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Original Communication

Prognostic significance of baseline fatigue for overall survival: A patient-level meta-analysis of 43 oncology clinical trials with 3915 patients

Jeff A. Sloan[1,*], H. Liu[2], D. V. Satele[2], S. Puttabasavaiah[2], J. S. Kaur[2], J. Hubbard[2], A. Dueck[3], P. J. Stella[4] and Jasvinder A. Singh[5]

[1]Department of Health Sciences Research; [2]Department of Oncology, Mayo Clinic, Rochester, MN; [3]Department of Health Sciences Research, Mayo Clinic, Scottsdale, AZ; [4]St. Joseph Mercy Hospital Cancer Center, Canton, MI; [5]Birmingham Veterans Affairs Medical Center, and the Departments of Medicine and Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA.

ABSTRACT

We have previously identified a single-item measure for baseline overall quality of life (QOL) as a strong prognostic factor for survival, and that fatigue was an important component of patient QOL. To explore whether patient-reported fatigue was supplemental or redundant to the prognostic information of overall QOL, we performed a patient-level pooled analysis of 43 North Central Cancer Treatment Group (NCCTG) and Mayo Clinic Cancer Center (MCCC) oncology clinical trials assessing the effect of baseline fatigue on overall survival (OS). 3,915 patients participating in 43 trials provided data at baseline for fatigue on a single-item 0-100 point scale. OS was tested for association with clinically deficient fatigue (CDF, score 0-50, n = 1,497) versus not clinically deficient fatigue (nCDF, score 51-100, n = 2,418). We explored whether fatigue contributed to overall survival in the presence of performance status and overall QOL. We used Cox proportional hazards models that adjusted for the effects of overall QOL, performance score, race, disease site, age and gender. Baseline fatigue was a strong predictor of OS for the entire patient cohort (CDF vs. nCDF: 31.5 months vs > 83.9 months, $p < 0.0001$). The effect sizes of fatigue on survival were more variable across different disease sites than was seen for overall QOL (GI, esophageal, head and neck, prostate, lung, breast and others). After controlling for covariates, including performance status and overall QOL, baseline fatigue remained a strong prognostic factor in multivariate models (CDF vs. nCDF: HR = 1.23, $p = 0.02$). Baseline fatigue is a strong and independent prognostic factor for OS over and above performance status (PS) and overall QOL in a wide variety of oncology patient populations. Single-item measures of overall QOL and fatigue can help to identify vulnerable subpopulations among cancer patients. We recommend these single-item measures for routine inclusion as a stratification factor or key covariate in the design and analysis of oncology treatment trials.

KEYWORDS: quality of life, fatigue, survival, prediction, cancer, patient-reported outcomes.

INTRODUCTION

Fatigue is the most prevalent and debilitating symptom that cancer patients suffer [1-4]. There are numerous guidelines for the assessment and management of fatigue, but it remains both an acute and chronic problem among cancer patients of all types [5-7].

Fatigue impacts other aspects of patient well-being and has been indicated as a major contributor to overall QOL [8]. Fatigue exacerbates virtually every other symptom reported by cancer patients as it

*Corresponding author: jsloan@mayo.edu

makes coping with other symptoms more difficult [8]. In fact some studies have indicated that fatigue is the singularly largest contributor to overall QOL of all patient-reported symptoms [9].

The impact of fatigue and deficits in overall QOL on a patient's ability to carry on activities of daily living are profound [10]. The interplay among patient performance status, fatigue and QOL is clearly present but not completely understood.

The prognostic capability of patient-reported outcomes such as QOL and fatigue has been explored in individual studies of breast cancer patients [11, 12], bladder cancer [13], lung cancer [14], and pancreatic cancer [15]. Other evidence from the literature has identified various patient-reported outcomes (PROs) significantly associated with overall survival [16].

Our research team has carried out previous individual studies and meta-analyses exploring the prognostic nature of PROs related to QOL domains [17-19]. We have demonstrated elsewhere that a single-item measure of overall QOL is prognostic for survival over and above performance status. We further hypothesize that a single-item fatigue measure could enhance prognostic capability of clinical researchers and clinicians in estimating cancer patient survival over and above performance status and overall QOL (Figure 1).

