Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods.

Procedures

Tumor assessments, including contrast-enhanced computed tomographic and/or magnetic resonance imaging scans and/or digital photography were performed at screening, every 8 weeks through week 24, and every 12 weeks until disease progression or death. Positron emission tomography-computed tomography (CT) may have also been obtained, but only CT data were used to determine response and/or progression by Response Evaluation Criteria in Solid Tumors. Serial blood samples for biomarker analysis were obtained prior to Cycle 1 and 2, and at the end of treatment.

Adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events. Patients randomized to etirinotecan pegol (EP) received loperamide for the treatment of diarrhea and/or prophylaxis starting at Cycle 1 at the discretion of the investigator to mitigate the risk of late-onset diarrhea. The use of prophylactic growth factor therapy was permitted for \geq Grade 2 neutropenia.

Patients completed health-related quality of life (HRQoL) assessments at screening, prior to administration on Day 1 of each cycle, and at the end of treatment. Patient-reported outcomes were measured using the European Organisation for Research and Treatment of Cancer (EORTC; version 3.0) Quality of Life Core 30 (QLQ-C30) with the brain neoplasms 20-question (BN-20) subscale (Taphoorn MJB, et al. *Eur J Cancer*. 2010;46(6):1033-1040) the EuroQol 5D (EQ-5D-5L), questionnaire (EuroQol Group. *Health Policy*. 1990;16(3):199-208) and the Brief Fatigue Inventory (BFI) (Mendoza et al. *Cancer*. 1999;85(5):1186-1196).

Statistical Analysis

The study was originally planned to have a sample size of 350 patients, with a maximum number of death events of 260. Based on results from the BEACON study, a protocol amendment was made that reduced the required sample size to 220 patients, the conditional power to 80%, and the maximum number of death events to 191 for the final analysis. The study was powered to detect a hazard ratio (HR) of 0.75 or better, at a two-sided significance level of 0.05. An adaptive design powered for detecting superiority of EP was utilized for the primary endpoint of overall survival (OS), whereby a pre-specified interim analysis (data cut-off: July 15, 2019) after 91 death events generated a minimum number of death events required of 106 using the promising zone adaptive method.

OS was assessed using the Cui, Hung, and Wang test with pre-specified weights to ensure type I error control; the conventional test with equal weights for each patient was conducted as a sensitivity analysis. Progression-free survival (PFS) was analyzed using a two-sided, log-rank test (with the use of stratification factors). OS and PFS were summarized using Kaplan-Meier methods, and the HR and its 95% confidence interval were calculated using a Cox proportional hazards model adjusting for stratification factors.

Objective response rate was analyzed using Fisher's exact test. Clinical benefit rate was compared between groups using a Cochran Mantel-Haenszel test stratified by the randomization factors. The Clopper Pearson exact method was used to calculate two-sided 95% confidence limits.

For HRQoL measures, summary statistics of absolute scores at each assessment point and changes from baseline were calculated by treatment group for each subscale.

Statistical analyses were performed with SAS® Proprietary Software 9.4 (TS1M4).

Survival analysis, ITT population ^a	Etirinotecan-pegol (n=92)	Physician's choice chemotherapy (n=86)
Progression-free survival		
Non-CNS metastases, median months	3.9	2.1
HR (95% CI), <i>P</i> value	0.73 (0.45-	–1.19), .20
3-month PFS rate, %	55.3	43.9
6-month PFS rate, %	34.8	19.3
CNS metastases, median months	5.1	3.7
HR (95% CI), <i>P</i> value	0.71 (0.36-	–1.39), .31
3-month PFS rate, %	68.8	56.3
6-month PFS rate, %	31.2	44.8
CNS + non-CNS metastases, median months	2.1	1.9
HR (95% CI), <i>P</i> value	0.62 (0.40	-0.96), .03
3-month PFS rate, %	48.1	29.0
6-month PFS rate, %	20.4	7.1
Response analysis, evaluable population ^b	(n=83)	(n=73)
Non-CNS metastases, n (%)		
Objective response	6 (7.2)	6 (8.2)
95% CI	2.7–15.1	3.1–17.0
CR	0	0
PR	6 (7.2)	6 (8.2)
SD	32 (38.6)	17 (23.3)
PD	34 (41.0)	30 (41.1)
Not evaluable ^c	11 (13.3)	20 (27.4)
Missing	0	0
CNS metastases, n (%)		
Objective response	0	1 (1.4)
95% CI	0.0–4.3	0.0–7.4
CR	0	1 (1.4)
PR	0	0
SD	44 (53.0)	26 (35.6)
PD	16 (19.3)	14 (19.2)
Not evaluable ^c	23 (27.7)	32 (43.8)
Missing	0	0
CBR ^d (non-CNS metastases), %	25.0	12.8
CBR ^d (CNS metastases), %	15.2	9.3
Duration of response (non-CNS metastases), median months	26.5	9.2

eTable 1. Summary of PFS and Response by Investigator Assessment

Abbreviations: BM, brain metastases; CBR, clinical benefit rate; CI, confidence interval; CNS, central nervous system; CR, complete response; HR, hazard ratio; ITT, intent-to-treat; NR, not reported; OS, overall survival; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

^aThe ITT population included all patients who were randomized in the study.

