SUPPLEMENTARY ONLINE MATERIAL FOR: The role of a palliative care intervention in moderating the relationship between depression and survival among individuals with advanced cancer

Supplementary Analyses

As discussed in the main manuscript, one possible mechanism by which the intervention improves survival among patients depressed at baseline is that the intervention alleviates depression, which in turn lengthens survival. In other words, reduction in depression may *mediate* the effect of the intervention on survival.

In the sections that follow, the mediational hypothesis is tested using an analytical approach similar to Pirl and colleagues (2012) that is based on the general guidelines for tests of mediation put forward by Baron and Kenny (1986). First, analyses focus on whether those who received the intervention demonstrated greater subsequent reduction in depression compared to those who did not receive the intervention. Subsequent analyses focus on whether greater reduction in depression was associated with greater improvement in survival. All analyses were conducted using SPSS software, version 22.

Testing any hypothesis involving reduction in depression as a mediator requires a measurement of change in depression over time. Fortunately, in addition to including the CES-D in the baseline assessment administered upon enrollment in both Study 1 and Study 2, the CES-D was also collected at regular time intervals throughout both studies. Following the method of Pirl and colleagues (2012), change in depression was assessed by calculating the difference between CES-D scores measured at baseline and at an assessment that occurred approximately 3 months following baseline. Although the interval differed slightly for the two studies (4 months for

Study 1 versus 3 months for Study 2) depression change scores calculated across these roughly equivalent time intervals are sufficient for exploratory analyses.

Association of the palliative care intervention with reduction in depression

According to the mediational hypothesis, patients who received the intervention should subsequently demonstrate improved depression compared to patients receiving usual cancer care. Because patients in the delayed intervention condition from Study 2 began the intervention after a 3-month delay, no intervention-related change in depression was expected during the 3 months following baseline. For this reason, the present analyses grouped the delayed intervention condition (Study 2) with the usual care control condition (Study 1). The depression change scores of patients in this combined group were then compared to those of patients in the early intervention conditions from both studies. A regression controlling for baseline depression showed no effect of the intervention on change in depression, $t = -1.172$, $p = .242$. Those who received the intervention decreased an average of 1.26 points ($SD = 7.53$) on the CES-D compared to the decrease of only 0.55 points ($SD = 8.47$) among those who did not receive the intervention.

Following the approach of Pirl and colleagues (2012), sensitivity analyses were conducted to account for missing depression change scores of patients who died within 3 months of baseline. Three regression analyses were used, each of which was identical to the analysis described above but assigned a different depression change value for patients who died within 3 months following baseline: baseline value carried forward (change score = 0), average change score of the full sample (change score = -0.884), and average change score of all patients whose depression worsened over the first 3 months (change score = 6.151). These results are presented in Table S2. Importantly, receiving the intervention was not significantly associated with

changes in depression in any of these analyses, whether or not baseline depression was controlled.

Association of change in depression with survival

According to Baron and Kenny (1986), in the context of mediation analyses a proper test of the association between depression change and survival requires inclusion of both depression change and the intervention as predictors of survival within a single model. A Cox regression was conducted with intervention as a time-varying categorical covariate and 3-month depression change scores as simultaneous predictors. There was no evidence that change in depression was associated with survival in this analysis (p = .837) or in an analysis that also controlled for baseline depression (p = .356).

Sensitivity analyses were again conducted to account for missing depression change scores of participants who died within 3 months of baseline, as described above. Detailed results of each Cox model are presented in Table S3. Results showed that when patients who died within three months were assumed to remain steady in their depression levels (last end point carried forward) depression change was associated with survival. However, this was only the case when baseline depression was controlled. When these patients were instead assigned the mean depression change for the entire sample, there was no relationship between depression change and survival. In contrast, depression change was significantly associated with survival when these patients were assumed to experience worsening depression (an increase of over 6 points on the CES-D scale). These results suggest that in one of three hypothetical situations (in which all patients who died within 3 months of baseline demonstrated a particular pattern of depression change) we find evidence that worsening depression was associated with worsening

survival. However, this conclusion rests upon fairly strong assumptions regarding the nature of missing data and should therefore be considered with caution.