The objective of this study was to assess whether baseline fatigue as assessed by single linear analogue self-assessment (LASA) scale can predict mortality in patients with a variety of cancers over and above performance status and overall QOL.

PATIENTS AND METHODS

Patients

For this patient-level pooled meta-analysis, data was drawn from 43 clinical trials conducted either at the Mayo Clinic Cancer Center or in the North Central Cancer Treatment Group. Over 3900 patients provided data. Studies included a wide variety of patient populations. We included 33 cancer control studies, 8 chemotherapy studies, 2 radiation therapy studies. Brief details of the studies are provided in Appendix 1.

Fatigue and QOL assessment

Fatigue and overall QOL were measured at baseline on a simple, single item 0-10 point scale as indicated in figure 2, then transformed on to a 0-100 scale by reversal of the fatigue score and simply multiplying by 10. Performance score was assessed on an ordinal scale ranging from 0-4, fully active to totally disabled [20].

Outcome and statistical analyses

Overall survival was used as the primary endpoint. Fatigue and QOL were dichotomized using a cutoff to indicate a clinically significant deficit. A score of 50 or less on the 100-point scale was indicative of a deficit that required clinical intervention or at least further clinical investigation and assessment [21, 22]. This scoring cut-off has been further validated by others [23-25]. We used Cox proportional hazards models that adjusted for the effects of performance status score, race, site, age and gender. The analysis was stratified for study type and patient population. Since we had the advantage of such a large cohort of individual patient data, we plotted each individual patient's baseline QOL versus their actual survival time, removing the censored observations.

RESULTS

Characteristics of included studies and patients

The majority of the 3,915 patients in this analysis were white, female, with median age of 61 years (Table 1). About 37.5% of these patients had performance status (PS) score of 1-2. Patients were more likely to have tumor site from breast (25.8%), followed by lung (15.7%), prostate (8.5%), esophageal (8.1%) and other (41.9%).

Figure 3 presents boxplots for the baseline fatigue scores for each of the 43 trials. The graph illustrates that the population of patients reporting a clinically significant deficit in fatigue (CDF) varies widely. 17 of the 43 trials had over half of the patients reporting CDF at baseline. Only 9 studies showed fatigue distribution indicating all the patients studied had no CDF.

Figure 4 is a Kaplan-Meier estimate survival plot, which indicates that patients reporting a clinically deficient level of fatigue with a score of 50 or below have a huge deficit in median survival relative to those who did not have clinically deficient baseline QOL. In figure 4, the survival curve estimates indicate a median survival time of 31.5 months for individuals with a CDF versus a

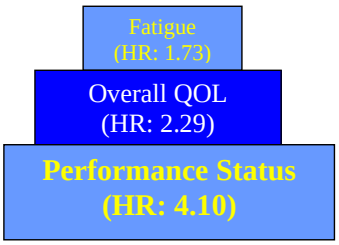

Figure 1. Pyramid graphic of PS, QOL, and fatigue.

2A.

Please mark with an 'X' the appropriate place within the bar to indicate your rating of this person's quality of life during the past week.

Lowest Quality | X | Highest Quality

(Please mark one 'X' within the bar)

2B.

Directions: Please circle the number (0-10) best reflecting your response to the following that describes your feelings **during the past week, including today.**

How would you describe:

1. your overall Quality of Life?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

2. your level of fatigue, on the average?

0	1	2	3	4	5	6	7	8	9	10
No fatigue										Fatigue as bad as it can be

Figure 2. Assessment scales used in the studies: Visual analog scale uniscale (2A) and Numeric rating scale (2B).

