Supplemental Online Content

Tripathy D, Tolaney SM, Seidman AD, et al; ATTAIN Investigators. Treatment with etirinotecan pegol for patients with metastatic breast cancer and brain metastases: final results from the phase 3 ATTAIN randomized clinical trial. *JAMA Oncol*. Published online May 12, 2022. doi:10.1001/jamaoncol.2022.0514

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 ≥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).

eTable 1. Summary of PFS and Response by Investigator Assessment

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), *P* 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), *P* 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), *P* 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

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.

[a]The ITT population included all patients who were randomized in the study.

[b]The response-evaluable population included patients who had measurable disease in the periphery by RECIST v1.1 at baseline.

[b]In the response-evaluable population, patients who did not have a post-baseline tumor response assessment were counted as not evaluable.

[d]The denominator is the ITT population.

eTable 2. Patient-Reported Outcomes

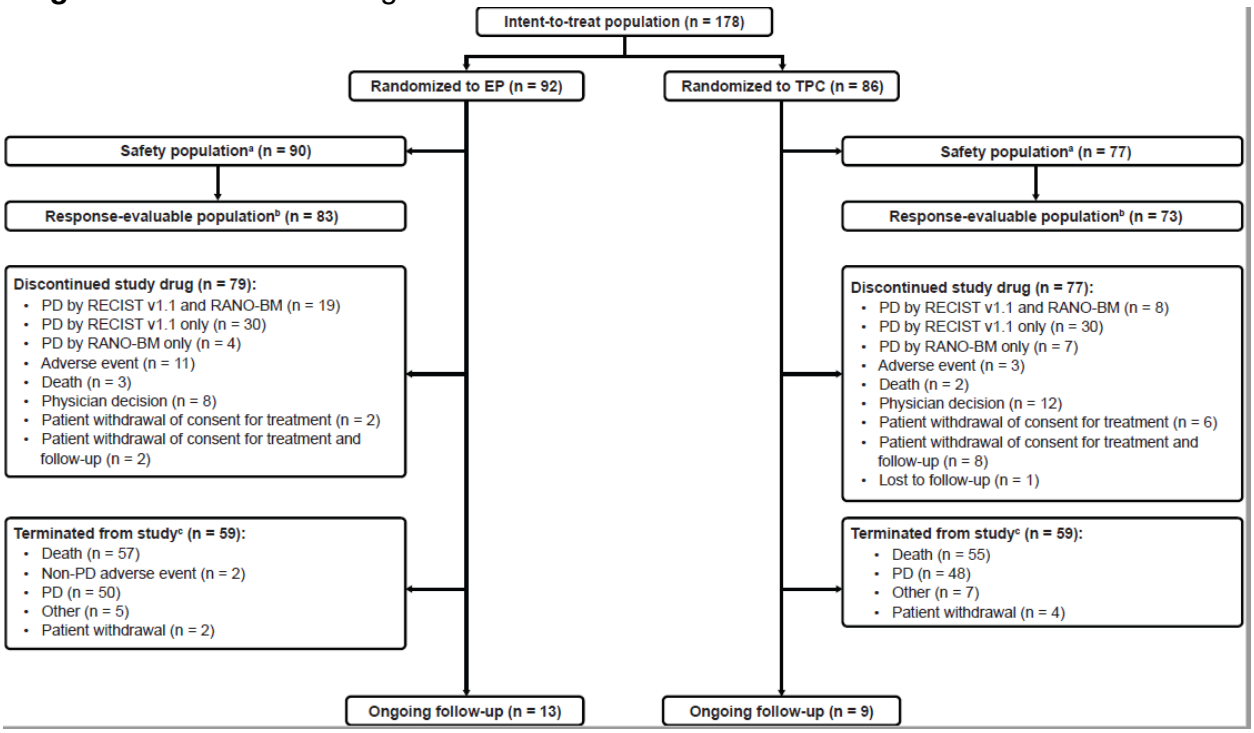
	Mean baseline scores (standard deviation)		Baseline to end of treatment difference using MMRM, LS mean (SE)	95% CI
	Etirinotecan-pegol (n=79)	Physician's choice chemotherapy (n=63)		
EORTC QLQ-C30 global health status and functional domains				
Global health status	57.6 (21.6)	52.3 (24.2)	–1.4 (3.0)	–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.

