Stress and Immunity in Lung Cancer:

Pilot Test of A Biobehavioral/Cognitive (ABC) Treatment for Depression and Anxiety

Dissertation

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By

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Abstract

Lung cancer is the most prevalent type of cancer and the leading cause of cancer mortality worldwide. The predominant histological subtype – non-small cell lung cancer (NSCLC) – is most frequently diagnosed in its advanced stage (Stage IV), when the cancer has metastasized beyond the lungs, is most symptomatic, and is least responsive to treatment. Patients with lung cancer experience a substantial psychological and physical symptom burden. However, these patients, especially those with advanced disease, have received minimal attention in psychosocial research over the years. Prior research was conducted in the era of cancer treatments using chemotherapy alone, which have since been replaced or enhanced by modern treatments utilizing immunotherapies and targeted therapies. It is critical that psychosocial interventions targeting depressive and anxiety symptoms are developed for patients with advanced lung cancer and implemented as part of an integrated treatment approach, in order to improve quality of life and overall survival. To address this need, this Phase IIa pilot examined the feasibility and effectiveness of A Biobehavioral/Cognitive (ABC) Treatment to improve psychological symptoms, physical symptoms, and systemic inflammation for patients (N=30 enrolled, 19 treated) with stage IV NSCLC and comorbid depression and/or anxiety. The intervention was found to be tolerable, acceptable, and mostly feasible for this patient population. Longitudinal mixed-effects modeling using three assessment time points (baseline, week 5, week 10) and including relevant covariates revealed that ABC patients experienced statistically and clinically significant reductions in depressive and anxiety symptoms, stability in physical symptoms and systemic inflammation, and an increase in perceived social support over

the course of treatment. From baseline to follow-up, depressive and anxiety symptoms decreased from ‘moderate’ to ‘minimal’ severity. Exploratory analyses compared ABC group outcomes with those of matched controls (*N*=19) with stage IV NSCLC who, as part of an observational cohort study, completed the same assessments and blood draws at equivalent time points. Random intercept models indicated a significant group by time interaction in depressive symptoms, such that depressive symptoms decreased at a more rapid rate in the ABC group compared to the control group. The ABC group reached the ‘minimal’ symptom classification, while controls remained moderately depressed at follow-up. The comparison between groups across time suggests that improvements in depressive symptoms in the ABC group were not simply due to the passage of time. Significant group by time interactions were not found for the other outcomes. The clinical significance of the study’s findings, as well as their contributions to advancing knowledge and improving clinical practice, are discussed. Conducting this pilot study revealed valuable insights into the implementation of a psychosocial intervention for patients with advanced lung cancer in the context of modern cancer treatments. We aim to incorporate these insights into the development of a randomized controlled trial, such that ABC may become widely accepted as the first evidence-based, manualized psychosocial treatment for addressing depression and anxiety, reducing systemic inflammation, and potentially prolonging survival for patients with advanced lung cancer.

Dedication

To my parents, who have encouraged me from the beginning to “never, never, never give up.”

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Fields of Study

Major Field: Psychology
Clinical Psychology
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Chapter 1: Introduction

Lung cancer is the most common type of cancer worldwide, with an estimated 2.2 million new cases each year, and is the leading cause of cancer mortality, responsible for 1.8 million deaths annually (Zhou et al., 2022). This year alone, over 238,000 U.S. adults will be diagnosed, accounting for 12% of new cancer cases and 21% of cancer deaths (Siegel et al., 2023). Of the two main histological subtypes—small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC)—NSCLC is predominant, accounting for approximately 85% of cases (Xiong et al., 2021). NSCLC is most commonly diagnosed in its advanced stage, when the cancer has metastasized beyond the lungs, is most symptomatic, and is least responsive to treatment (Wadowska et al., 2020). The prognosis for advanced NSCLC is poor, with a 5-year survival rate of less than 10% (Simeone et al., 2019). Previously, overall survival has averaged 4-9 months with treatment, and 2 months without treatment (David et al., 2017).

However, the state of lung cancer is rapidly evolving. We have entered an era of lung cancer treatment in which immunotherapies and targeted therapies are taking the place of, or are being used together with, conventional chemotherapies (Mamdani et al., 2022). These treatment methods have facilitated a paradigm shift in lung cancer treatment, achieving increased survival rates as compared to prior decades of treatment using chemotherapy only (Cho, 2017; Mamdani et al., 2022). In a longitudinal study of 305 NSCLC patients randomized to receive immunotherapy (pembrolizumab) versus chemotherapy, the median overall survival for patients treated with immunotherapy was 26.3 months, as compared to 13.4 months for the chemotherapy group (Reck et al., 2021). The 5-year overall survival rate was 31.9% for the immunotherapy

group, almost double the 16.3% for the chemotherapy group. Other recent studies have demonstrated that immunotherapies or targeted therapies can be combined safely and effectively with chemotherapies, such that this combination is now routine for many cases of advanced NSCLC (Reck et al., 2022). For example, the combination of pembrolizumab and pemetrexed plus platinum-based chemotherapy has been shown to improve overall survival from 10.6 months (chemotherapy alone) to 22.0 months, and has also nearly doubled 3-year overall survival (31.3% vs. 17.4%), without impairing quality of life (Garassino et al., 2020).

With treatment advances, there are now lung cancer survivors. Yet patients with lung cancer are the most psychologically disabled of all cancer groups, reporting lower quality of life than in other cancers (Sullivan et al., 2016; Weaver et al., 2012). Most relevant to the present study is that patients with lung cancer are reliably found with high prevalence rates of depression and suicide (Chang & Lai, 2022; Linden et al., 2012). Of all cancer types, lung cancer has the second-highest prevalence of anxiety symptoms, with 74% of patients reporting clinical or subclinical levels (Blevins et al., in press; Linden et al., 2012; Pitman et al., 2018). Physical symptoms in advanced NSCLC are substantial, with the majority of patients reporting fatigue, loss of appetite, shortness of breath, cough, pain, and hemoptysis (Andersen et al., 2020; Iyer et al., 2014). Together, the psychological and physical symptoms of lung cancer take a toll on functional capacity, leading to impairment in activities of daily living (Lilenbaum et al., 2008; Presley et al., 2021).