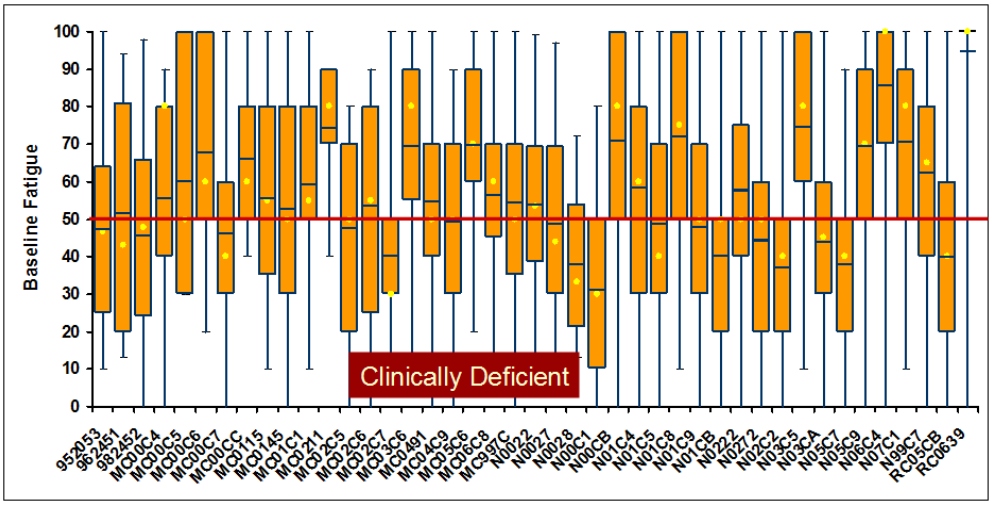

Figure 3. Boxplot of individual study fatigue scores.

Table 1. Overall patient characteristics.

	Mean (standard deviation) or n (%)
Median age (range)	61 (19-95)
% male	39.1%
Race/ethnicity, n(%)	
White	3,454 (88.2%)
Black/African American	145 (3.7%)
Native Hawaiian/Other Pacific Islander	1 (0.3%)
Asian	16 (4.1%)
American Indian/Alaskan Native	18 (4.6%)
Not reported	281 (10.7%)
Performance score	
Missing	517
0	2,125 (62.5%)
1-2	1,273 (37.5%)
Major tumor site	
Breast	1009 (25.8%)
Lung	614 (15.7%)
Prostate	333 (8.5%)
Esophageal	318 (8.1%)
Other	1641 (41.9%)

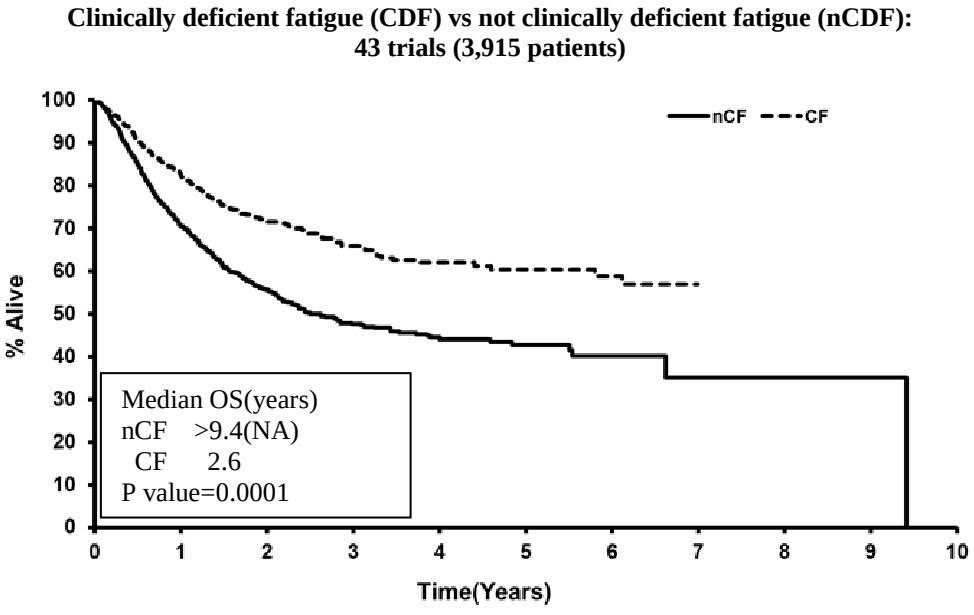

Figure 4. Survival plot for OS comparing patients with clinically deficient baseline fatigue (≤ 50) and those without clinically deficient baseline fatigue (> 50). The figure shows 'Years' in the X-axis and '% Alive' in the Y-axis.

median survival time of 83.9 months for individuals reporting no CDF (p = 0.001). The survival analysis was repeated for individual tumor types. Comparisons of median survival in months in breast, lung, prostate and esophageal cancer patients all indicated survival deficits among patients who reported clinically deficient baseline QOL (Table 2).

