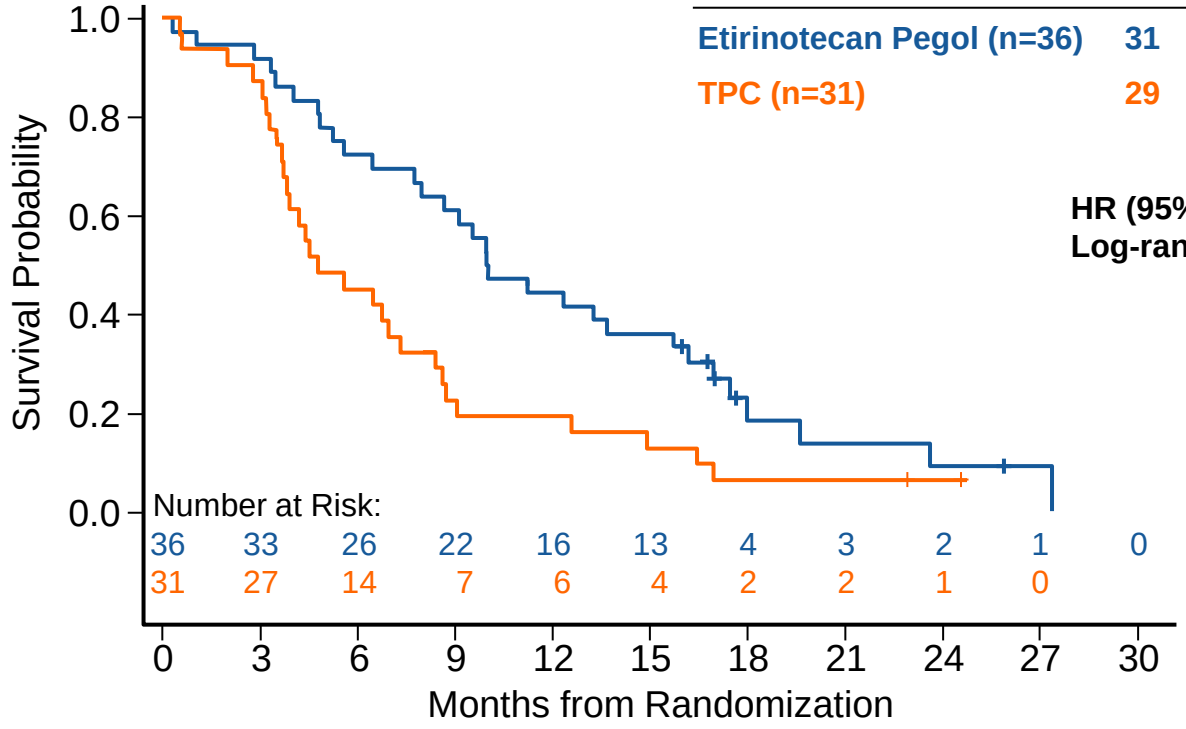


Overall Survival in Patients With History of Brain Metastases (n=67)

	Events	OS	(95% CI)
Etirinotecan Pegol (n=36)	31	10.0 mo	(7.8-15.7)
TPC (n=31)	29	4.8 mo	(3.7-7.3)