Although studies speak to the psychological and physical effects of lung cancer, very little has been done to examine lung cancer survivorship, especially of those with advanced disease (Rajapakse, 2021). Prior literatures come from the era of chemotherapy-only treatment. In the transition to immunotherapies and targeted therapies, it would seem patients' needs,

particularly for psychological care, remain unmet throughout their life course, even as survival improves (Hall et al., 2019). Our data show that 36% of patients newly diagnosed with lung cancer endorse moderate to severe depressive symptoms, with depression occurring in a matrix of hopelessness, generalized anxiety symptoms, traumatic cancer-related stress, impaired functional status, severe pain, and other physical symptoms (Andersen et al., 2020). Moreover, data using joint model analyses show that the trajectory of depressive symptoms from diagnosis to 24 months predicted survival (HR=1.09, 95% CI 1.03-1.16, p=0.002), such that worsening depression predicted poorer survival beyond all controls, including baseline depressive symptoms and type of cancer treatment received (Andersen et al., 2022). The mechanisms for this effect are many, but intervening behavioral as well as biologic (immune) variables are likely instrumental (Andersen et al., 2018; Boen et al., 2018; Mundy-Bosse et al., 2011).

It is critical that effective psychosocial interventions to reduce depressive and anxiety symptoms are developed for patients with advanced lung cancer and implemented as part of an integrated treatment approach. Preliminary data support the overarching objective of the present study, which is to test the provision of a psychological treatment to reduce psychological and physical symptoms and improve health for patients with advanced lung cancer and comorbid depression and/or anxiety. Within this overarching goal, there are primary, secondary, and tertiary aims. The primary aim is to conduct a Phase IIa pilot of A Biobehavioral/Cognitive (ABC) therapy intervention (N=30) and assess feasibility and treatment adherence. The secondary aim is to determine the effectiveness of ABC by studying change over time in depressive and anxiety symptoms, stress, physical symptoms, and disease biomarkers. The tertiary aim is to compare ABC's patient-reported outcomes (PROs), physical symptoms, and

biomarker data with those of a matched sample of patients with lung cancer, to test the effects of ABC beyond passage of time.

In the sections that follow, the rationale for the development of the ABC treatment will be provided, describing prior research which implemented the major components of the present treatment. Literature on the relationship between depression and immunity in patients with advanced NSCLC will be reviewed. Methods for assessing the relevant psychological and biomarker outcomes will be described. Specific aims and hypotheses for the present study are provided.

Effectiveness of A Biobehavioral Cognitive (ABC) Therapy

The ABC intervention combines two efficacious treatments. Based on the Biobehavioral Model of cancer stress and disease course (Andersen et al., 1994), the Biobehavioral Intervention (BBI) is incorporated, as its components (e.g., progressive muscle relaxation [PMR], problem-solving, addressing cancer- and treatment-related symptoms, assertive communication, enhancing social support) are relevant and empirically supported.

BBI was first tested in a breast cancer setting. In the initial randomized controlled trial, 227 patients with breast cancer were randomized to BBI or assessment only. Post-intervention data at 4 and 12 months found that BBI reduced negative mood and physical symptoms, and improved performance status, health behaviors, and T-cell immunity (Andersen et al., 2004). Additionally, BBI alleviated depression for those entering the trial with moderate to severe symptoms (Thornton et al., 2009). BBI has since been adapted and disseminated to treat patients with any cancer type (Ashmore et al., 2019).

We combine BBI with the most successful and extensively studied treatment for depressive and anxiety disorders, Cognitive Behavioral Therapy (CBT; Carpenter et al., 2018;

Etzelmueller et al., 2020; Lopez-Lopez et al., 2019; van Dis et al., 2020). In the American Society of Clinical Oncology's (ASCO) newly updated guidelines for the management of anxiety and depression in adult survivors of cancer, cognitive behavioral therapy is recommended as first-line treatment for cancer patients experiencing moderate to severe symptoms of depression and/or anxiety (Andersen, Lacchetti, et al., 2023). This recommendation prescribes CBT as the standard of care for patients with cancer.

The combined treatment, ABC, has demonstrated effectiveness in reducing stress and treating major depressive disorder (MDD) in a Phase II trial (N=36) with a mixed-cancer-type sample (Brothers et al., 2011). Relevant to the current study, 55% of the patients had advanced disease and 72% were currently receiving cancer treatment. All met Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria for MDD, and 53% met criteria for a comorbid anxiety disorder. Patients received ABC as described here, and improved significantly. On the Hamilton Rating Scale for Depression (HRSD), the mean intake score was 20 (SD=5) and mean post-treatment score was 7 (SD=4). On the Beck Depression Inventory (BDI-II), the mean intake score was 26 (SD=9), with 18% categorized as mild, 53% moderate, and 31% severe. The mean post-treatment BDI-II score was 9 (SD=8), with all but 2 patients in the "normal" symptom range. Mixed effects modeling analyses showed significant, session-by-session BDI-II change (p<.001), with a steady decline during the 16 weeks of intensive treatment and gains maintained through the next 3 months.

These data provide support for the use of ABC for patients with cancer and comorbid depression. However, the existing support originates from the era of chemotherapy-only treatment, and includes a range of cancer types rather than focusing on the groups with the highest prevalence rates of depression and anxiety. The present study addresses these needs by

investigating the use of ABC for patients with metastatic lung cancer in the context of immunotherapy and targeted treatments.