A Cox proportional hazards model was built to include the data source/population type, age, gender, overall QOL and performance status (PS). It indicated a hazard ratio of 1.73 for patients with a clinically deficient fatigue versus those who did not report a clinically deficient fatigue. The type of cancer and performance status contributed significantly to the overall survival (hazard ratios for GI, lung, breast and GU of 0.04, 6.56, 0.31 and 0.14, respectively; for overall QOL, the hazard ratio was 2.29; and for PS, the hazard ratio was 4.10). Performance score accounts for 15-20% of the variance in overall survival, overall QOL accounts for 10-15%, and fatigue accounts for 8-12% individually. On adding QOL on top of PS in the model, 12% of the survival variance is added. Adding fatigue to the model subsequently adds a further 8%. In the presence of performance score and overall QOL, a deficit in overall fatigue was still prognostic for survival (Table 3). Figure 5 presents adjusted Kaplan-Meier survival curves, emphasizing this point. After adjusting for covariates as indicated, the hazard ratio for a deficit in fatigue was 1.23.

DISCUSSION

Our results indicated that, as has been seen by others, baseline fatigue is a prognostic indicator of patient survival across a broad spectrum of cancer patients. There is a strong and demonstrable relationship between baseline fatigue and OS for patients on cancer clinical trials. Fatigue is a strong and independent prognostic factor for OS over and above PS and overall QOL in a wide variety

Table 2. Median survival (months) across tumor sites.

Site	Clinically deficient fatigue (Score ≤ 50)	Not clinically deficient fatigue (Score > 50)	P-value
Breast	NA (> 83)	NA (> 80)	< 0.3619
Esophagus	NA (> 84)	NA (> 83)	0.5793
Lung	11.5	10.9	0.9314
Prostate	NA (> 72)	NA (> 82)	0.0001
Other	25.3	NA (> 773)	< 0.0001

NA, not applicable since this end-point was not reached, projected.

Table 3. Multivariable-adjusted cox regression model for overall survival.

Variable	Hazard ratio (95% CI)	P-value
Fatigue ≤ 50	1.23 (1.03, 1.46)	0.021
QOL ≤ 50	1.44 (1.05, 1.47)	< 0.013
Performance score 1-2	2.00 (1.66, 2.42)	< 0.001
Age	1.00 (1.00, 1.01)	0.013
Minority race/ethnicity	0.92 (0.63, 1.34)	0.649
Esophagus*	1.81 (0.67, 4.89)	0.241
Lung*	2.14 (1.77, 2.59)	< 0.001
Breast*	0.44 (0.28, 0.67)	< 0.001
Prostate*	0.18 (0.11, 0.32)	< 0.001

*Reference category is other cancer sites.

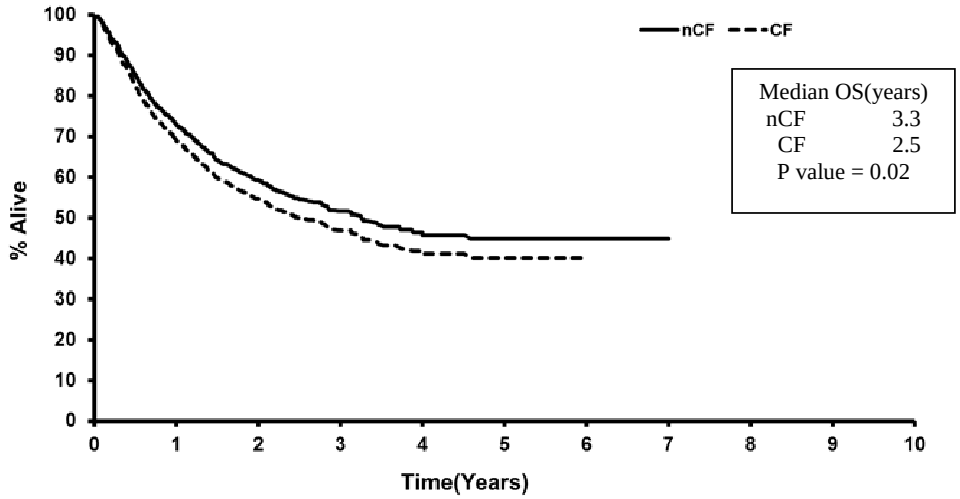

Figure 5. Adjusted Kaplan-Meier survival curves.

of oncology patient populations. Our study adds the knowledge that the prognostic power for fatigue and overall QOL can each be captured in a single, simple LASA item.

