SUPPLEMENTARY METHODS

Clinical Trials

The first study (NCT00401362) was a phase III trial, which enrolled 134 patients, including 78 patients with advanced cancers and 56 patients with other advanced illness including chronic obstructive pulmonary disease (COPD), cardiovascular disease and severe neurologic disease. Patients were randomized to receive a single dose of subcutaneous MNTX (*N*=63; 8mg for patients <62 kg and 12mg for patients ≥62 kg body weight) or placebo (*N*=71) every other day for 14 days. The co-primary efficacy endpoints of this study were: 1) the proportion of patients with laxation within 4 hours after the first dose of study drug, and 2) the proportion of patients with laxation within 4 hours after 2 of the first 4 doses (the first week of double-blind treatment). Of the patients who completed the double-blind phase, 80 (placebo 39, MNTX 41) elected to proceed with a 12 week open-label phase, during which they could receive one dose of MNTX (0.15 mg/kg subcutaneously, which could be reduced to 0.075 mg/kg or increased to 0.3 mg/kg) as often as every 24 hours as needed. Patients received 30-days follow-up after the last study dose.

The second study (NCT00672477) was a phase IV trial, which enrolled 229 patients (including 151 patients with advanced cancers and 78 patients with cardiovascular, pulmonary or neurologic disorders), who were randomized to a single dose of subcutaneous MNTX (*N*=116, 8mg for patients <62 kg and 12mg for patients ≥62 kg body weight) or placebo (*N*=113) administered every other day for 14 days. The primary endpoint was laxation without any additional rescue medication within 4 hours after at least 2 of the first 4 doses. Of the patients who completed the double-blind phase, 142 (placebo 69, MNTX 73) elected to proceed with a 10-week open label phase of subcutaneous MNTX as needed. Both studies were approved by appropriate Institutional Review Boards.

SUPPLEMENTARY TABLES

Supplementary Table 1. Patients' characteristics

Category	All patients	MNTX	Placebo	*P* value
All patients	229	117	112	
Male	124 (54%)	64 (55%)	60 (54%)	0.90
Female	105 (46%)	53 (45%)	52 (46%)	
Median age (range)	63 (27-91)	63 (27-91)	64 (32-90)	0.82
Albumin <3.5 g/dL	94 (41%)	44 (38%)	50 (45%)	0.35
Albumin ≥3.5 g/dL	129 (56%)	69 (59%)	60 (54%)	
Albumin missing	6 (3%)	4 (3%)	2 (2%)	
Lung cancer	58 (25%)	32 (27%)	26 (23%)	0.54
Prostate cancer	30 (13%)	13 (11%)	17 (15%)	0.43
Breast cancer	23 (10%)	14 (12%)	9 (8%)	0.38
Pancreatic cancer	16 (7%)	8 (7%)	8 (7%)	1.00
Renal cancer	12 (5%)	8 (7%)	4 (4%)	0.38
Head and neck cancer	11 (5%)	6 (5%)	5 (4%)	1.00
Colorectal cancer	10 (4%)	4 (3%)	6 (5%)	0.53
Melanoma	8 (3%)	3 (3%)	5 (4%)	0.49
Esophageal cancer	7 (3%)	3 (3%)	4 (4%)	0.72
Brain tumor	6 (3%)	4 (3%)	2 (2%)	0.68
Hepatocellular cancer	6 (3%)	1 (1%)	5 (4%)	0.11
Uterine cancer	6 (3%)	0 (0%)	6 (5%)	**0.01**
Cervical cancer	5 (2%)	3 (3%)	2 (2%)	1.00
Lymphoma	4 (2%)	2 (2%)	2 (2%)	1.00
Myeloma	4 (2%)	2 (2%)	2 (2%)	1.00
Sarcoma	3 (1%)	1 (1%)	2 (2%)	0.62
Bladder cancer	3 (1%)	2 (2%)	1 (1%)	1.00
Biliary cancer	3 (1%)	2 (2%)	1 (1%)	1.00
Other	14 (6%)	9 (8%)	5 (4%)	0.41

MNTX, methylnaltrexone

Supplementary Table 2. Cochrane Collaboration's tool for risk of bias assessment

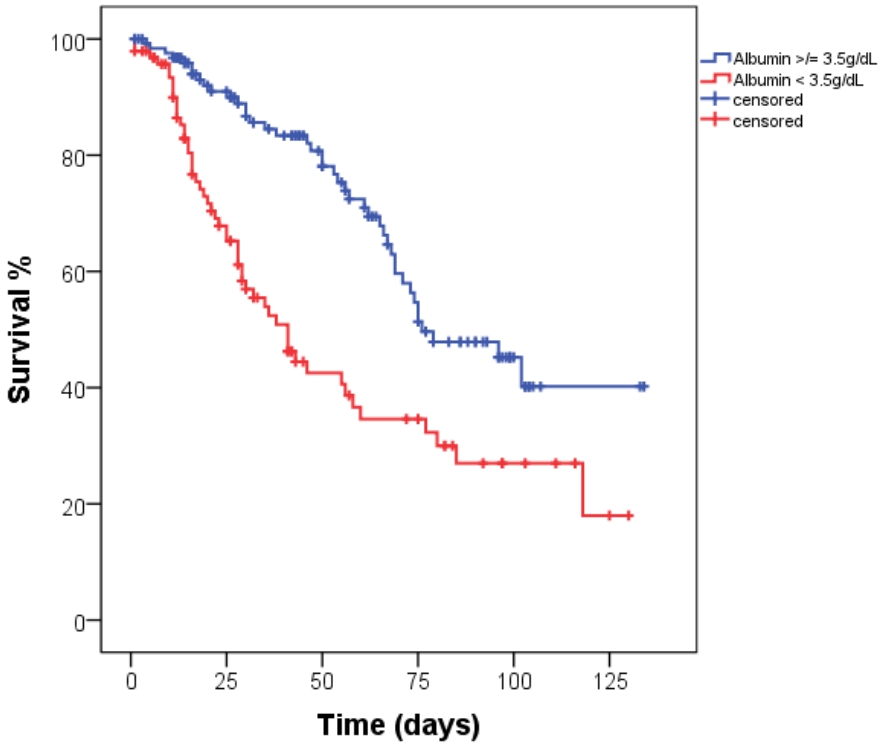
Type of bias	Source of bias	Risk of bias	Comment
Selection bias	Random sequence generation	Unclear	Studies were not designed for survival outcomes
	Allocation concealment	Low	
Performance bias	Blinding of participants and personnel	Low	
Detection bias	Blinding of outcome assessment	Low	
Attrition bias	Incomplete outcome data	High	Studies followed patients only for limited period of time and 58% of patients were censored at last follow up
Reporting bias	Selective reporting	Low	
Other bias	Any	Low	

SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure 1. Total of 223 patients had available albumin levels at the time of study entry. Patients (n=128, blue) with albumin ≥ 3.5 g/dL had longer overall survival (OS) compared to patients (n=95, red) with albumin < 3.5 g/dL (76 days, 95% CI 55-97 vs. 41 days, 95% CI 30-52; p<0.001).

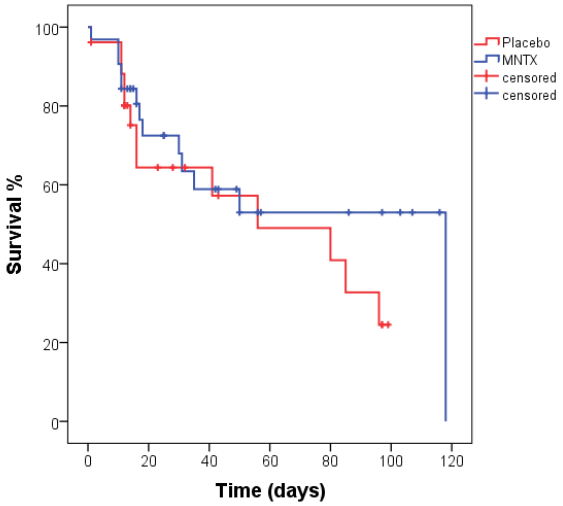
Supplementary Figure 2. A. In 58 patients with lungs cancer, 32 patients (blue) treated with methylnaltrexone (MNTX) had statistically similar median overall survival (OS) compared to 26 patients (red) treated with placebo (118 days vs. 56 days; p=0.34). **B.** In 30 patients with prostate cancer, 13 patients (blue) treated with MNTX had similar OS compared to 17 patients (red) treated with placebo (medians not reached; p=0.85). **C.** In 23 patients with breast cancer, 14 patients (blue) treated with MNTX had similar OS compared to 9 patients (red) treated with placebo (medians not reached; p=0.46). **D.** In 16 patients with pancreatic cancer, 8 patients (blue) treated with MNTX had a trend to longer median OS compared to 8 patients (red) treated with placebo (76 days vs. 28 days; p=0.14).

Supplementary Figure 1



Supplementary Figure 2

A.



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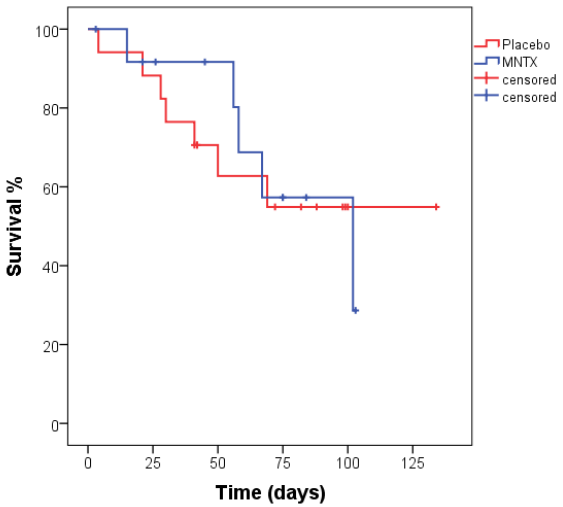

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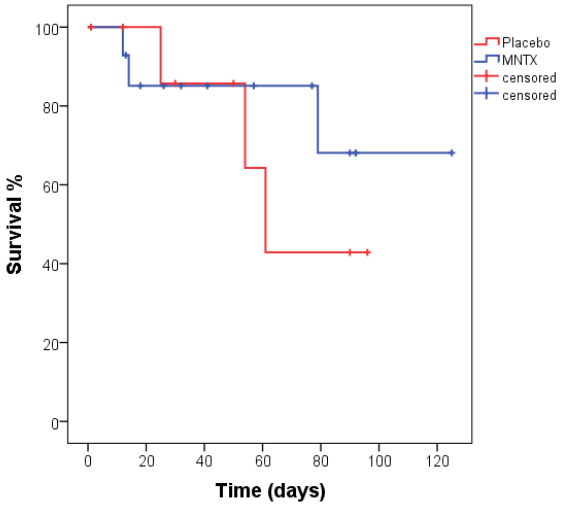

D.