

# Complementary Medicine Use Amongst Patients with Metastatic Cancer Enrolled in Phase III Clinical Trials

J. Connor Wells<sup>1</sup>, Aven Sidhu<sup>2</sup>, Keyue Ding<sup>3</sup>, Martin Smoragiewicz<sup>3</sup>, Daniel Y.C. Heng<sup>4</sup>, Frances A. Shepherd<sup>5</sup>, Peter M. Ellis<sup>6</sup>, Penelope A. Bradbury<sup>7</sup>, Derek J. Jonker<sup>8</sup>, Lillian L. Siu<sup>5</sup>, Karen A. Gelmon<sup>8</sup>, Christos Karapetis<sup>9</sup>, Jeremy Shapiro<sup>10</sup>, Louise Nott<sup>11</sup>, Christopher J. O’Callaghan<sup>3</sup>, Wendy R. Parulekar<sup>3</sup>, Lesley Seymour<sup>3</sup>, Jose G. Monzon<sup>4,\*</sup>

<sup>1</sup>Queen’s University, Kingston, ON, Canada

<sup>2</sup>Fraser Health and Veralife Health Centre, Surrey, BC, Canada

<sup>3</sup>Canadian Cancer Trials Group, Kingston, ON, Canada

<sup>4</sup>Tom Baker Cancer Centre, University of Calgary, Calgary, AB, Canada

<sup>5</sup>Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada

<sup>6</sup>Juravinski Hospital and Cancer Centre, McMaster University, Hamilton, ON, Canada

<sup>7</sup>The Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada

<sup>8</sup>BC Cancer Agency, Vancouver, BC, Canada

<sup>9</sup>Flinders Medical Centre and Flinders University, Adelaide, Australia

<sup>10</sup>Cabrini Health, Melbourne, Australia

<sup>11</sup>Royal Hobart Hospital, Tasmania, Australia

\*Corresponding author: Jose G. Monzon, Department of Medical Oncology, Tom Baker Cancer Center, University of Calgary, 1331 29 St NW, Calgary, AB, Canada T2N 4N2. Tel: +1 403 521 3688; Email: [jose.monzon@albertahealthservices.ca](mailto:jose.monzon@albertahealthservices.ca)

## Abstract

**Background:** Complementary medicines (CM) are frequently used by patients with cancer. Controversy exists over the effectiveness and risk that CM may add to conventional cancer therapy. The incidence of CM use among patients enrolled in phase III clinical trials is unknown.

**Methods:** Medication lists from 6 international phase III clinical trials were retrospectively reviewed to identify patients using CM. Patients had metastatic breast, colorectal, or lung cancers. Quality of life, adverse events, overall survival, and progression-free survival were compared between CM users and non-users. Baseline differences between groups were adjusted with propensity score matching groups.

**Results:** Seven hundred and six of 3446 patients (20.5%) used at least one CM. CM use was highest among patients with breast cancer (35.6%). CM users had more favorable baseline prognostic factors (ECOG 0-1, non-smoking status, younger age, and fewer metastases). CM use was associated with lower rates of adverse events (50% vs. 62%,  $P = .002$ ) and quality of life was similar between both groups. After adjustment with propensity score matching, CM use was also associated with longer overall survival in patients with lung cancer (adjusted hazard ratio 0.80, 95%CI, 0.68-0.94,  $P = .0054$ ). However, several key control variables like EGFR status were not available.

**Conclusion:** One in 5 patients in phase III clinical trials report using CM. CM was not associated with worse cancer-specific outcomes. However, CM users had more favorable baseline prognostic factors, and likely other confounders that may have contributed to improved outcomes observed in the lung cohort. Physicians should monitor for CM use and potential interactions with clinical trial drugs.

**Key words:** complementary medicine; cancer; clinical trial.

## Implications for Practice

This retrospective study reviewed complementary medicine use among patients with metastatic breast, lung, and colorectal cancers who were enrolled in phase III clinical trials. We found that at least 20% of patients enrolled in phase III cancer clinical trials were also using complementary medicines. Complementary medicines were not associated with worse cancer specific-outcomes; however, this may be influenced by having more favorable baseline characteristics and other uncaptured variables. Physicians should continue to monitor for potential interactions between complementary medicines and clinical trial drugs.

## Background

Complementary medicine (CM) includes a broad range of substances used concurrently with conventional medical therapies, such as herbal and dietary supplements, homeopathy,

and traditional medicines.<sup>1,2</sup> CM use is popular amongst the general public and cancer patients, with typical CM usage rates varying from% 34 to 88%.<sup>3-6</sup> A previous assessment of phase I clinical trials suggested that up to 88% of patients

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were using CM.<sup>4</sup> No study has yet tried to assess CM use in large randomized clinical trials.