The major advantage of the single-items for fatigue and QOL assessment is their simplicity, in administration, scoring, and interpretation. Other work has demonstrated that such single-items can actually display superior sensitivity to longer multiple item measures [26, 27]. The disadvantage of the single-item of course is that it does not indicate precisely which aspect of QOL is clinically deficient [28]. As a screening tool in clinical practice or stratification variable in clinical trials, the single-item assessment can be the trigger that launches a further more comprehensive investigation into uncovering the specific QOL deficit and/or initiating appropriate clinical interventions.

What could these findings mean for clinical trials? Using baseline fatigue and QOL as stratification factors could increase trial efficiency, over and above the use of performance status. It may improve the efficiency of trial by removing the confounding of fatigue and QOL impact on treatment outcomes, which may not be balanced across treatment arms. Alternatively, including fatigue and overall QOL as a covariate in the modeling will improve the efficiency of the analysis.

What could these findings mean for cancer patients? If subpopulations with deficits in fatigue and QOL can be identified, interventions can be applied to improve cancer patient fatigue and QOL. These interventions could be prophylactic to prevent the onset of the fatigue and QOL deficits or involve a watchful waiting approach to fatigue and QOL monitoring. One could intervene for patient reported deficits using one of the numerous existing alternative behavioral or pharmacologic approaches to prevent the deficit, ease the deficit, and improve the ability to cope. The ultimate goal would be to use baseline fatigue and QOL to tailor individualized treatments for cancer patient well-being in the same manner that has been envisioned for treating the tumor itself.

CONCLUSION

In conclusion, we found that fatigue was a strong and independent prognostic factor for overall survival in various oncology patient populations, above and beyond physical status. We think that single-item measures of fatigue can help to identify vulnerable subpopulations among cancer patients. Fatigue may be considered as a key covariate in the design and analysis of oncology treatment trials.

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CONFLICT OF INTEREST STATEMENT

There are no financial conflicts related directly to this study. Dr. Singh has received research grants from Takeda and Savient and consultant fees from Savient, Takeda, Regeneron and Allergan. Dr. Singh is a member of the executive of OMERACT, an organization that develops outcome measures in rheumatology and receives arms-length funding from 36 companies, a member of the American College of Rheumatology's Guidelines Subcommittee of the Quality of Care Committee and a member of the Veterans Affairs Rheumatology Field Advisory Committee.

IRB approval: This study was approved by the Mayo Clinic Institutional Review Board and all investigations were conducted in conformity with ethical principles of research.

Disclaimer: "The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government".

Appendix 1. Summary of included studies.

Protocol	Description	Site	Accrual	Fatigue	Other QOL	Dataset
952053 [29] [30]	A Pilot Study of High-Dose Thoracic Radiation Therapy With Concomitant Cisplatin/Etoposide in Limited-Stage Small Cell Lung Cancer	Lung	82	LCSS-bl, week 12, prior to last chemo, then q3 mon x 9 mon, q4 mon x 1 yr, q6 mon x 3 yr, q yearly	Uniscale-same schedule as LCSS	LCSS, Uniscale
962451 [31]	A Phase II Study of LU 103793 in the Treatment of Advanced Non-Small Cell Lung Cancer	Lung	17	LCSS-bl, each cycle	Uniscale-same as LCSS	LCSS, Uniscale
9824521 [32]	Randomized Phase II Study of Docetaxel and Gemcitabine for Stage IIIB/IV Non-Small Cell Lung Cancer	Lung	106	LCSS-bl, q4 wks	Uniscale-bl, q4 wks	QOL
MC00C4*	Pilot Evaluation of Nefazadone (Serzone) for Treating Hot Flashes	Multiple sites	11	Self-assessment sheet fatigue-bl, wk 5	POMS-bl, wk 5	Booklet
MC00C5*	Phase II Evaluation of Bupropion (Zyban) for the Treatment of Hot Flashes	Other	12	Self-assessment sheet fatigue-bl, wk 5 SED-wkly for 5 wks	POMS-bl, wk 5	Booklet
MC00C6 [33]	Pilot Evaluation of Citaloprim (Celexa) for the Treatment of Hot Flashes	Multiple sites	26	SED-wkly for 5 wks	POMS-bl, wk 5	Booklet
MC00C7 [34]	Pilot Evaluation of Mirtazapine (Remeron) for the Treatment of Hot Flashes	Multiple sites	27	Self-assessment sheet fatigue-bl, wk 5 SED-wkly for 5 wks	POMS-bl, wk 5	Booklet
MC00CC [35]	Pilot Evaluation of Gabapentin (Neurontin) for the Treatment of Hot Flashes	Multiple sites	24	Self-assessment sheet fatigue-bl, wk 5 SED-wkly for 5 wks	POMS-bl, wk 5	Booklet