Depression and Inflammation in Patients with Advanced NSCLC

Lung cancer is a product of a dysfunctional immune system. Lung cancer cells, mutated with damage throughout the genome, hide from attack by low antigen presentation and active suppression of the immune anti-cancer response, leading to immune-surveillance escape. This scenario may be the "perfect storm" for patients with advanced lung cancer suffering from depression or experiencing stress, as both are associated with heightened inflammation and impaired immunity (Antoni & Dhabhar, 2019; Beurel et al., 2020; McFarland et al., 2020). Only two studies have utilized a cross-sectional design to evaluate the relationship between inflammation and patient-reported depression in individuals with advanced lung cancer. One study showed an association between elevated C-reactive protein (CRP) and depression in patients with stage IV lung cancer in active treatment (McFarland et al., 2019). Another study showed associations between Interleukin (IL)-6, tumor necrosis factor (TNF)-a, salivary cortisol, and depression in patients with stage II-IV lung cancer who were diagnosed with depression after the cancer diagnosis (Du et al., 2013). For these patients, IL-6 and salivary cortisol performed as biomarkers in the diagnosis of depression, such that higher 24-hour levels of IL-6 and flattened diurnal salivary cortisol slopes were associated with higher scores on the Hospital Anxiety and Depression Scale (HADS) and the Hamilton Depression Rating Scale (HAM-D).

Cellular components of the systemic inflammatory response (i.e., neutrophils, lymphocytes, and platelets) have been used as systemic inflammation biomarkers and have been shown to predict cancer survival, including lung cancer (Ono et al., 2020; Russo et al., 2020). The biomarkers are neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR),

and platelet-to-albumin ratio (PAR). Additionally, the advanced lung cancer inflammation index (ALI) can be calculated using these ratios and body mass index (BMI). The ratios reflect inflammatory imbalances. Briefly, the inflammatory response is characterized by a rise in circulating neutrophil levels and a fall in circulating lymphocyte levels. An increase in neutrophils may promote tumor progression and escape from antitumor effect, while a reduction in lymphocytes weakens the immune system's ability to attack tumor cells (J. Wang et al., 2020). As such, a ratio of high neutrophils to low lymphocytes reflects the inflammatory imbalance of pro-tumor efficacy and anti-tumor capacity of the host. Further, platelet elevation accelerates tumor progression by promoting the formation of new blood vessels and the production of adhesion molecules (Motta Guerrero et al., 2020). Elevations in the ratio of neutrophils to lymphocytes and platelets to lymphocytes are predictive of lower overall survival in patients with lung cancer (Russo et al., 2020).

For NLR, PLR, and PAR, higher values (above 5; 200; and 8.6, respectively) are reliably associated with poor prognosis and higher mortality in NSCLC (Banna et al., 2020; Guo et al., 2021; Li et al., 2022; Motta Guerrero et al., 2020; Platini et al., 2022; Russo et al., 2020; Yun et al., 2021). For ALI, a *low* value (below 50) indicates greater systemic inflammation (Lu et al., 2021; Y. Wang et al., 2020). Recent studies in NSCLC have demonstrated that patients with biomarker cell ratios on the favorable side of (i.e., below or above) these cutoffs had improved progression-free survival (PFS) and overall survival (OS). Across studies, it was shown that these patients experienced an average of 2-5 months longer PFS and 17-18 months longer OS than patients with higher systemic inflammation (Banna et al., 2020; Guo et al., 2021; Lu et al., 2021; Motta Guerrero et al., 2020; Russo et al., 2020; Y. Wang et al., 2020; Yun et al., 2021).

Considering the role of these biomarkers in the prediction of survival, in conjunction with data showing the depression trajectory to predict survival (Andersen et al., 2022), the relationship between the biomarkers and depression was tested. A recent study reported the association between biomarker levels (NLR, PLR, and ALI) and depressive symptoms in 186 patients with newly diagnosed stage IV NSCLC (Andersen, Myers, et al., 2023). In concordance with the findings described above, analyses confirmed that higher NLR and PLR, along with lower ALI, were predictive of worse OS. Moreover, after adjusting for covariates, depression was reliably associated with biomarker levels ($p \leq .02$), and patients with moderate to severe depressive symptoms were 2-3 times more likely to have prognostically poor biomarker levels. To build on our understanding of this strong relationship, a valuable next step would be to test if a reduction in depressive symptoms would yield a reduction in the biomarker values.

Focus of the Present Investigation

Advanced lung cancer is a challenging illness experience with a substantial psychological and physical symptom burden. For decades, the extent of difficulties faced by patients with lung cancer has been disproportionate to the minimal attention received in psychosocial research. Little is known about ideal methods to reduce psychological and physical symptoms in patients with advanced lung cancer, both in the short and long term. There has been minimal examination of lung cancer survivorship in the era of novel immunotherapies and targeted therapies, which are extending survival. There is a need for studies that test the effectiveness of new and existing behavioral treatments in this population, with the goal of improving quality of life, the standard of care, and survival rates.

To address these gaps, a Phase IIa study examined the effectiveness of the ABC treatment to improve patient outcomes: psychological symptoms, physical symptoms, and systemic inflammation. Prior research has demonstrated the effectiveness of the Biobehavioral Intervention and Cognitive Therapy in improving psychological and physical symptoms in other cancer types; the two treatments were combined here and tailored to create A Biobehavioral/ Cognitive (ABC) therapy for patients with advanced NSCLC. The study tested the provision of an efficacious psychological treatment for patients with NSCLC and depression and/or anxiety to improve quality of life and health. Outcomes were measured at two follow-ups: ABC week 5 (mid-treatment) and ABC week 10 (post-treatment). This design allows for tracking symptom change over time, identifying the point(s) at which the intervention may have the greatest effect, and utilizing robust repeated measures analyses. Exploratory analyses compared ABC group outcomes with archival data from NSCLC patients accrued at diagnosis to an observational cohort study.