Although CM is typically viewed as “natural” and therefore less toxic, there are concerns that CM may have drug interactions, especially among patients enrolled in clinical trials with experimental agents.<sup>7-10</sup> Among women with newly diagnosed early-stage breast cancer who receive standard therapies, the new use of alternative medicine was a marker of greater psychosocial distress and worse quality of life.<sup>11</sup> Studies by Johnson et al suggested that the complementary and alternative medicine use were associated with worse overall survival (OS) among patients with non-metastatic cancers.<sup>12,13</sup> These data suggest that there may be detriment associated with CM use in terms of toxicity, quality of life, and survival.

The goal of this study was to determine the incidence of CM use among patients with metastatic cancers enrolled in phase III clinical trials and to evaluate for negative associations between the CM use and cancer-specific outcomes. To this end, we retrospectively reviewed the CM use in 6 large randomized control trials conducted by the Canadian Clinical Trials Group (CCTG).

## Methods

### Clinical Trials and Patient Population

Six prospective randomized controlled clinical trials conducted by the CCTG were used in this analysis. Trials were conducted between 2003 and 2014. Three trials were performed in patients with metastatic colorectal cancer (NCT00079066, NCT00640471, and NCT01830621), 2 in metastatic non-small cell lung cancer (NCT00036647 and NCT01000025), and one in metastatic HER2 positive breast cancer (NCT00667251).<sup>14-19</sup> See [Supplementary Table S1](#) summarizing the trial details. All patients had progressive disease despite previous anti-neoplastic therapy with the exception of the breast cancer trial, which was performed in a first-line setting. NCT00667251 (MA.31; lapatinib versus trastuzumab with taxane therapy in metastatic breast cancer) was the only trial that explicitly prohibited medications that may interact with CYP3A4, of which, St John’s wort, star fruit, pawpaw, ginkgo biloba, kava, grape seed, valerian, ginseng, and echinacea were mentioned specifically.

### CM and Patient Classification

Per trial protocols, medications at the time of enrollment were recorded for each patient. Medication lists were reviewed by 2 independent investigators (JCW and AS) who assessed for complementary medicines based on the following criteria:

- a. Products found on natural medicine databases including:
  - i. The Natural Medicines Comprehensive Database<sup>20</sup>
  - ii. The Memorial Sloan Kettering Cancer Centre Integrative Medicine Database<sup>21</sup>
  - iii. The National Center for Complementary and Integrative Health<sup>22</sup>
  - iv. The National Cancer Institute list of complementary medicines<sup>23</sup>
  - v. The Cochrane Complementary Medicine list of Operational definition of complementary medicine<sup>24</sup>
- b. Products not located in a natural medicine database but collectively thought to be consistent with a CM (present on herbal websites/absence in drug databases)

Interrater reliability was assessed with Cohen’s kappa. All discrepancies were reviewed by additional authors (DYCH, JGM, and MS) and final coding was decided through consensus. The final list was then reviewed and approved by all authors prior to statistical analysis. CM were not assessed for intention (ie, used as anti-cancer therapy) as this information was not available. Vitamins and minerals were not included as CM in this analysis.

## Outcomes and Statistical Analysis

### Baseline Factors Associated with CM Use

Patients were considered users of CM if their medication list included one or more CMs. Patients using CM were compared to those not using CM. Baseline demographic data were obtained from variables reported in the original clinical trials. These variables (listed in [Tables 1-3](#)) were also used to develop a logistic regression model for each disease site, stratified by study treatment arms, to identify factors that predicted CM use, using backward variable elimination and a .05 significance level.

### Patient Outcomes/Statistical Analysis

Outcomes between CM and non-CM users were analyzed collectively and by disease site. The baseline factors listed in [Tables 1-3](#) were used to generate a logistic regression model; a propensity score analysis model was then applied to further optimize patient matching. Propensity score analysis was performed by each disease site, using a linear propensity score to generate the linear propensity scores by CM users and non-users. Patients whose propensity score was below the larger of the 2 minimums (for CM users and non-users) were excluded, as were patients whose score was above the smaller of the 2 maximums. The propensity scores were then used to stratify patients into 5 approximately sized subgroups. Stratified analysis was performed on the classified strata. Final groups were compared with Cochran-Mantel-Haenszel chi-square testing to ensure the balance of baseline characteristics.

OS was defined as the time from randomization to the date of death or censored at the last follow-up. Progression-free survival (PFS) was defined as the time from randomization until the date of progressive disease, death, change of therapy, or censored at the date of change of therapy or last disease assessment. Kaplan-Meier curves were generated and data were compared with a log-rank test stratified by propensity score group and treatment arms. Adjusted hazard ratios (aHR) and 95%CI were generated from the Cox regression model stratified by propensity score group and treatment arms.