Appendix 1 continued..

MC0115*	Quality of Life (QOL) Assessment of Patients and Caregivers Participating in Phase I Clinical Trials	Lung	46	LASA		Patient
MC0145 [36]	Esophageal Adenocarcinoma and Barrett's Esophagus Registry	Lung (esophageal)	6017	LASA-bl		QOL
MC01C1 [37]	Pilot Evaluation of Paroxetine (Paxil) for Treating Hot Flashes in Men	Prostate	26	Self-assessment sheet fatigue-bl, wk 5 SED-wkly for 5 wks	POMS-bl, wk 5	Booklet
MC0211*	Phase I Study of Daily Oral Sirolimus (RAPA) and Cisplatin with Concurrent Thoracic Radiation Therapy for Thoracic Malignancies	Thoracic	7	LCSS-bl and weekly x 7 weeks + 4 weeks post RT		LCSS
MC02C5 [38]	Phase II Evaluation of Desipramine for the Treatment of Hot Flashes	Multiple sites	26	Self-assessment sheet fatigue-bl, wk 5 SED-wkly for 5 wks	POMS-bl, wk 5	Booklet
MC02C6*	Phase II Evaluation of Dehydroepiandrosterone (DHEA) for the Treatment of Hot Flashes	Multiple sites	28	LASA, Self-assessment sheet fatigue-bl, wk 5 SED-wkly for 5 wks		Booklet
MC02C7 [39]	Phase II Evaluation of Citalopram (Celexa) for the Treatment of Hot Flashes in Women with Inadequate Benefit from Venlafaxine (Effexor)	Multiple sites	30	Self-assessment scale, LASA-bl, wk5, SED-wkly for 5 wks		Booklet
MC03C6 [40]	Pilot Evaluation of Aprepitant (EMEND) for the Treatment of Hot Flashes	Multiple sites	25	Self-assessment sheet fatigue-bl, wk 5 SED-wkly for 5 wks	POMS-bl, wk 5	Booklet
MC0491*	A Structured Multidisciplinary Intervention to Improve Quality of Life of Patients Receiving Active Oncological Treatment: A Randomized Trial	Multiple sites	138	LASA fatigue-bl, wk 4, 27, 52	FACT-G, POMS, FACIT-SP etc.	LASA, FACT, POMS
MC04C9 [41]	Phase II Evaluation of Flaxseed for the Treatment of Hot Flashes	Multiple sites	30	Self-assessment scale, LASA-bl, wk 5, SED-wkly for 5 wks		Booklet
MC05C6 [42]	Phase II Evaluation of Levetiracetam for the Treatment of Hot Flashes	Multiple sites	30	Self-assessment scale, fatigue-bl, wk 5	LASA6, POMS same as fatigue	Booklet
MC06C8 [43]	Paced Breathing for Hot Flashes: A Randomized Phase II Study	Multiple sites	105	SED fatigue, BFI-bl, wk 2-4, 5, 6-8,9	POMS-same as BFI	Booklet

Appendix 1 continued..