HR (95% CI): 0.511 (0.304-0.858)
Log-rank P-value = 0.0099



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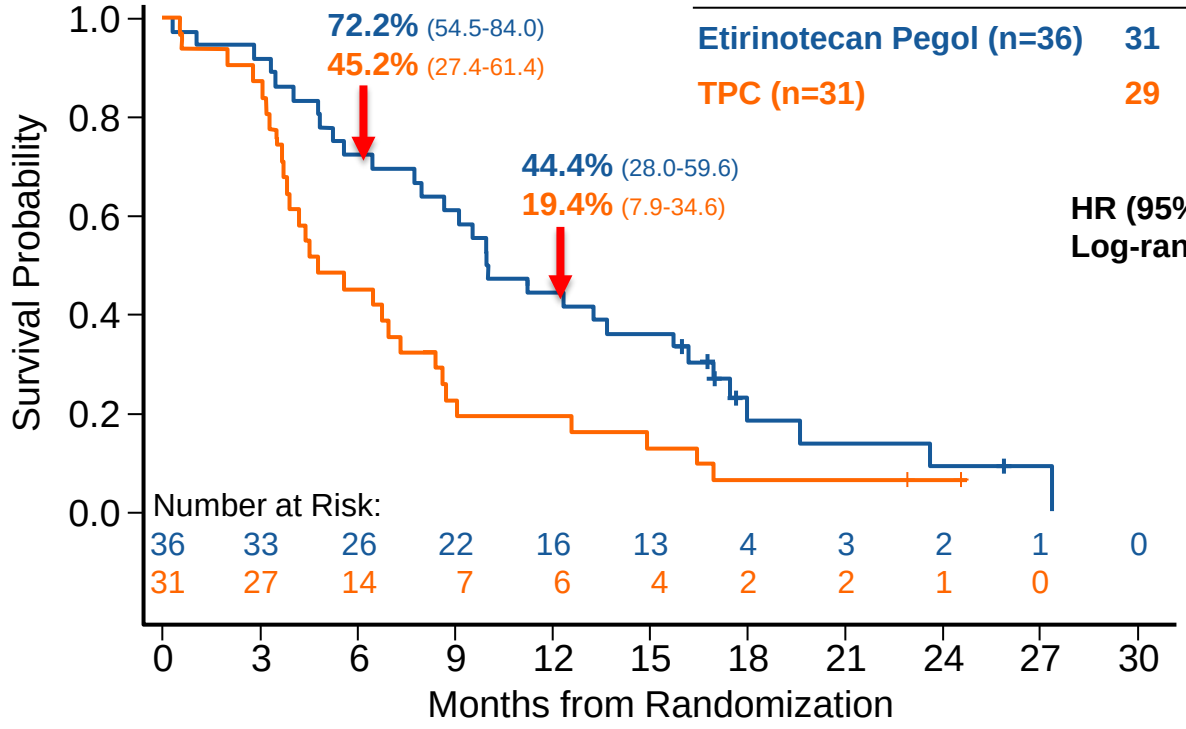