Aims and Hypotheses

A Phase IIa design with repeated measures will evaluate the feasibility and effectiveness of ABC to improve psychological and physical health and prevent worsening of systemic inflammation for patients with NSCLC (N=30) reporting significant depressive and/or anxiety symptoms. As an exploratory aim, data from the ABC study will be compared to data from a matched control sample drawn from patients (N=220 available) enrolled in an ongoing observational NSCLC cohort study (Beating Lung Cancer in Ohio [BLCIO]). Matching variables will be baseline PHQ-9 score, sex, partner status, and treatment type. Controls received standard

of care treatment for lung cancer, and completed the same measures and routine blood draws for laboratory tests at comparable time points.

Aim 1

To conduct a Phase IIa pilot of A Biobehavioral/Cognitive (ABC) therapy intervention (*N*=30) to determine feasibility, tolerability, and acceptability.

Hypothesis. ABC will be a) feasible: accrual of *N*=30, with 75% completing 5 of 10 sessions, and 70% achieving 12-week retention (among those surviving 12 weeks); b) tolerable: depressive and anxiety symptoms will not worsen; and c) acceptable: patients will be satisfied with treatment.

Aim 2

To determine the effectiveness of ABC by assessing change over the course of treatment in patient-reported outcomes (PROs) and disease biomarkers.

Hypothesis 2a. Patients receiving ABC treatment will show significant reductions in depression, anxiety, and stress, and no worsening of physical symptoms. It is unclear if there will be change in systemic inflammation, as assessed by biomarker cell ratios (NLR, PLR, PAR, ALI). For patients beginning ABC with a diagnosis (e.g., MDD), remission is predicted.

Hypothesis 2b. Patients' self-reported depressive symptoms (measured by the Center for Epidemiological Studies Depression scale [CES-D]) during ABC intervention will show a significant session-by-session decline.

Exploratory Aim 3

PROs and disease biomarker data from the ABC group will be compared with archival data from BLCIO patients (*N*=30). Groups will be matched on baseline PHQ-9 score and the following demographic and treatment variables: sex (male vs. female), due to sex differences in

rates of depressive disorder diagnosis and presentation (Cavanagh et al., 2017; Salk et al., 2017); partner status (present vs. absent), as being partnered is a protective factor for individuals with depression (Buckman et al., 2021); and treatment type (e.g., chemotherapy vs. immunotherapy), due to differences in adverse event profiles (Schirrmacher, 2019).

Hypothesis. On the variables specified, significant Group (ABC vs. BLCIO) by Time (baseline vs. follow-up) interactions are hypothesized. It is predicted that the ABC group will show, across time, significant improvements on psychological and physical health measures and stability (no significant increases) in inflammation, in comparison to the BLCIO group.

Chapter 2: Method

Design

A Phase IIa single-group design with repeated measures (baseline, follow-up 1 at ABC treatment week 5, follow-up 2 at ABC treatment week 10) was used to test the feasibility and effectiveness of ABC treatment for patients diagnosed with advanced (stage IV) NSCLC and comorbid depression and/or anxiety. Of those enrolled (N=30), N=19 engaged in study activities after providing informed consent. An exploratory aim compared ABC patients to matched control patients (N=19) from the BLCIO (NCT03199651) observational cohort receiving standard care. Matched variables were baseline PHQ-9 score, sex (male vs. female), partner status (present vs. absent), and treatment type (e.g., chemotherapy vs. immunotherapy).

Procedures

All study procedures were approved by the Cancer Institutional Review Board of The Ohio State University. Patients were accrued at The Ohio State University Comprehensive Cancer Center from May 2021 to June 2022. Eligibility was determined via review of patients' historical and present electronic medical records (EMR) and consent by the patient when approached in the clinic. Inclusion criteria were: 1) advanced (stage IV) NSCLC; 2) moderate to severe symptoms of depression (≥8 on Patient Health Questionnaire-9 [PHQ-9]) and/or moderate to severe symptoms of anxiety (≥10 on Generalized Anxiety Disorder-7 [GAD-7]); 3) English-speaking; 4) willingness to provide access to EMR and responses to PRO assessments; and 5) ability to understand and willingness to sign informed consent document. Exclusion criteria

were: 1) treatment with definitive chemo-radiotherapy; 2) presence of untreated brain metastases; 3) previous lung cancer diagnosis; 4) presence of disabling hearing, vision, or impairing psychiatric conditions preventing consent or completion of self-report measures; 5) imminent risk of suicide that precludes outpatient treatment; and 6) currently receiving psychological treatment/counseling.

Patients were approached for participation in the clinic or by telephone by a trained research staff member. Appendix C provides the patient recruitment brochure utilized in the clinic. Figure 1 provides the CONSORT flow diagram representing patient screening, recruitment, and retention. The essential elements of obtaining informed consent included description of the study and of ABC treatment and assessments; description of the process of withdrawal from the study; and explanation of the risks, benefits, and limits of study participation. Following consent, patients completed baseline assessments in-person or via RedCap survey sent by email, and research personnel conducted a Structured Clinical Interview for DSM-5 (SCID-5; modules for major depressive disorder, persistent depressive disorder, adjustment disorder, and generalized anxiety disorder) to establish current psychiatric diagnoses. The presence/absence of a psychiatric diagnosis was not an inclusion/exclusion criterion.

Once assessed, ABC sessions began as soon as feasible. Sessions were conducted in person or via telehealth, according to each patient's preference. Sessions occurred once per week for 60 minutes each. At the start of each session, the therapist verbally administered the CES-D depression symptom measure; the patient's score was used to inform the conduct of the session. At baseline (pre-treatment), follow-up 1 (ABC week 5), and follow-up 2 (ABC week 10), self-report assessments were completed (in person, via RedCap survey sent by email, or via

telephone, per patient preference). Patients received a $5 gift card for each completed assessment.