^bThe response-evaluable population included patients who had measurable disease in the periphery by RECIST v1.1 at baseline.

^bIn the response-evaluable population, patients who did not have a post-baseline tumor response assessment were counted as not evaluable.

^dThe denominator is the ITT population.

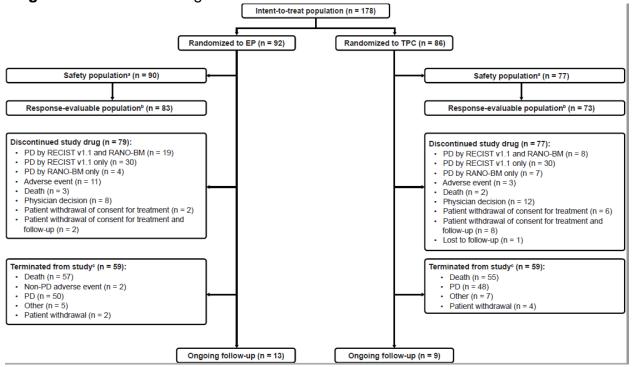
eTable 2. Patient-Reported Outcomes

	Mean baseline scores (standard deviation)		Baseline to end		
	Etirinotecan- pegol (n=79)	Physician's choice chemotherapy (n=63)	of treatment difference 95 using MMRM, LS mean (SE)	95% CI	
EORTC QLQ-C30 global health status and functional domains					
Global health status	57.6 (21.6)	52.3 (24.2)	-1.4 (3.0)	-7.4, 4.6	
Physical functioning	71.9 (19.5)†	65.7 (28.4)	-2.7 (2.7)	-8.1, 2.6	
Role functioning	64.4 (28.7)†	59.7 (34.7)‡	-0.7 (3.8)	-8.1, 6.8	
Emotional functioning	73.5 (22.3)	71.8 (25.9)	-3.2 (2.9)	-9.0, 2.5	
Cognitive functioning	77.0 (25.6)	78.0 (23.2)	0.8 (3.3)	-5.8, 7.4	
Social functioning	65.0 (30.8)	66.1 (30.2)	-3.6 (3.9)	-11.2, 4.1	
EORTC QLQ-C30 symptom scales					
Fatigue	4.2 (2.3)	4.0 (2.4) [‡]	0.1 (3.3)	-6.4, 6.6	
Nausea and vomiting	13.3 (19.9)†	12.7 (21.7)	6.1 (2.8)	0.5, 11.6	
Pain	31.9 (28.6)†	39.2 (36.4)	-4.6 (3.5)	-11.4, 2.3	
EuroQoL 5D	61.4 (19.7)†	60.3 (23.0)	-0.2 (2.2)	-4.5, 4.2	
BFI	4.2 (2.3)	4.0 (2.4)	-0.2 (0.3)	-0.8, 0.3	

EORTC QLQ-C30 and EuroQoL 5D raw scores were transformed to a linear scale ranging from 0 to 100, with a higher score representing a higher level of functioning or higher level of symptoms. For symptom scales, negative values favor etirinotecan-pegol and positive values favor chemotherapy. For BFI, response options range from 0–10 with higher scores correspond to greater self-reported levels of fatigue. $^{\dagger}n = 80. ^{\ddagger}n = 62.$

BFI, Brief Fatigue Inventory; CI, confidence interval; EORTC QLQ-C30, European Organisation for Treatment of Cancer Quality of Life Core 30 questionnaire; LS, least squares; MMRM, mixed model for repeated measures; SE, standard error.

eFigure 1. CONSORT Diagram



Abbreviations: EPC, etirinotecan-pegol; PD, progressive disease; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumors; TPC, treatment of physicians' choice.

aThe safety population consisted of all randomized patients that received at least one dose of study treatment (n=167); n=11 patients did not receive study treatment (n=2 for etirinotecan-pegol and n=9 for chemotherapy).