CM use effect on the quality of life (QoL) was assessed in each trial using the EORTC QLQ-C30, a self-administered cancer-specific questionnaire assessing 5 functional domains (physical, role, emotional, cognitive, and social), 3 symptom domains (fatigue, nausea, and pain), and 6 single symptom items (dyspnea, sleep, appetite, bowels, and global assessment). For each domain, a linear transformation was applied to standardize the raw score from 0 to 100.

QoL data was also used to assess time to deterioration in physical function and global QoL, defined as the time from randomization to the time that the patient’s first evaluation as deteriorated; this condition was met if a 10-point decrease in function’s score from baseline was recorded. Patients without deterioration were censored at the time of last assessment in QoL. Kaplan-Meier curves were used with log-rank testing stratified by propensity score group and treatment arms to assess median time to deterioration.

**Table 1.** Baseline characteristics for CM and non-CM users in colorectal cancer patients from CO.20, 21, and 23.

Variable	CM yes (%) N = 251	CM no (%) N = 1353	Total (%)	Univariate P value
<b>Gender</b>				
Female	90 (35.9)	481 (35.6)	571 (35.6)	.926
Male	161 (64.1)	872 (64.4)	1033 (64.4)	
<b>Age**</b>				
≤65	167 (66.5)	745 (55.1)	912 (56.9)	.001
>65	84 (33.5)	608 (44.9)	692 (43.1)	
<b>ECOG Performance Status**</b>				
ECOG PS 0 or 1	236 (94.0)	1159 (85.7)	1395 (87.0)	<.001
ECOG PS 2 or 3	15 (6.0)	194 (14.3)	209 (13.0)	
<b>Presence of liver metastases</b>				
No	62 (24.7)	338 (25.0)	400 (24.9)	.925
Yes	189 (75.3)	1015 (75.0)	1204 (75.1)	
<b>Number of previous chemo drug classes</b>				
>2	240 (95.6)	1306 (96.5)	1546 (96.4)	.479
≤2	11 (4.4)	47 (3.5)	58 (3.6)	
<b>Number of disease sites**</b>				
>2	65 (25.9)	509 (37.6)	574 (35.8)	<.001
≤2	186 (74.1)	844 (62.4)	1030 (64.2)	
<b>Hemoglobin**</b>				
Grade ≥1	132 (52.6)	913 (67.5)	1045 (65.1)	<.001
Grade 0	119 (47.4)	440 (32.5)	559 (34.9)	
<b>LDH</b>				
Missing	4 (1.6)	57 (4.2)	61 (3.8)	.089
>UNL	154 (61.4)	880 (65.0)	1034 (64.5)	
≤UNL	93 (37.1)	416 (30.7)	509 (31.7)	
<b>Alkaline phosphatase</b>				
Missing	2 (0.8)	12 (0.9)	14 (0.9)	.440
>UNL	155 (61.8)	869 (64.2)	1024 (63.8)	
≤UNL	94 (37.5)	472 (34.9)	566 (35.3)	
<b>Study treatment in each trial</b>				
Napabucasin + BSC (CO23)	21 (8.4)	117 (8.6)	138 (8.6)	.031
Placebo + BSC (CO23)	23 (9.2)	121 (8.9)	144 (9.0)	
BSC (CO17)	34 (13.5)	251 (18.6)	285 (17.8)	
Cetuximab + BSC (CO17)	51 (20.3)	236 (17.4)	287 (17.9)	
Cetuximab + Brivanib (CO20)	47 (18.7)	329 (24.3)	376 (23.4)	
Cetuximab + Placebo (CO20)	75 (29.9)	299 (22.1)	374 (23.3)	

\*\*Significance in univariate and multivariate analysis ( $P < .05$ )

QoL was also assessed through changes in the domains outlined above; a change in score of 10 points from baseline was considered clinically relevant. Patients were considered improved if a score was 10-points or higher than baseline at any time in QoL assessment whereas, patients were considered worsened if a score 10 or more points lower than baseline