Patient medical records were accessed for sociodemographic information, lung cancer diagnoses and treatments, and survival. All accrued patients were followed until withdrawal of consent, regardless of ABC or cancer treatment adherence. Patients completing all ABC sessions were engaged in study activities for approximately 6 months in total (about 3 months of weekly engagement, followed by about 3 months of monthly engagement).

For the comparison group enrolled in the Beating Lung Cancer in Ohio (BLCIO) study, research procedures were approved by the Cancer Institutional Review Board of The Ohio State University. BLCIO was an observational cohort study conducted by the Ohio State University Comprehensive Cancer Center (OSUCCC; accrual from June 2017 to June 2021). Inclusion criteria were: 1) stage IV NSCLC; 2) receiving treatment at an Ohio institution within the network established for this study; 3) English-speaking; and 4) willing to provide access to EMR and biospecimens and to complete questionnaires. Exclusion criteria were: 1) treatment with definitive chemo-radiotherapy or surgery; 2) less than 18 years of age; 3) receiving treatment for advanced lung cancer for over one month before enrollment; and 4) hearing or vision impairments that would prevent ability to complete consent or study procedures.

Regarding accrual to BLCIO, patients were approached for participation in the clinic by trained recruiters. Within 2 weeks of enrollment, patients were contacted via phone by trained, non-university-affiliated interviewers (Strategic Research Group [SRG] staff) for baseline assessment. Thereafter, patients were contacted every month for the first 8 months and then every 2 months until 24 months. BLCIO measures included all ABC measures except the Center for Epidemiological Studies Depression (CES-D) scale. The BLCIO baseline assessment was

approximately 40 minutes in duration, and each follow-up assessment was 20-30 minutes in duration. Patients were compensated $40 for the baseline assessment and $15 for each follow-up.

ABC Treatment

ABC was manualized for therapists and patients (Appendix D). For therapists, this enabled procedural consistency of content delivery, between-session homework assignments, and assessments. A corresponding manual for patients provided added guidance for content and procedures, and also served as a record of the treatment material and the patient's progress toward treatment goals.

Treatment was provided by MA-level clinical psychologists with supervision by a PhD-level, licensed psychologist. All SCID-5 assessors (*n*=4) and therapists (*n*=3) received 6 hours of training (2 hours for SCID-5, 4 hours for ABC) at the start of their engagement with the study, followed by monthly supervision (1 hour per month).

All SCID-5 assessments and ABC sessions were video- and audio-recorded and saved in a password-protected digital folder available to study personnel only. Recordings enabled video review to ensure 1) interrater reliability on diagnoses determined per SCID-5 assessments and 2) adequate delivery of treatment material for each ABC session. To reduce potential bias, study therapists did not administer the SCID-5 to patients for whom they delivered the intervention.

Table 1 (Appendix B) delineates the major treatment components by session. Of note, session 2 and all subsequent sessions began with a brief, therapist-led practice of progressive muscle relaxation (PMR) and review of homework completion.

Biobehavioral Intervention Components

Sessions 1 through 10 have the Biobehavioral Intervention (BBI) as their foundation. Session 1 orients the patient to therapy by giving a treatment overview and rationale, which includes education on the bidirectional relationship between cancer and stress and identifies stress as a treatment target. The patient is prompted to reflect on their reaction to initially hearing their cancer diagnosis, and the General Adaptation Syndrome (Selye, 1950) is discussed and applied to the patient's experience. An introduction to PMR is provided and the protocol is practiced in session. Patients are encouraged to practice PMR on their own, using CD or MP4 audio files provided.

Session 2 provides skills to support patients in seeking and asking for disease- and treatment-related information. The action of gathering information is described as a coping skill for patients and family members. Using manual worksheets, the therapist and patient work together to reflect on disease and treatment information already known and questions that remain. The "take PART" (prepare, ask, repeat, take action) method for communicating with one's medical team is introduced. Patients are encouraged to apply this method over the week, and to continue practicing PMR at home.

Session 3 provides a step-by-step method to approach problem-solving. The patient chooses a current personal problem, and together with the therapist completes the following steps: define the problem, brainstorm solutions, and weigh options to choose the best solution. They then discuss carrying out the plan, and the possibility of needing to repeat the process with an alternate solution is normalized. The manual provides detailed worksheets to guide each step.

Session 4 addresses two of the most common symptoms reported by patients with advanced lung cancer: dyspnea (breathlessness) and sleep disturbance. Patients are asked to describe their existing methods for coping with dyspnea, and are then provided with two

evidence-based techniques to manage this symptom: pursed-lip breathing and postural changes. The rationale for the effectiveness of these methods is discussed, and illustrations to guide learning and practice are provided. The skills are practiced together in session. Then, the relationship between sleep quality and mental health is described. Sleep hygiene techniques, such as stimulus control and maintaining a nightly routine, are discussed. Patients are encouraged to practice breathing techniques and sleep hygiene habits over the coming week.

Session 5 focuses on teaching and developing assertive communication skills. Assertiveness is defined and examples from the patient's experience are discussed. The mnemonic "CODE" is introduced, encouraging the patient to speak with clarity, own the message, direct the communication, and then evaluate. In addition, the impact of non-verbal cues is incorporated into the discussion. Therapist and patient brainstorm methods to support the patient in practicing assertive communication with family, friends, and even strangers.

Session 6 guides the patient through identifying their social network. The patient is asked to reflect on ways in which relationships have changed expectedly or unexpectedly since their cancer diagnosis. Psychoeducation is provided on the relationship between stress and social support. Multiple types of support (e.g., emotional support, task support) are defined and discussed. The patient creates a list of individuals in their social network, and then uses that information to complete the 'Closeness Circle' diagram provided in the study manual. The patient is encouraged to reflect on social network satisfaction vs. needs for further support.