^bThe response-evaluable population included all randomized patients that received at least one dose of study treatment and had measurable disease in the periphery by RECIST v1.1 at baseline (n=156); compared with the safety population n=7 patients for etirinotecan-pegol and n=4 patients for chemotherapy did not have measurable disease in the periphery at baseline.

^cStudy therapy was terminated for the following protocol-defined reasons: disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and/or Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria, unacceptable toxicity, death, investigator decision to discontinue treatment, patient withdrawal of consent, non-compliance, pregnancy, loss to follow-up, or study termination by the sponsor.

eFigure 2. Overall Survival by Subgroup

Subgroup		N	Hazard Ratio	86% CI
PR receptor status				
PR Positive PR Negative	⊢• <u>↓</u> ·	82 91	0.830	0.479-1.439
Number of prior regimens		31	0.550	0.36/-1.613
24		159	0.742	0.502-1.098
s3 Number of lesions	•	19	4.937	1.257-19.390
24	⊢	38	1.006	0.443-2.285
<4	` ⊢ ∎∔⊣ `	116	0.780	0.492-1.237
Time since local therapy for BCBM >3 months		90	1.257	0.739-2.137
≤3 months		87	0.655	0.385-1.113
>28 days		127	1.119	0.720-1.739
≤28 days Initial progression-free Interval		50	0.447	0.210-0.948
≥2 years	L	14	0.878	0.177-4.369
<2 years		162	0.883	0.602-1.295
initial dicease-free interval >2 years		115	0.882	0.560-1.389
≤2 years		61	0.925	0.475-1.802
HER2 status				
HER2 Positive HER2 Negative		29 142	1.030	0.371-2.858
GPA soore		142	0.004	0.500-1.320
2.5-4		97	0.689	0.409-1.160
0-2	⊢ ●	81	1.232	0.716-2.117
ER receptor status ER Positive		101	0.802	0.492-1.307
ER Negative		74	1.040	0.581-1.859
ECOG P8				
1		128 50	0.919 0.897	0.599-1.412
Country		50	0.657	0.420-1.005
US		85	0.790	0.452-1.379
France		16	0.920	0.254-3.323
Spain Belgium		21 17	1.496	0.509-4.400
Age	-		1.277	0.310-3.140
≥65 years		29	0.733	0.302-1.780
<65 years Tumor receptor status		149	0.924	0.611-1.398
TNBC		71	1.072	0.596-1,928
HR+HER2		79	0.743	0.423-1.303
HER2+		28	0.862	0.330-2.251
Time since diagnosis of LR/MBC >2 years		61	0.582	0.307-1.105
Time since initial BC diagnosis				
>6 months		109	1.087	0.663-1.784
s5 months Time since diagnosis of BCBM		69	0.677	0.383-1.195
>4 years	⊢	129	0.752	0.486-1.162
s4 years	► -	49	1.527	0.742-3.142
Treatment with steroids Yes		114	0.818	0.520-1.286
No		64	0.790	0.382-1.634
Region				
US		85	0.790	0.452-1.379
ROW Race		93	1.005	0.609-1.658
White		123	0.792	0.510-1.228
Not Reported	i → • · · · · · · · · · · · · · · · · · ·	38	1.043	0.449-2.425
Prior treatement with WBRT Yes		88	0.736	0.450-1.204
No		90	0.991	0.547-1.796
Prior treatment with stereotactic radiosurgery				
Yes		101	0.946	0.553-1.617
No Number of prior tumor sites		77	0.885	0.528-1.484
23		150	0.721	0.484-1.077
≤2	•	28	2.522	0.857-7.425
Prior lung or liver metastases Lung Yes		98	0.811	0.482-1.364
Lung No		80	1.013	0.590-1.741
Liver Yes	iiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiiii	110	0.836	0.534-1.309
Liver No Delay frantiscant with hormonal therapy		68	0.866	0.444-1.685
Prior treatment with hormonal therapy Yes		100	0.766	0.466-1.260
No		78	1.127	0.642-1.978
Prior treatment with eribuiin				
Yes No		75 103	0.823	0.479-1.413
NO Prior brain metastases		103	0.992	0.535-1.655
Yes		154	0.883	0.595-1.311
No	⊢ ⊢ • • • • • • • • • • • • • • • • • • •	24	1.373	0.430-4.389
0				
	Hazard Ratio (86% CI)			
	Favors EP Favors TPC			
	- Teres Percento			

BC, breast cancer; BCBM, breast cancer with brain metastases; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ER, estrogen receptor; GPA, Graded Prognostic Assessment; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LR, local recurrence; MBC, metastatic breast cancer; PR, progesterone receptor; ROW, rest of world; TNBC, triple-negative breast cancer; WBRT, whole-brain radiotherapy.