†n = 80. ‡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



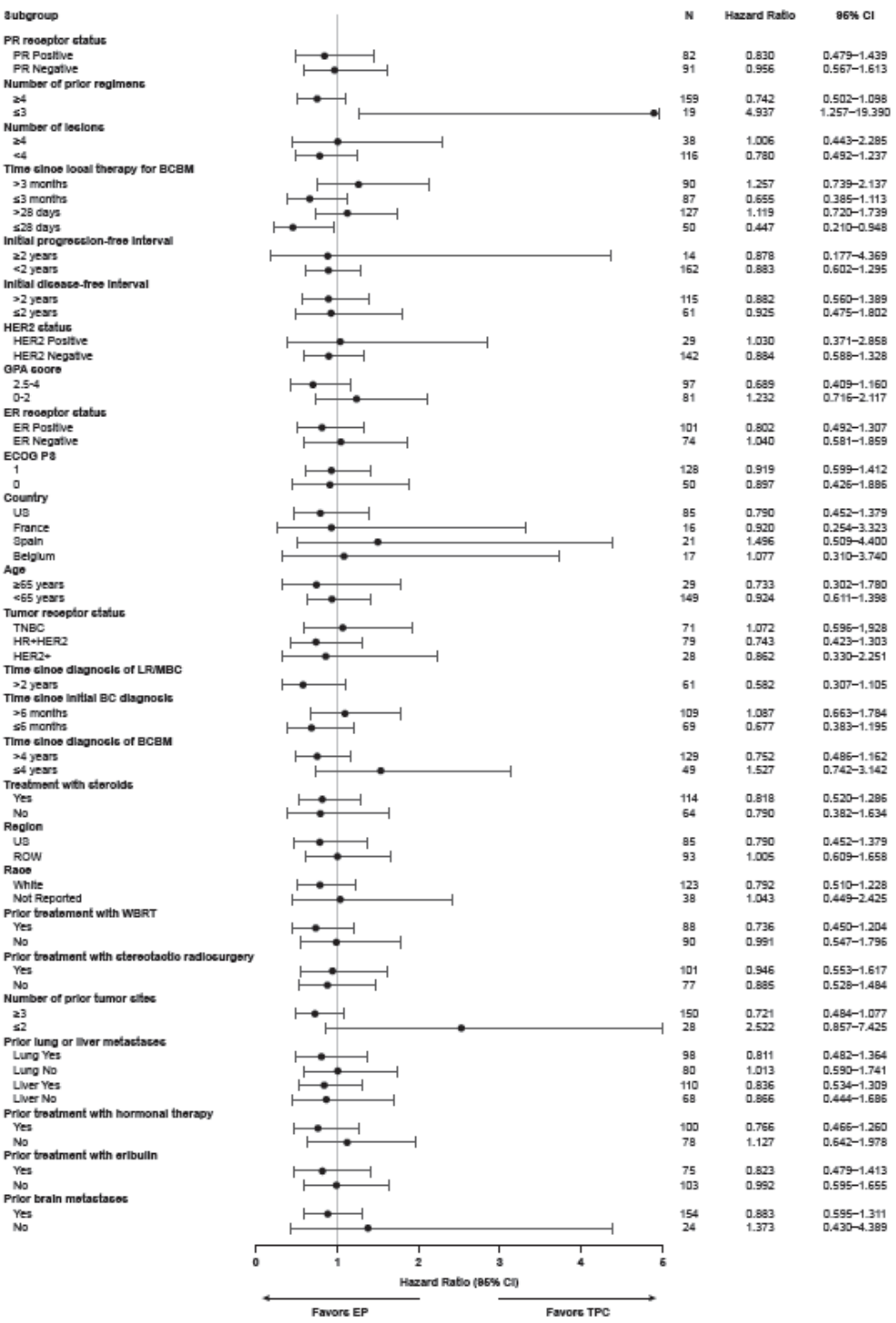
Abbreviations: EPC, etirinotecan-pegol; PD, progressive disease; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RECIST, Response Evaluation Criteria in Solid Tumors; TPC, treatment of physicians' choice.