**Table 2.** Baseline patient characteristics for CM and non-CM users in lung cancer patients from BR.21 and BR.26.

Variables	CM yes (%) N = 269	CM no (%) N = 1182	Total (%)	Univariate P value
<b>Gender</b>				
Female	118 (43.9)	494 (41.8)	612 (42.2)	.534
Male	151 (56.1)	688 (58.2)	839 (57.8)	
<b>Age</b>				
≤65	164 (61.0)	686 (58.0)	850 (58.6)	.379
> 65	105 (39.0)	496 (42.0)	601 (41.4)	
<b>ECOG Performance Status**</b>				
ECOG PS 0 or 1	214 (79.6)	815 (69.0)	1029 (70.9)	.001
ECOG PS 2 or 3	55 (20.4)	367 (31.0)	422 (29.1)	
<b>Weight Loss in previous 6 months*</b>				
Missing	5 (1.9)	27 (2.3)	32 (2.2)	.034
≥5%	51 (19.0)	295 (25.0)	346 (23.8)	
< 5%	213 (79.2)	860 (72.8)	1073 (73.9)	
<b>Smoking Status**</b>				
Never-smoker	94 (34.9)	311 (26.3)	405 (27.9)	.006
Unknown	5 (1.9)	35 (3.0)	40 (2.8)	
Ever smoked	170 (63.2)	836 (70.7)	1006 (69.3)	
<b>Race*</b>				
Others	196 (72.9)	953 (80.6)	1149 (79.2)	.005
Eastern Asian	73 (27.1)	229 (19.4)	302 (20.8)	
<b>Study treatment in each trial</b>				
BR21 Placebo (BR21)	44 (16.4)	199 (16.8)	243 (16.7)	.702
BR26 Placebo (BR26)	51 (19.0)	189 (16.0)	240 (16.5)	
Erlotinib (BR21)	87 (32.3)	401 (33.9)	488 (33.6)	
Dacomotinib (BR26)	87 (32.3)	393 (33.2)	480 (33.1)	

\*Significance in univariate analysis ( $P < .05$ ).

\*\*Significance in both univariate and multivariate analysis ( $P < .05$ ).

occurred at any time without improvement. Patients with scores between 10 points of baseline were considered stable. Domains were compared for stable, improved, and worsened between CM users and non-CM users with Chi-square test stratified by propensity score group and treatment arms; this was followed by Mantel-Haenszel chi-square test for trend.

Adverse events (AE) were assessed using the Common Toxicity Criteria of the National Cancer Institute (versions 2.0 and 3.0). Incidence of grade 3+ AEs was compared between CM users and non-users using the Cochran-Mantel-Haenszel chi-square test, stratified by propensity score group and treatment group.

For all comparisons, a  $P$ -value of  $<.05$  was considered significant.  $P$ -values were unadjusted for multiple comparisons.

## Results

### Medication and Population Characteristics

A total of 24,908 medications were reviewed for all 3707 patients. Agreement between medication reviewers was

**Table 3.** Baseline characteristics for CM and non-CM users in patients with breast cancer from MA.31.

Variables	CM yes (%) N = 232	CM no (%) N = 420	Total	Univariate P value
<b>Age**</b>				
<50	104 (44.8)	118 (28.1)	222 (34.0)	<.001
≥50	128 (55.2)	302 (71.9)	430 (66.0)	
<b>ECOG Performance Status</b>				
ECOG PS 0 or 1	227 (97.8)	403 (96.0)	630 (96.6)	.200
ECOG PS 2 or 3	5 (2.2)	17 (4.0)	22 (3.4)	
<b>Presence of liver metastases</b>				
No	120 (51.7)	233 (55.5)	353 (54.1)	.357
Yes	112 (48.3)	187 (44.5)	299 (45.9)	
<b>ER Status</b>				
Unknown/missing	10 (4.3)	18 (4.3)	28 (4.3)	.889
Negative	73 (31.5)	130 (31.0)	203 (31.1)	
Positive	149 (64.2)	272 (64.8)	421 (64.6)	
<b>PR Status</b>				
Unknown/missing	16 (6.9)	22 (5.2)	38 (5.8)	.417
Negative	134 (57.8)	260 (61.9)	394 (60.4)	
Positive	82 (35.3)	138 (32.9)	220 (33.7)	
<b>Prior adjuvant anti-HER2/neu targeted therapy</b>				
No	193 (83.2)	341 (81.2)	534 (81.9)	.526
Yes	39 (16.8)	79 (18.8)	118 (18.1)	
<b>Prior other adjuvant chemotherapy</b>				
No	119 (51.3)	226 (53.8)	345 (52.9)	.538
Yes	113 (48.7)	194 (46.2)	307 (47.1)	
<b>Study treatment in each trial</b>				
Lapatinib plus taxane	121 (52.2)	205 (48.8)	326 (50.0)	.413
Trastuzumab plus taxane	111 (47.8)	215 (51.2)	326 (50.0)	

\*\*Significance in both univariate and multivariate analysis ( $P < .05$ ).

substantial (Kappa value = 0.65). After the final review, a total of 651 medications were identified as CMs. The most frequent CMs included herbal/natural products (46.6%), dietary supplements (22.1%), fish oils (18.0%), glucosamine (11.0%), and homeopathy (2.3%). Overall, 20.3% (752/3707) of patients used at least one type of CM. CM use was more common among patients with breast cancer [232/652 (35.6%)], and less so among patients with colorectal cancer [251/1604 (15.6%)] and lung cancer [269/1451 (18.5%)].