MC997C [44]	A Structured Multidisciplinary Intervention to Improve Quality of Life in Patients with Advanced Stage Cancer	Multiple sites	115	LASA-4 weeks, 8 weeks, 27 weeks	POMS, SDS, SF-36, QOL for the caregiver	Booklet, ptquesta, ptquestb
N0022 [45]	Oral Vinorelbine For the Treatment of Metastatic Non-Small Cell Lung Cancer in Patients ≥ 65 Years of Age: A Phase II Trial of Efficacy, Toxicity, and Patients' Perceived Preference for Oral Therapy	Lung	59	LCSS-bl, each cycle	Uniscale-same as LCSS	Booklet
N0027 [46]	Phase II Trial of Oral Topotecan and Intravenous Carboplatin with G-CSF (Filgastim) Support in Previously Untreated Patients with Extensive Stage Small Cell Lung Cancer	Lung	27	LCSS-bl, q3wks	none	LCSS
N0028*	Phase I/II Study of Concurrent Chemotherapy and Escalating Doses 3-D Conformal Radiotherapy (RT) Followed by Three Cycles of Chemotherapy for Unresectable Non-Small Cell Lung Cancer (NSCLC) Using a New RT Paradigm	Lung	28	LCSS-bl, one time during RT, then q3 months x 24 months	none	LCSS
N00C1*	Phase III Placebo-Controlled, Randomized, Double-Blind Comparison of Etanercept (Enbrel) Versus Placebo for the Treatment of Cancer-Associated Weight Loss and Anorexia	Other	66	LASA-bl, weekly x 4 weeks, monthly afterwards	FACT-AN, QOL-uniscale	QOL
N00CB [47]	A Phase III Randomized, Double-Blind, Placebo-Controlled Trial of Gabapentin in the Management of Hot Flashes in Men	Prostate	223	SED-wkly for 8 wks	POMS-bl, wk 5, wk 8	Booklet
N01C4 [48]	Phase III Double-Blind, Placebo-Controlled Randomized Comparison of Zinc Sulfate Versus Placebo for the Prevention of Altered Taste in Patients with Head and Neck Cancer During Radiation	Head and Neck	173	LASA-bl, weekly x 6 weeks, then monthly for 2 months, then at 3 months and 6 months		QOL

Appendix 1 continued..

N01C5 [49]	The Use of Valeriana Officinalis (Valerian) in Improving Sleep in Patients Who Are Undergoing Treatment for Cancer: A Phase III Randomized, Placebo-Controlled, Double-Blind Study	Multiple sites	227	BFI-bl, wks 4, 8, 12, 16	POMS-same schedule as BFI SED-baseline, wkly x 12 wks	QOL base, QOL database
N01C8 [50]	Osteoporosis Prevention in Prostate Cancer Patients Receiving Androgen Ablation Therapy: A Phase III Randomized, Placebo-Controlled, Double-Blind Study	Prostate	71	SED-bl, 6 mon, 1yr, 2yr	FACT-C-monthly for 6 mons, every other month, 1 yr, 2yr	Booklet
N01C9 [51]	Docetaxel and Infliximab/Placebo in Non-Small Cell Lung Cancer (NSCLC) Patients ≥ 65 Years of Age or in NSCLC Patients With Poor Performance Status: A Double-Blind, Randomized, Placebo-Controlled Trial to Prevent and Treat Wasting, Anorexia, and Asthenia in Chemotherapy-Naive and Previously-Treated Patients	Lung	67	LASA, BFI-bl, weekly x 8 weeks, then monthly	FACT-G	QOL
N01CB [52]	The Efficacy of Lidocaine Patch in the Management of Postsurgical Neuropathic Pain in Patients with Cancer: A Phase III Double-Blind, Crossover Study	Multiple sites	30	LASA-bl and end of weeks 4 and 8	POMS (bl + end of wks 4 and 8), SGIC (weekly)	QOL base, QOL wkly
N0222 [53]	Parallel Phase II Trials of ZD1839 (Iressa) Alone or Weekly Carboplatin and Paclitaxel Followed by ZD1839 (Iressa) (Oncologists Must Choose) for Metastatic Non-Small Cell Lung Cancer in Patients ≥ 65 Years of Age	Lung	65	LCSS-bl and 8wks		QOL
N0272*	Phase I/II Trial of Imatinib Mesylate; (Gleevec; STI-571) in Treatment of Recurrent Oligodendroglioma and Mixed Oligoastrocytoma	Neuro	64	LASA-bl, cycle 3, 5, 7, 9 . . .		LCSS
N02C2 [54]	A Phase III, Randomized Study of Two Different Dosing Schedules of Erythropoietin in Anemic Patients With Cancer	Multiple sites	365	LASA, BFI-bl, monthly	FACT-AN,	Ptquest

Appendix 1 continued..