Interpretation of Mediation Results

The analyses reported above offer limited support for the hypothesis that improvement in depression is associated with improved survival, but the evidence on which it is based requires assuming certain values for missing data. These results also offer no evidence that receiving the palliative care intervention leads to improvement in depressive symptoms following study enrollment in the combined trial samples. These results argue against the explanation considered in our discussion that direct alleviation of depression is the mechanism through which the intervention improves survival among patients depressed at baseline (although an earlier analysis of a portion of the present data found an improvement in depressive symptoms, see Bakitas et al., 2009, current analyses based on an expanded sample do not find statistically significant effects). Taken as a whole, the results of present analyses offer only minimal support for the mediation hypothesis.

It should be noted that these exploratory analyses are limited in several ways and thus should be interpreted with caution. For example, because not all patients provided follow-up measurements after baseline due to death or other reasons, analyses involving change in depression necessarily involve reduced sample sizes compared to those in the main manuscript that involved only baseline measurements and time of death. Including additional covariates as controls in mediational analyses reduced the usable sample even further, rendering the results difficult to interpret. These results are available from the authors upon request.

Although the present results cast doubt on the mediation hypothesis, it is possible that a more nuanced mediational process could still apply. This is because the mediational analyses

presented above test for evidence of direct mediation only, whereas the relationships involved in the present data set might be better understood as an example of *conditional* mediation (Hayes, 2013). The conditional mediation hypothesis can be described as follows: reduction in depression mediates the effect of the intervention on improved survival, but this is only true to the extent that patients are depressed at baseline. Of note, the main manuscript discusses the depression by intervention interaction in terms of the intervention moderating the link between depression and survival. However, the conditional mediation interpretation only makes sense if the depression by intervention interaction is instead conceptualized as depression moderating the effect of the intervention on survival.

As a first step toward addressing this conditional mediation possibility, the analyses described above were conducted among only the 78 participants who demonstrated clinically significant levels of depression at baseline, namely CES-D scores of 16 or greater (Okun, Stein, Bauman, & Silver, 1996). These analyses failed to show a statistically significant relationship between the intervention and reduction in depression ($p = .096$) or between reduction in depression and improved survival ($p = .404$) although both results were in the predicted direction (detailed results are available from the authors). Without the ability to test the conditional mediation hypothesis directly, it is not advisable to read too closely into these results. Instead, future research using a design that allows for such tests is recommended.

References

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Table S1. Correlation of baseline depression (CES-D) with control covariates

	N	r	p
Demographic variables			
Age	471	-.108	**.019**
Gender (male)	471	-.028	.547
Rural residence	471	-.043	.349
College graduate	467	-.062	.182
Married	468	.017	.716
Employed	467	-.071	.127
White	470	-.086	.063
Cancer site			
Lung	471	.094	**.041**
Gastrointestinal	471	.003	.944
Genitourinary	471	-.042	.359
Breast	471	-.048	.302
Hematological	471	-.059	.199
Other cancer	471	-.054	.242
Illness-related variables			
Days in hospital	470	.046	.320
Days in ICU	348	-.017	.758
ER visits	471	.073	.112
Advanced directives	469	.067	.147
Do not resuscitate	458	.061	.191
Chemotherapy	471	.000	.993
Radiation	471	.023	.612

CES-D = Center for Epidemiologic Studies Depression; ICU = Intensive Care Unit; ER = Emergency Room. Analyses used pairwise deletion and significance values are not corrected for multiple comparisons.