Baseline characteristics by disease site are listed in Tables 1-3. Multivariate analysis demonstrated that CM use in patients with lung cancer was associated with the favorable ECOG status (0 or 1) and non-smoker status; weight loss <5% and Eastern Asian ethnicity were significantly associated with CM use in univariate but not multivariate analysis. CM used in CRC patients was associated with age ≤65 years old, ECOG 0 or 1, ≤2 sites of metastases, and normal hemoglobin after multivariate analysis. CM use in patients with breast cancer was associated with age less than 50 after multivariate analysis.

## Propensity Score Matching

All preselected baseline factors were included in the logistic regression model to generate the linear propensity score as the means to balance all factors between the CM use groups. After propensity matching analysis, all baseline characteristics were well balanced following the propensity match (data not shown). This resulted in the inclusion of 706 patients using the CM and 2740 patients using non-CM for the final analysis. See Supplementary Fig. S1 for a consort-flow depiction of the study design.

## Overall Survival and Progression-Free Survival

Collectively, CM use was associated with longer OS (aHR 0.84, 95%CI, 0.75-0.93,  $P = .001$ ). By site, CM use was associated with longer OS in lung cancer (aHR 0.80, 95%CI, 0.68-0.94,  $P = .0054$ ) but not in CRC (aHR 0.87, 95%CI, 0.75-1.02) or in patients with breast cancer (aHR 0.85, 95%CI, 0.61-1.19) (see Fig. 1a-d). Similarly, the collective risk of progression was also significantly lower in patients using CM (aHR 0.90, 95% CI, 0.82-0.987,  $P = .024$ ) and in patients with lung cancer but not in CRC or patients with breast cancer (Fig. 2a-d).