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).

[b]The 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.

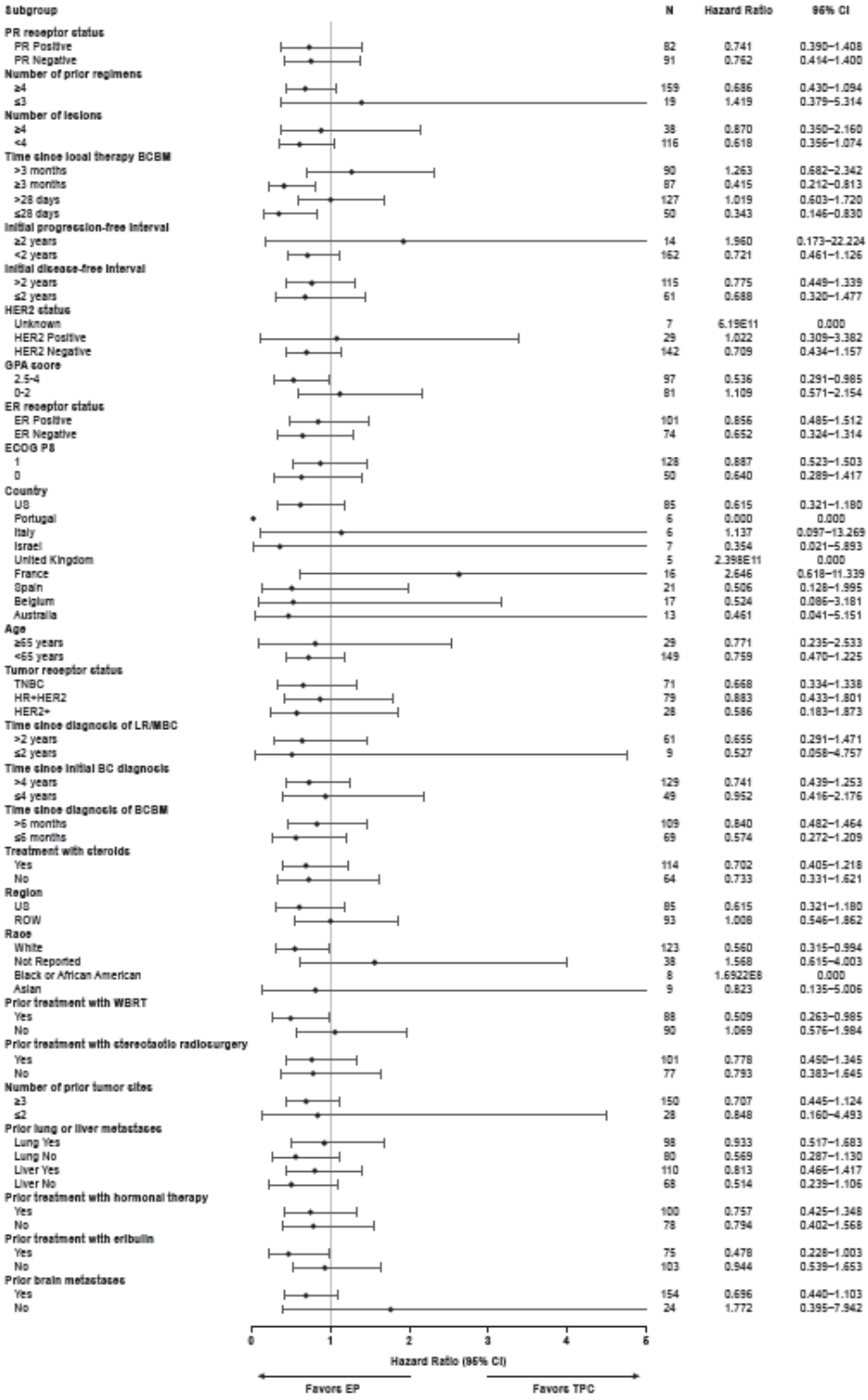
[c]Study therapy was terminated for the following protocol-defined reasons: disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and/or Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria, unacceptable toxicity, death, investigator decision to 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



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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