Session 7 continues the discussion on social network, now applying the previously learned assertive communication skills to help the patient ask for the support they need. The goal is to enhance communication in order to mobilize support. In-session role play is utilized to

allow the patient to practice these skills. The therapist introduces the option of lung cancer support groups and references local and national opportunities to join such groups.

Session 8 is the final session concentrating on social support. The activities completed and skills learned in the previous two sessions are reviewed. The patient is asked to reflect on any changes in support received and the ways in which assertive communication may have contributed to change. The topic of mutual support is introduced and discussed. For patients with a partner, strategies for improving support within the relationship are discussed. The patient is encouraged to consider how their partner is coping, communication strategies that have been effective in the past, and areas for improvement in providing/receiving support in the relationship.

Session 9 emphasizes the importance of maintaining physical activity throughout the lung cancer illness and treatment experience. The discussion is tailored to the patient's abilities and limitations at present. Possible assumptions about the definition of physical activity are challenged and restructured. The physiological and psychological benefits of physical activity are discussed. Therapist and patient collaboratively create short-term and long-term physical activity goals for the patient. The manual provides an activity log for the patient to track progress toward goals over the coming weeks.

Session 10 guides the therapist and patient through a review of the major topics covered and skills learned during the biobehavioral treatment sessions. The manuals provide worksheets to facilitate goal-setting as related to maintaining or refining these skills. This session also includes a discussion of next steps, i.e., completing the cognitive therapy sessions or transitioning to monthly maintenance sessions, depending on results of the SCID-5 reassessment.

Cognitive Behavioral Therapy Components

Sessions 11 through 14 focus on the cognitive elements of cognitive behavioral therapy (CBT). When compared to previous research, the depth of cognitive elements in the current study approximates that in cognitive therapy trials for treating depression (Hollon & Dimidjian, 2014; Pasarelu et al., 2017; Strunk et al., 2010).

Session 11 introduces the CBT model and the process of identifying automatic negative thoughts. The manual provides a thought log to facilitate in-session and homework practice in identifying and recording thoughts. Additionally, problematic thinking patterns (e.g., all-or-nothing thinking, jumping to conclusions) are explained and discussed as they relate to the patient's experience.

Session 12 builds on the previous session by teaching the patient to generate alternative thoughts to automatic negative thoughts. After reviewing the patient's logged thoughts from the previous week and collaboratively identifying patterns or recurring themes, the therapist and patient work to challenge the negative thoughts and restructure them. An example of a completed thought record is used to facilitate this task. The patient is asked to complete their thought record 3 times per day over the next week.

Session 13 involves a review and continued practice of the skills from the previous two sessions. After reviewing completed homework, the therapist and patient continue to practice restructuring the patient's current/recent thoughts, as well as hypothetical thoughts provided by the therapist based on common experiences in lung cancer. Identification of problematic thinking patterns is incorporated into the practice. Additionally, this session introduces the importance of behavioral activation and its positive effects on mood. The patient is encouraged to identify activities that provide a sense of pleasure and/or accomplishment, and to plan specific activities for the coming week. A calendar worksheet for scheduling activities is provided in the manual.

Session 14 further reviews the skills learned and applied in the past three sessions, and utilizes motivational interviewing to prepare the patient for the maintenance phase. After reviewing homework completion, the major CBT topics (identifying negative automatic thoughts, generating alternative thoughts, recognizing problematic thinking patterns, using behavioral activation to improve mood) are discussed as a cohesive unit. The patient is encouraged to continue applying these skills moving forward. The manual's "Reasons for Committing" and "Actions to Take" worksheets are completed in session to enhance motivation and identify actionable steps for continued use of the cognitive and behavioral skills.

Maintenance Components

Four monthly sessions provide a review of the treatment's major topics, monitor patients' progress toward goals, and deliver any necessary assistance for maintaining progress and/or setting new goals. Maintenance session 1 reviews the social support topics (e.g., identifying existing network and further support needs, distinguishing between task and emotional support) and assertive communication (e.g., speaking in "CODE," utilizing nonverbal cues, active listening). Therapist and patient reflect on any changes since the introduction of these topics. A goals worksheet provided in the manual is completed in session.

Maintenance session 2 reviews the physical activity and sleep hygiene topics. The connections between these behaviors and physical and mental health are revisited. The patient is asked to reflect on any developments in these areas since initial discussion. Therapist and patient engage in problem-solving to address any barriers to the patient's progress toward physical activity and/or sleep goals. Motivational interviewing is used as appropriate.

Maintenance session 3 focuses on monitoring the patient's progress toward previously established goals, and provides another opportunity for the therapist to support the patient in

addressing any potential barriers. The “SMART” goal-setting technique is utilized throughout the discussion. Patient feedback is solicited.

Maintenance session 4 serves as the final check-in and provides an opportunity for the therapist and patient to reflect on ongoing progress toward goals and any other reflections from the patient. The patient’s efforts and accomplishments are reinforced, and they are encouraged to maintain use of skills learned over the course of treatment. A detailed worksheet describing each of the ABC skills and suggestions for appropriate goals is provided in the manual for long-term reference.

Modifications to ABC Delivery and Assessments

The following changes were implemented. A stepped approach (BBI, followed by CBT if needed, ending with maintenance for all) was found to be infeasible due to patient attrition and mortality. Additionally, the criteria for treatment adherence and the assessment time points were changed. Originally defined as 75% of patients completing 7 of 14 sessions (core BBI treatment plus CBT), adherence was redefined as 75% completing 5 of 10 sessions (core BBI treatment only). The proposed assessment time points (pre-treatment, post-treatment, and two follow-ups for maintenance) were modified to baseline (pre-treatment), follow-up 1 (ABC week 5, “mid-treatment”), and follow-up 2 (ABC week 10, “post-treatment”).