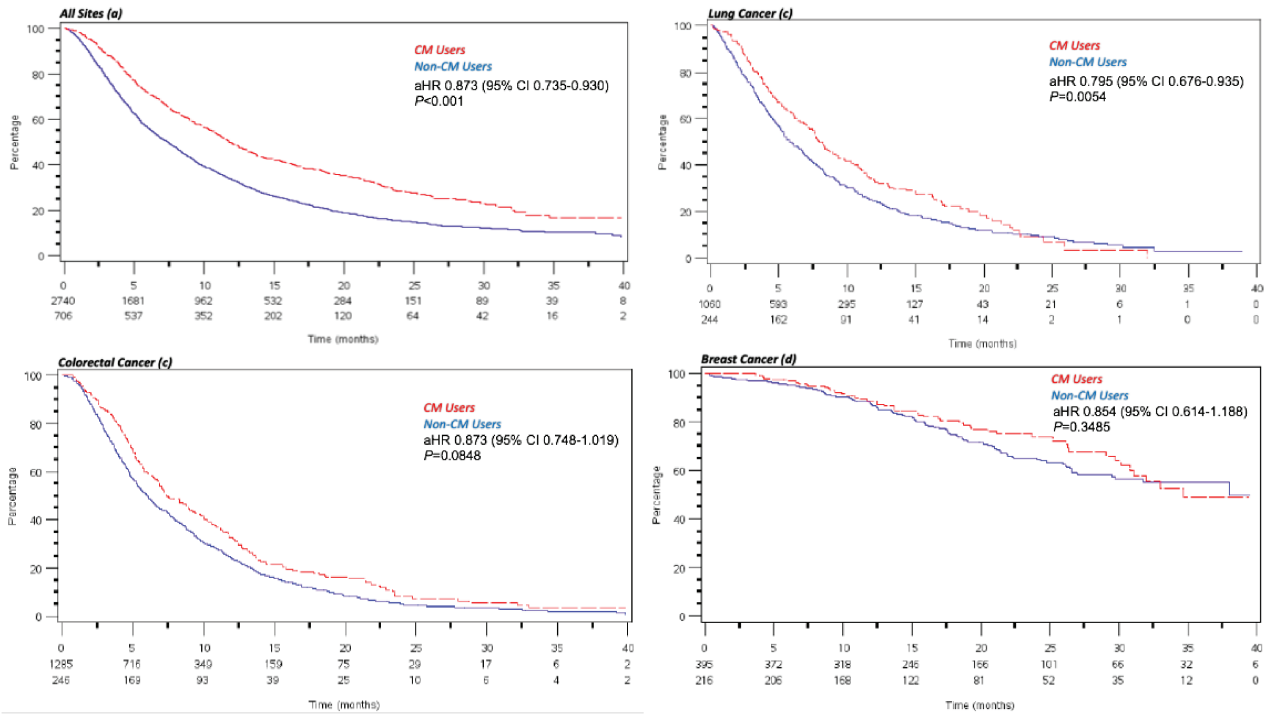
## Quality of Life and Adverse Events

CM was not associated with improved QoL between CM and non-CM users. Time to deterioration of global quality of life was similar between CM users and non-users (aHR 1.07,  $P = .94$ , Supplementary Fig. S2). Time to deterioration of physical function QoL was also similar between CM users and non-users (aHR 0.97, 95% CI, 0.85-1.11,  $P = .67$ ). CM use was associated with less improvement in pain, constipation, and role identity in the QoL response analysis. (Table 4) Grade 3+ adverse events were collectively lower in patients using CM (50.0% vs. 61.6%,  $P = .002$ ).

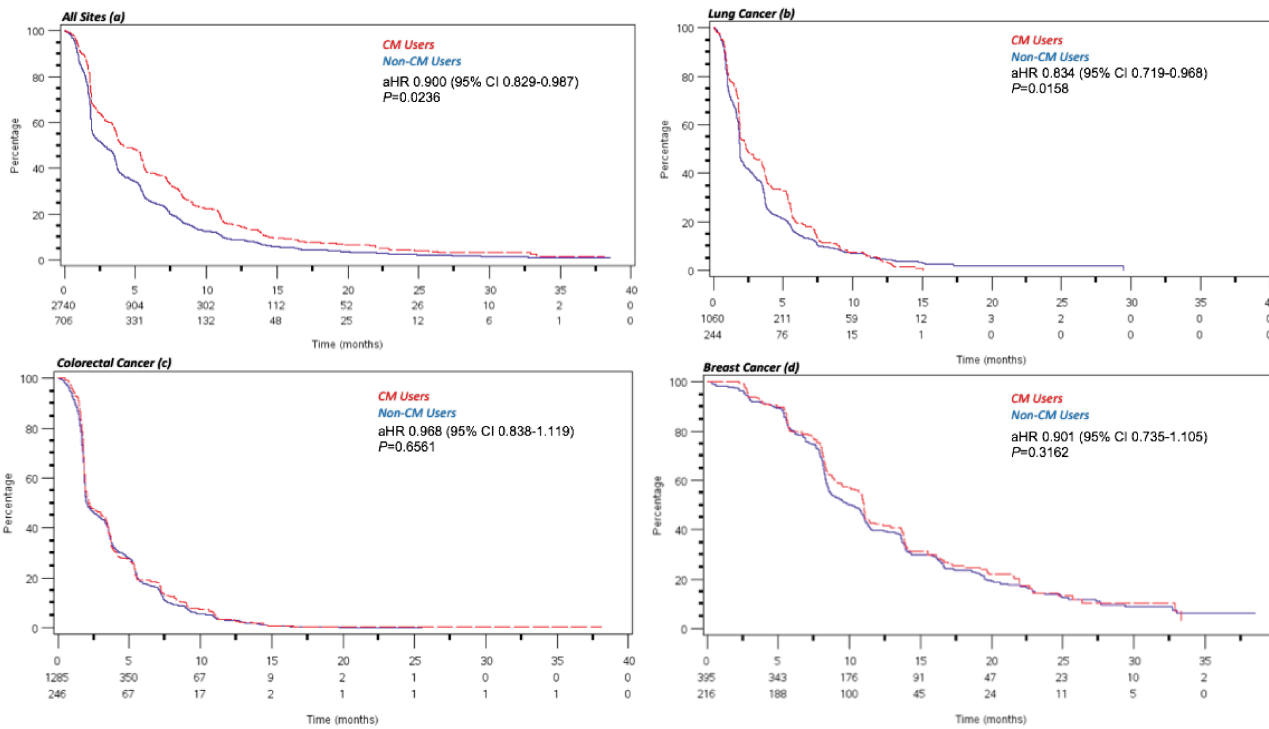
## Discussion

This large, retrospective analysis of CM use in patients enrolled in phase III clinical trials has several important findings. First, we demonstrate that CM use remains high among patients with advanced cancers who are receiving experimental therapies and was highest amongst women with breast cancer. Previous reports on the incidence of CM use among patients with cancer have varied tremendously, from as low as 6% in the 2018 ASCO National Cancer Opinion Survey, to as high as 88% in a 2004 survey of patients enrolled in phase I clinical trials at the Mayo Center in the US.<sup>4,25</sup> Such variation is expected based on study design (ie, medication list chart review versus survey-based studies) and definition of CM, as other studies have included non-pharmacological agents such as meditation and acupuncture.<sup>4,26</sup> Our study included only pharmacological CMs identified by reputable sources and explicitly excluded vitamins and minerals, which would contribute to a lower incidence of CM compared to other studies.<sup>27,28</sup> Collectively, the high incidence of CM use in this patient population supports the role of screening for CM at the time of trial enrollment, especially in women with breast cancer.