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Adverse Events: All Grades

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

[1]Neutropenia=neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic sepsis

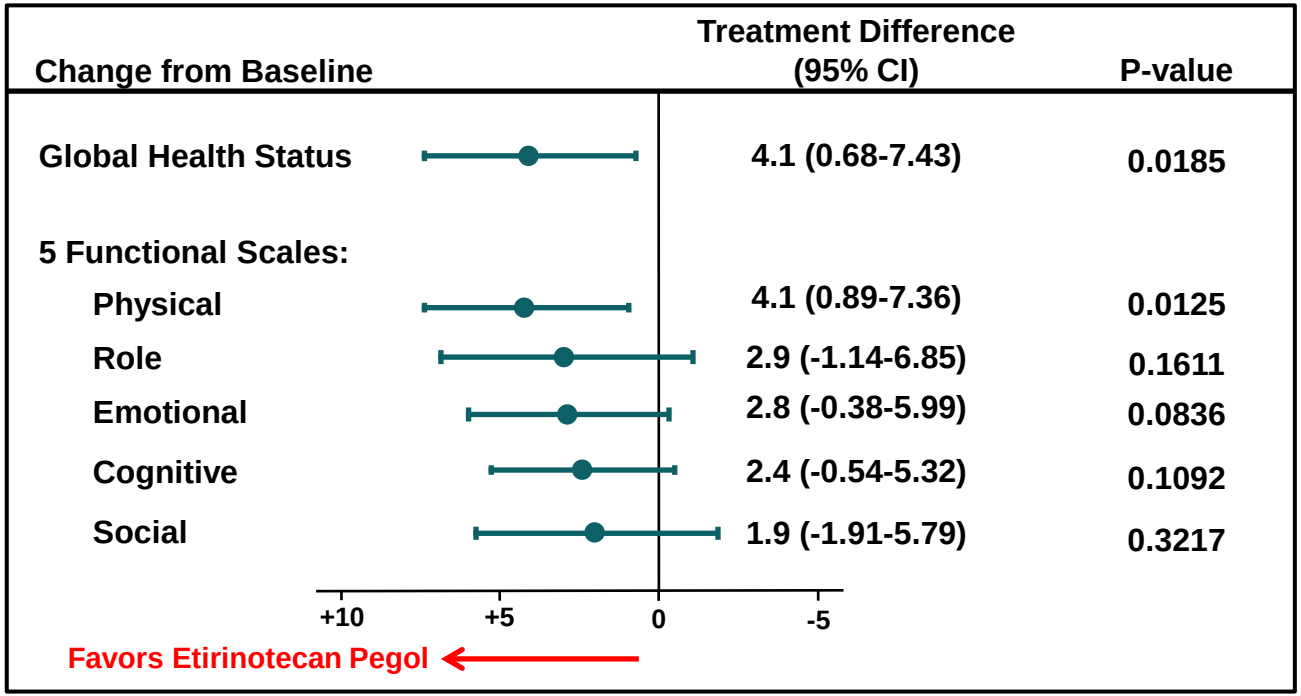
Adverse Events: Grade ≥ 3

	Etirinotecan Pegol (n=425)		TPC (n=406)	
Grade ≥ 3 Toxicity Regardless of Causality (≥ 3% Difference)	**48%**		**63%[1]**	
More Common on Etirinotecan Pegol	**Grade 3**	**Grade 4**	**Grade 3**	**Grade 4**
Diarrhea	10%	0	1%	0
More Common on TPC				
Neutropenia[2]	8%	2%	20%	11%
Peripheral neuropathy[3]	<1%	<1%	4%	0

[1]P < 0.001
[2]Neutropenia=neutropenia, neutrophil count decreased, febrile neutropenia, neutropenic sepsis
[3]Peripheral neuropathy is a combination of 12 Preferred Terms

Health-Related Quality of Life (EORTC QLQ-C30[1])

Difference in Mean Scores Over 32 Weeks



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

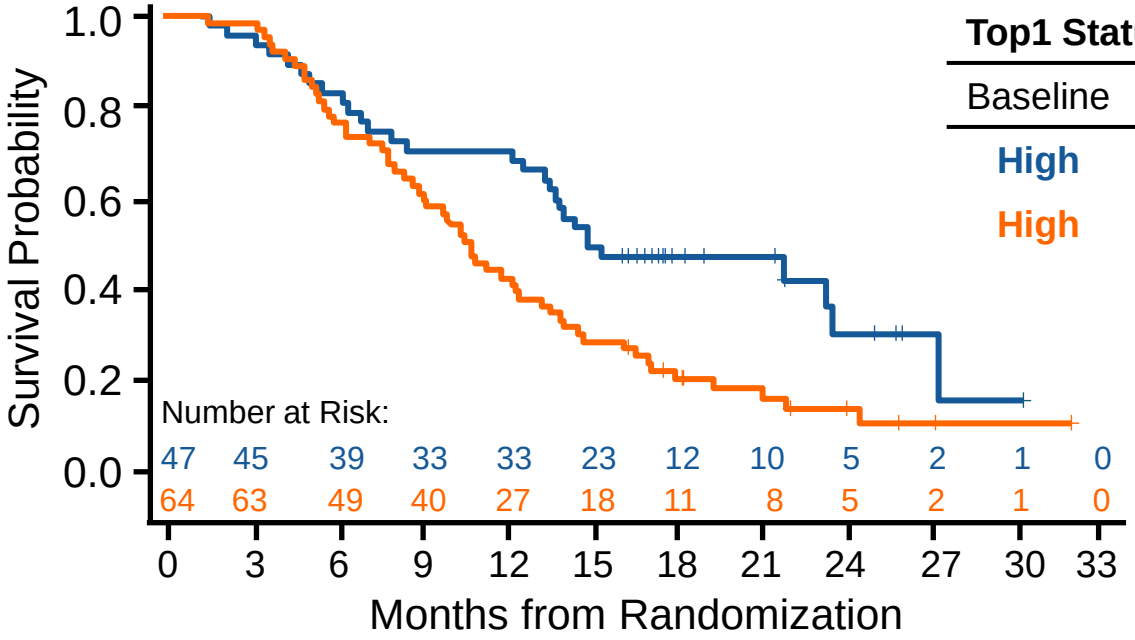
1. Fayers P, et al. EORTC Monograph. 1998.

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



Top1 Status (n=111)

Baseline	C2D1	OS	HR	p-value
High	Low	14.9 mo	0.54	0.007
High	High	10.7 mo		

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 ≥ 3 toxicities and improved quality of life compared to TPC
- Exploration of potential predictive biomarkers ongoing

Acknowledgements

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- Data Monitoring Committee: Kathy Miller, Banu Arun, James Boyett