Control Group (BLCIO)

BLCIO patients received standard of care (SOC) in the OSUCCC Thoracic Oncology clinic. SOC did not include screening for psychological disorders or triaging to social services. BLCIO assessments did include measures of depression (PHQ-9) and anxiety (GAD-7)

symptoms, which were monitored. If elevated, a letter was sent to the oncology team with the ASCO guidelines for assessment and treatment of depression and anxiety (Andersen et al., 2014). The BLCIO archive also provided clinical data, including lab values relevant for the present study's examination of biomarkers.

Measures

Measures are listed in Table 2 by name and frequency of assessment. See Appendix E for full description of items comprising each measure.

Sociodemographic and Disease Characteristics

Sociodemographics determined were age, sex, race, marital status, smoking history, education level, employment status, and household income. Disease characteristics were NSCLC histology, metastatic sites, time since diagnosis, treatment type (e.g., chemotherapy, immunotherapy), and treatment line at study enrollment. Psychiatric history (i.e., former diagnoses, psychotherapy, and psychiatric medications) was obtained via patient report and EMR data abstraction.

Aim 1 Measures

Feasibility, Tolerability, and Acceptability. Records of patient enrollment and attendance were used to calculate accrual and retention. The pilot was considered feasible if 30 patients were accrued, 75% completed 5 of 10 sessions, and 70% were retained 12 weeks after enrollment. The intervention was considered tolerable if depressive and anxiety symptoms, measured by the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 scale (GAD-7; see below) did not worsen over the course of treatment. Acceptability was measured at each patient's final study session by the experimenter-derived Patient Satisfaction

Survey (PSS). The PSS is a 15-item measure which asks patients to rate each intervention component on a 4-point Likert scale ranging from 1 ("not at all helpful") to 4 ("very helpful"). For example, patients were asked, "How helpful were the problem-solving skills discussed and practiced during ABC?" Items are summed and averaged, in line with previous research (Andersen et al., 2007). An average score of 3 or higher is considered to represent treatment satisfaction.

Aim 2 Primary Measures

Psychiatric Diagnoses at Enrollment. The Structured Clinical Interview for DSM-5 Disorders (SCID-5; First et al., 2015) determined psychiatric diagnoses. Four modules were used: those for major depressive disorder, persistent depressive disorder, adjustment disorder, and generalized anxiety disorder. Each interview was conducted via telehealth and took 20-40 minutes.

Depressive Symptoms. 1) The Patient Health Questionnaire-9 (PHQ-9; Kroenke & Spitzer, 2002) assesses depressive symptomology experienced during the preceding two weeks. Its 9 items are scored on a 4-point scale ranging from 0 ("not at all") to 3 ("nearly every day"). Total scores range from 0 to 27, with higher scores indicating more severe depressive symptoms. Cutoff scores indicate mild (5-9), moderate (10-14), moderately severe (15-19), and severe (20-27) depressive symptoms. Internal consistency of 0.86 to 0.89 and 48-hour test-retest reliability of 0.84 have been reported (Kroenke et al., 2010). For the present study, Cronbach's alpha for the PHQ-9 at baseline was 0.88.

2) The Center for Epidemiological Studies Depression scale (CES-D; Radloff, 1977) assesses depressive symptomology experienced during the preceding week. Its 20 items are scored on a 4-point scale ranging from 0 ("rarely or none of the time") to 3 ("most or all of the

time"). Total scores range from 0 to 60, with higher scores indicating more severe depressive symptoms. A score of 16 points or higher is considered to represent a clinical level of depression. Internal consistency > 0.85 has been reported (Hann et al., 1999). For the present study, Cronbach's alpha for the CES-D at baseline was 0.90.

Anxiety Symptoms. The Generalized Anxiety Disorder 7-item scale (GAD-7; Spitzer et al., 2006) assesses generalized anxiety symptoms experienced during the preceding two weeks. Its 7 items are scored on a 4-point scale ranging from 0 ("not at all") to 3 ("nearly every day"). Total scores range from 0 to 21, with higher scores indicating more severe anxiety symptoms. Clinical levels and corresponding scores are as follows: mild (5-9), moderate (10-14), and severe (15-21). Internal consistency of 0.92 and 1-week test-retest reliability of 0.83 have been reported (Kroenke et al., 2010). For the present study, Cronbach's alpha for the GAD-7 at baseline was 0.91.

Cancer-Specific Stress. The Impact of Events Scale-Revised (IES-R; Horowitz et al., 1979; Weiss & Marmar, 1997) assesses cancer-specific stress, operationalized by intrusive thoughts about lung cancer and avoidant thoughts/behaviors (e.g., "I tried not to talk about lung cancer"), present in the past week. Its 22 items are scored on a 5-point scale from 0 ("not at all") to 4 ("extremely"). Total scores range from 0 to 88, with higher scores indicating more severe cancer-specific stress. Cutoff scores are as follows: $\geq$24 indicates stress as a clinical concern; $\geq$33 indicates a post-traumatic stress level; and $\geq$37 indicates stress capable of suppressing immune system function. Internal consistency of 0.88 has been reported (Weiss & Marmar, 1997). For the present study, Cronbach's alpha for the IES-R at baseline was 0.86.

Physical Symptoms. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Lung Cancer Module (LC-13; Bergman et al., 1994) assesses lung

cancer-associated symptoms, such as coughing, hemoptysis, dyspnea, and pain, as well as treatment side effects, such as alopecia, neuropathy, sore mouth, and dysphagia. The 14 items are each scored on a 4-point scale from 1 ("not at all") to 4 ("very much"). Total scores range from 0 to 42, with higher scores indicating greater symptom severity/frequency. For the present study, Cronbach's alpha for the LC-13 at baseline was 0.74.