Table S2. Linear regression models testing the relationship between intervention condition and change in depression during the first three months following baseline

	Intervention			Baseline Depression		
	B [95% CI]	**t-value**	**p**	**B [95% CI]**	**t-value**	**p**
Models with baseline depression						
Complete case analysis (N=258)	-0.529 [-1.42:0.36]	-1.172	.242	-0.397 [-0.50:-0.30]	-7.850	**<.001**
Sensitivity analyses (N=316)						
Last end point carried forward (change = 0)	-0.602 [-1.35:0.15]	-1.580	.115	-0.307 [-0.39:-0.23]	-7.359	**<.001**
Assign mean change in sample (change = -0.88)	-0.590 [-1.34:0.16]	-1.558	.120	-0.314 [-0.40:-0.23]	-7.575	**<.001**
Assign mean change of those who worsened (change = 6.15)	-0.683 [-1.41:0.14]	-1.626	.105	-0.256 [-0.35:-0.17]	-5.567	**<.001**
Models without baseline depression						
Complete case analysis (N=258)	-0.354 [-1.34:0.63]	-0.705	.481	.	.	.
Sensitivity analyses (N=316)						
Last end point carried forward (change = 0)	-0.320 [-1.13:0.49]	-0.781	.436	.	.	.
Assign mean change in sample (change = -0.88)	-0.302 [-1.11:0.50]	-0.737	.462	.	.	.
Assign mean change of those who worsened (change = 6.15)	-0.448 [-1.31:0.41]	-1.023	.307	.	.	.

B = Unstandardized beta coefficient; CI = Confidence Interval; Intervention = having the palliative care intervention (vs. not having it, as evaluated during first 3 months of study).
Complete case analyses include only participants with complete data for all variables included. Sensitivity analyses involved imputing the specified depression change score for each patient who died within 3 months of study enrollment. Models were conducted both with and without baseline depression included as a covariate. All variables were entered into each linear regression model simultaneously.

Table S3. Cox regression models testing the relationship between change in depression and subsequent mortality risk

	Depression Change During First 3 Months			Intervention			Baseline Depression		
	Wald	**HR [95% CI]**	**p**	**Wald**	**HR [95% CI]**	**p**	**Wald**	**HR [95% CI]**	**p**
Models with baseline depression									
Complete case analysis (N=258)	0.85	1.011 [0.99:1.03]	.356	0.24	1.090 [0.77:1.54]	.626	3.28	1.017 [0.99:1.04]	.070
Sensitivity analyses (N=316)									
Last end point carried forward (change = 0)	4.07	1.019 [1.00:1.04]	**.044**	0.03	1.027 [0.77:1.37]	.855	14.22	1.029 [1.01:1.05]	**<.001**
Assign mean change in sample (change = -0.88)	2.44	1.015 [0.99:1.03]	.119	0.02	1.018 [0.77:1.36]	.900	12.86	1.028 [1.01:1.04]	**<.001**
Assign mean change of those who worsened (change = 6.15)	26.25	1.046 [1.03:1.06]	**<.001**	0.31	1.084 [0.82:1.44]	.580	22.84	1.036 [1.02:1.05]	**<.001**
Models without baseline depression									
Complete case analysis (N=258)	0.04	1.002 [0.98:1.03]	.837	0.17	1.076 [0.76:1.52]	.679	.	.	.
Sensitivity analyses (N=316)									
Last end point carried forward (change = 0)	0.34	1.006 [0.99:1.02]	.558	0.00	0.994 [0.75:1.32]	.969	.	.	.
Assign mean change in sample (change = -0.88)	0.02	1.001 [0.98:1.02]	.886	0.01	0.987 [0.74:1.31]	.929	.	.	.
Assign mean change of those who worsened (change = 6.15)	13.34	1.034 [1.02:1.05]	**<.001**	0.09	1.045 [0.79:1.39]	.762	.	.	.

CI = Confidence Interval; HR = Hazard Ratio (risk of death); Wald = Wald statistic; Intervention = having the palliative care intervention (vs. not having it) entered as a time-varying covariate.
Complete case analyses include only participants with complete data for all variables included. Sensitivity analyses involved imputing the specified depression change score for each patient who died within 3 months of study enrollment. Models were conducted both with and without baseline depression included as a covariate. All variables were entered into each Cox proportional hazards regression model simultaneously.