eFigure 3. Progression-Free Survival	(CNS + Non-CNS metastases) by Subgroup

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Subgroup			N	Hazard Ratio	96% CI
PR receptor status PR Positive			82	0.741	0.390-1.408
PR Negative			91	0.762	0.414-1.400
Number of prior regimens 24			159	0.686	0.430-1.094
s3			19	1.419	0.379-5.314
Number of legions 24			38	0.870	0.350-2.160
e4	i • • • • •		116	0.618	0.356-1.074
Time since local therapy BCBM >3 months			90	1.263	0.682-2.342
≥3 months			87	0.415	0.212-0.813
>28 days ≤28 days			127 50	1.019 0.343	0.603-1.720 0.146-0.830
initial progression-free interval ≥2 years			14	1.960	0.173-22.224
<2 years	' F •		162	0.721	0.461-1.126
initial disease-free Interval >2 years			115	0.775	0.449-1.339
≤2 years			61	0.688	0.320-1.477
HER2 status Unknown			7	6.19E11	0.000
HER2 Positive	+ · · ·		29 142	1.022 0.709	0.309-3.382 0.434-1.157
HER2 Negative GPA soore					
2.5-4 0-2			97 81	0.536	0.291-0.985 0.571-2.154
ER receptor status					
ER Positive ER Negative			101 74	0.856 0.652	0.485-1.512 0.324-1.314
ECOG P8					
1			128 50	0.887 0.640	0.523-1.503 0.289-1.417
Country					
US Portugal	• • • • •		85 6	0.615	0.321-1.180 0.000
Italy Israel	+		6 7	1.137 0.354	0.097-13.269 0.021-5.893
United Kingdom	•		5	2.398E11	0.000
France Spain	· · · · · · · · · · · · · · · · · · ·		16 21	2.646 0.506	0.618-11.339 0.128-1.995
Belgium	· · · · · · · · · · · · · · · · · · ·		17	0.524	0.086-3.181
Australia Age			13	0.461	0.041-5.151
a65 years <65 years			29 149	0.771	0.235-2.533 0.470-1.225
Tumor receptor status					
TNBC HR+HER2			71 79	0.668	0.334-1.338 0.433-1.801
HER2+	· · · · ·		28	0.586	0.183-1.873
Time since diagnosis of LR/MBC >2 years			61	0.655	0.291-1.471
≤2 years	+ + +		9	0.527	0.058-4.757
Time since initial BC diagnosis >4 years	⊢ ∎–		129	0.741	0.439-1.253
s4 years Time since diagnosis of BCSM	+ +		49	0.952	0.416-2.176
>6 months			109	0.840	0.482-1.464
s5 months Treatment with sterolds			69	0.574	0.272-1.209
Yes No			114 64	0.702	0.405-1.218
Region				0.733	0.331-1.621
US ROW			85 93	0.615	0.321-1.180 0.546-1.862
Race					
White Not Reported			123 38	0.560	0.315-0.994 0.615-4.003
Black or African American Asian			8 9	1.6922E8 0.823	0.000 0.135-5.006
Prior treatment with WBRT					
Yes No			88 90	0.509	0.263-0.985 0.576-1.984
Prior treatment with stereotactic radiosurgery					
Yes No			101 77	0.778	0.450-1.345 0.383-1.645
Number of prior tumor sites ≥3			150	0.707	0.445-1.124
s2			28	0.848	0.160-4.493
Prior lung or liver metastases Lung Yes			98	0.933	0.517-1.683
Lung No			80	0.569	0.287-1.130
Liver Yes Liver No			110 68	0.813 0.514	0.466-1.417 0.239-1.106
Prior treatment with hormonal therapy			100	0.757	0.425-1.348
Yes No			78	0.794	0.402-1.568
Prior treatment with eribulin Yes			75	0.478	0.228-1.003
No	· · · ·		103	0.944	0.539-1.653
Prior brain metastases Yes			154	0.696	0.440-1.103
No	+		24	1.772	0.395-7.942
	1 2	3 4 5			
	Hazard Ratio (9				
	Favors EP	Favors TPC			
	FORME EF	reture IPU			

BC, breast cancer; BCBM, breast cancer with brain metastases; CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group Performance Status; ER, estrogen receptor; GPA, Graded Prognostic Assessment; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; LR, local recurrence; MBC, metastatic breast cancer; PR, progesterone receptor; ROW, rest of world; TNBC, triple-negative breast cancer; WBRT, whole-brain radiotherapy.