Second, we did not observe any negative association between CM use and cancer-specific outcomes. Our results did find that CM use was associated with longer OS, specifically in patients with lung cancer, however, this must be



**Figure 1. a-d:** Kaplan-Meier curves depicting overall survival between complementary medicine (CM) users ( $n = 706$ ) and non-CM users ( $n = 2740$ ). Risk of death was lower in CM users (aHR 0.873, 95% CI, 0.735-0.930,  $P < .001$ ) (a) and among CM users with lung cancer (aHR 0.795, 95% CI, 0.676-0.935,  $P = .005$ ) (b). No significant differences in OS are noted between CM users and non-users with colorectal cancer (c) or breast cancer (d).



**Figure 2. a-d:** Kaplan-Meier curves depicting progression-free survival between complementary medicine (CM) users ( $n = 706$ ) and non-CM users ( $n = 2740$ ). Risk of progression was lower in CM users (aHR 0.900, 95% CI, 0.829-0.987,  $P = .024$ ) (a) and among CM users with lung cancer (aHR 0.834, 95% CI, 0.719-0.968,  $P = .016$ ) (b). No significant differences in progression-free survival are noted between CM users and non-users with colorectal cancer (c) or breast cancer (d).

**Table 4.** Quality of life response analysis pooled for all trials.

Domain	CM use (N, %)			No CM use (N, %)			P CMH	P Mantel Haenszel
	Improved	Stable	Worsen	Improved	Stable	Worsened		
Physical	123 (21)	202 (34)	273 (46)	540 (25)	610 (28)	1014 (47)	.02	.13
Emotional	191 (32)	217 (36)	189 (32)	715 (33)	733 (34)	709 (33)	.10	.09
Role	166 (28)	147 (25)	279 (47)	752 (35)	397 (18)	1007 (47)	.00	.05
Cognitive	165 (28)	215 (36)	215 (26)	633 (29)	680 (32)	833 (39)	.28	.92
Social	200 (34)	143 (24)	250 (42)	797 (37)	459 (21)	885 (41)	.24	.20
Fatigue	241 (40)	63 (11)	292 (49)	936 (43)	197 (9)	1030 (48)	.28	.14
Nausea/vomiting	94 (16)	271 (45)	231 (39)	444 (21)	848 (39)	859 (40)	.05	.15
Pain	226 (38)	125 (21)	238 (40)	964 (45)	392 (18)	779 (36)	.00	.00
Dyspnea	149 (25)	220 (37)	225 (38)	582 (27)	780 (36)	795 (37)	.74	.44
Sleep	180 (30)	200 (34)	214 (36)	751 (35)	616 (29)	784 (36)	.01	.07
Appetite loss	142 (24)	201 (34)	253 (42)	565 (26)	615 (29)	974 (45)	.42	.31
Constipation	116 (19)	311 (52)	168 (28)	572 (27)	972 (45)	606 (28)	.00	.03
Diarrhea	81 (14)	240 (40)	274 (46)	358 (17)	846 (39)	952 (44)	.41	.42
Global health status	185 (31)	134 (22)	277 (46)	721 (34)	456 (21)	966 (45)	.15	.05

Abbreviation: CMH, Cochran-Mantel-Haenszel chi-square.

interpreted with caution given the retrospective and ad hoc nature of the study. Patients with Lung cancer using CM in this study had more favorable prognostic factors (better ECOG status, non-smokers) and while these were adjusted for, there are likely further unadjusted variables confounding the results. For example, EGFR mutation status was not assessed in many patients and therefore not controlled for in this study—CM patients were more likely to be Eastern Asian and non-smokers, both of which are associated with EGFR mutation status and consequently better response to the EGFR-targeted therapies evaluated in the lung cancer trials.<sup>29-31</sup> We were also unable to control for variables such as education and economic status—variables known to be associated with both CM use and more favorable cancer outcomes.<sup>32,33</sup> Our results are also limited by using trial enrollment medication lists, from which patients may not have reported or been asked about CM use. Based on the above, we cannot conclude that CM use improves cancer outcomes.