N03C5 [55]	A Phase III Randomized Trial of Gabapentin Alone or in Conjunction With an Antidepressant in the Management of Hot Flashes in Women Who have Inadequate Control with an Antidepressant Alone	Multiple sites	118	SED-wkly	LASA-wkly	Booklet
N03CA [56]	The Use of American Ginseng (panax quinquefolius) to Improve Cancer-Related Fatigue: A Randomized, Double Blind, Dose-Finding, Placebo-Controlled Study	Multiple sites	290	BFI-bl, q-monthly	LASA6, SF-36, SGIC same as BFI, SED-q-wkly for 16 wks	QOLbase QOLcont
N05C7 [57]	Long Acting Methylphenidate (Concerta) for Cancer-Related Fatigue: A Phase III, Randomized Double-Blind Placebo Controlled Study	Multiple sites	148	BFI-bl, q-wkly	SED, LASA, SF-36 VS same as BFI, SGIC, wk 4	QOL
N05C9 [58]	Phase III Randomized, Double-blind, Placebo-controlled Evaluation of Citalopram for the Treatment of Hot Flashes	Multiple sites	254	SED-bl, wkly for 6 wks	POMS-bl, wk 7	Booklet
N06C4 [59]	Phase III Randomized Double-Blind Study of Mometasone Furoate versus Placebo in the Prevention of Radiation Dermatitis in Breast Cancer Patients Receiving Radiation Therapy (RT)	Breast	176	SED fatigue-bl, wkly during RT, bi-wkly after RT	LASA6-same as SED	QOL
N07C1 [60]	A Phase III, Randomized, Double-Blind, Placebo-controlled Evaluation of Pregabalin for Alleviating Hot Flashes	Multiple sites	207	SED-bl, wkly for 6 wks	POMS-bl, wk 7	Booklet
N99C7 [61]	Phase III Comparison of Depomedroxyprogesterone Acetate (DPROV) to Venlafaxine for Managing Hot Flashes	Other	227	SED-wkly	UNISCALE-bl, end of wk 6 tx	Booklet
RC05CB [62]	RC05CB A Pilot Randomized Comparison of Standard Weekly Epoetin Alfa to Every-3-Week Epoetin Alfa and Every-3-Week Darbepoetin Alfa	Other	239	LASA10 fatigue, BFI-bl, wk 4, 7, 10, 13, 16	FACT-AN, SF-36, same as LASA, BFI	QOL

Appendix 1 continued..

RC0639*	RC0639 Phase II Study of Cardiac Safety and Tolerability of an Adjuvant Chemotherapy plus Trastuzumab with Lapatinib in Patients with Resected HER2 + Breast Cancer	Breast	122	LASA fatigue-bl, cycle 4, 8	SDS, FACT-B, same as LASA fatigue	QOL

*not published yet

Other, indicates that the condition was not a malignancy/cancer; Q, every; Tx, treatment/s; bl, baseline; bi-wkly, bi-weekly; wkly, weekly; mon, months; yr, years; ptquest, patient-quest database; SDS, Symptom Distress Scale; SED, Symptom Experience Diary; POMS, Profile of Mood States; LASA, Linear Analog Scale Assessment; FACIT, Functional Assessment of Chronic Illness Therapy; SF-36, Short-Form 36; BFI, Brief Fatigue Inventory; LCSS, Lung Cancer Symptom Scale; FACT-AN, Functional Assessment of Cancer Therapy-Anorexia/cachexia; FACIT-SP, Functional Assessment of Chronic Illness Therapy- Spiritual Well-being Scale; FACT-B, Functional Assessment of Cancer Therapy-Breast; SGIC, Subject Global Impression of Change; FACT-C, Functional Assessment of Cancer Therapy-Colorectal; FACT-G, Functional Assessment of Cancer Therapy-General.

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