A recent study by Johnson et al (2018) found that in patients with non-metastatic cancers, users of CM had a worse 5-year OS compared to no CM use (82.2% vs. 86.6%).<sup>12</sup> CM users were more likely to have delayed treatment or refuse additional treatment all together, suggesting that lack of additional treatment contributed to the greater mortality risk.<sup>12</sup> These populations are inherently different than the patients included in our study, who had advanced incurable cancer, were typically previously treated with cancer treatments, and were accepting of medical treatment via experimental clinical trials. Moreover, the data collected from our study was obtained from the lists of concomitant medications from the CCTG clinical trials database, while in the Johnson and other studies CM use was obtained from a non-trial database. These differences in study design may explain the different outcomes observed between studies and highlight the importance of designing studies to accurately collect this data.

Beyond attempting to improve OS, patients with cancer use CM to improve QoL and to decrease cancer- and treatment-associated symptoms.<sup>3,8,26</sup> Our results show no difference in

time to deterioration of QoL between CM users and non-users and overall lower incidences of AEs, however, similar limitations apply including better baseline ECOG status in the CM users. The evidence for CM improving QoL and symptomology are conflicting.<sup>34-37</sup> Non-pharmacological CMs including acupuncture, mindfulness, and relaxation therapies may have a short-term benefit toward the quality of life and symptom improvements such as nausea and pain, however, limited high-level data is available for pharmacological CMs.<sup>38-41</sup> Conversely, a study by Burstein and colleagues, demonstrated greater psychosocial distress and worse quality of life with CM use in women who had received standard therapy for early-stage breast cancer.<sup>11</sup>

While we did not observe any associations between CM use and worse patient outcomes, we recognize that the CMs used in this study were heterogeneous and included a variety of herbal products, probiotics, dietary supplements, and fish oils. As such, to generalize all CM as being safe would be untrue—indeed, there are many known CMs that can interact with cancer therapies.<sup>42</sup> As such, it remains pertinent to screen trial patients for CM use to identify and prohibit the use of CMs that have shared metabolism pathways, as done in the MA.31 breast cancer trial. Given the clear public interest in CMs and scarcity of data CM-drug interactions, further studies are warranted in the interest of patient safety.<sup>43-45</sup>

## Conclusion

Our study demonstrates that CM use remains popular among patients with cancer, with at least 20% use among those enrolled in phase III trials. We did not observe worse cancer-specific outcomes in CM users. CM use was associated with numerous favorable prognostic baseline factors. This, in conjunction with other unmeasured confounders, may have contributed to the more favorable outcomes in the lung cohort. Given the absence of conclusive clinical trial data demonstrating the efficacy of CMs, the use of these agents remains controversial. Our findings do not

replace the need for an open patient-physician relationship to encourage disclosure of CM use and for careful pharmacological review of CMs to identify potential drug interactions.

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## Conflict of Interest

**J. Connor Wells:** Pfizer (Other—travel support); **Daniel Y.C. Heng:** Pfizer, Novartis, BMS (C/A, RF); **Penelope Bradbury:** Abbvie, Lilly, Merck, Pfizer (H), Boehringer Ingelheim, Abbvie (SAB); **Lillian Siu:** Merck, Pfizer, Celgene, AstraZeneca/Medimmune, Morphosys, Roche, GeneSeeq, Loxo, Oncorus, Symphogen, Seattle Genetics, GSK, Voronoi, Treadwell Therapeutics (C/A), Novartis, Bristol-Myers Squibb, Pfizer, Boehringer-Ingelheim, GlaxoSmithKline, Roche/Genentech, Karyopharm, AstraZeneca/Medimmune, Merck, Celgene, Astellas, Bayer, Abbvie, Amgen, Symphogen, Intensity Therapeutics, Mirati, Shattucks, Avid (RF), Agios (OI-spouse); **Peter Ellis:** AstraZeneca, Pfizer, Abbvie, Takeda (H); **Jose Monzon:** Amgen, BMS, Merck, Novartis, Taiho (SAB), Merck (RF). The other authors indicated no financial relationships.

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## Author Contributions

Conception/design: J.C.W., A., K.D., M.S., D.Y.C., L.S., J.G.M. Provision of study material/patients: K.D., F.A.S., P.M.E., P.A.B., D.J.J., L.L.S., K.A.G., C.K., J.S., L.N., C.J.O., W.R.P., L.S., J.G.M. Collection and/or assembly of data: All authors. Data analysis and interpretation: J.C.W., A.S., K.D., M.S., L.S., J.G.M. Manuscript writing: J.C.W., A.S., K.D., M.S., J.G.M. Final approval of manuscript: All authors.

## Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

## Supplementary material

Supplementary material is available at *The Oncologist* online.

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