Systemic Inflammation Biomarkers. Abstraction of EMR laboratory reports provided cell counts, albumin values, and height/weight corresponding to patients' ABC assessment time points (+/- 5 days). Neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. Platelet-to-lymphocyte ratio (PLR) was calculated by dividing platelet count (10^9/L) by the absolute lymphocyte count. Platelet-to-albumin ratio (PAR) was calculated by dividing the platelet count (10^9/L) by the serum albumin level (g/L). The advanced lung cancer inflammation index (ALI) was calculated by multiplying body mass index (BMI) by the quotient of albumin (g/dL) and NLR (i.e., ALI = BMI × Albumin / NLR), where BMI = weight (kg) / height $(m)^2$.

Aim 2 Secondary Measures

Social Support. 1) The Social Network Index (SNI; Cohen et al., 1997) assesses participation in/closeness of 12 types of social relationships. For the present study, the following 6 items from the SNI were included and summed for a total score: number of individuals living in household, number of close relatives, number of close friends, number of relatives/friends in regular contact (i.e., communicate at least once monthly), group membership (e.g., social or professional organizations), and importance of religion. The items assessing number of close relatives, number of close friends, and number in regular contact were each coded on a 3-point scale: 0 (none), 1 (2-5 individuals) or 2 (6 or more individuals). Group membership was scored

yes (1) or no (0), and importance of religion was scored on a 5-point scale ranging from 0 ("not at all important") to 4 ("very important"). Total scores range from 0 to 15, with higher scores indicating greater social support. Cronbach's alpha for the SNI at baseline was 0.69.

2) The National Institutes of Health Social Support scale (NIH-SS; Cyranowski et al., 2013) assesses perception of social support, including emotional support, task support, friendship, loneliness, rejection, and hostility. Its 16 items are scored on a 5-point scale ranging from 0 ("never") to 4 ("always"). Total scores range from 0 to 64, with higher scores indicating greater perceived social support. Cronbach's alpha for the LC-13 at baseline was 0.87.

Functional Status. The European Quality of Life 5-dimension 5-level questionnaire (EQ-5D-5L; Herdman et al., 2011) is a 5-item measure of functional status and quality of life. The present study used the 3 functional status items (mobility, self-care, and completion of usual activities), each scored on a 5-point scale ranging from 0 ("unable to do") to 4 ("no problems"). Items were analyzed separately rather than as a summed score; higher individual scores indicate greater functional ability in that domain.

Overall Health. The European Quality of Life Visual Analogue Scale (EQ-VAS; Group, 1990) is a single-item visual analogue scale that assesses self-rated overall health status. It was designed to be used for individuals with a variety of health conditions. Patients are asked to select a numerical rating based on their current health. The anchors are 0 ("the worst health you can imagine") to 100 ("the best health you can imagine"). Thus, a higher score indicates perception of greater overall health. Three-month test-retest reliability of 0.84 has been reported (Macran, 2003).

Analytic Plan

Aim 1

Descriptive statistics of sociodemographic characteristics, NSCLC disease and treatment characteristics, psychiatric diagnoses upon enrollment, and psychiatric history were calculated for the ABC group. For patients beginning ABC with a diagnosis (e.g., MDD or GAD), descriptive analyses were performed to assess for remission.

To measure feasibility, descriptive statistics of patient enrollment, treatment adherence, and retention rate for ABC were conducted. For tolerability, dependent-samples *t*-tests examined whether depressive or anxiety symptoms worsened from baseline to follow-up. For acceptability, descriptive statistics examined if patient satisfaction scores for ABC were "mostly satisfied" (i.e., mean ≥ 3 on Patient Satisfaction Survey).

Aim 2

Primary Analyses. For all primary outcomes at all time points, descriptive statistics were run to determine mean, median, range, and standard deviation values. Paired-samples *t*-tests were conducted to evaluate change between baseline and follow-up values. For each outcome, the reliable change index (RCI) was calculated to serve as an indicator of clinically significant change.

Longitudinal mixed-effects modeling (Raudenbush & Bryk, 2002) was used with 3 data points (baseline, follow-up 1, follow-up 2) to determine change over the course of ABC treatment in each primary outcome: depressive symptoms, anxiety symptoms, cancer-specific stress, physical symptoms, and systemic inflammation. Pairwise comparisons determined change from baseline to each follow-up, and between the two follow-up points. Each analysis estimated baseline symptoms (random intercept) and rate of change (random slope), and included

covariates selected based on significant Spearman correlations with outcomes. A significant Time effect across outcomes was predicted.

Secondary Analyses. For all secondary outcomes at all time points, descriptive statistics were run to establish mean, median, range, and standard deviation values. Paired-samples *t*-tests were conducted to evaluate change between baseline and follow-up values.

Exploratory Aim 3

Matching. ABC patients and BLCIO patients were matched on the following variables: baseline PHQ-9 score, sex (male vs. female), partner status (present vs. absent), and treatment type (e.g., chemotherapy vs. immunotherapy). The two sample sizes were equivalent (each *N*=19).

Preliminary Analyses. Independent samples t-tests compared the ABC and BLCIO groups on baseline PHQ-9 scores, and descriptive statistics compared the two groups on baseline values of other matching variables (sex, partner status, treatment type). Then, the two groups were compared on all other relevant baseline variables (age, race, smoking status, education, employment status, annual household income, time since cancer diagnosis, cancer treatment line, prior psychiatric diagnosis, and baseline GAD-7 score).

Primary Analyses. Longitudinal mixed-effects modeling was used to determine differential rates of change in outcomes between groups (ABC, BLCIO). It was predicted that a significant Group x Time interaction would show differential rates of change in outcomes between the ABC and BLCIO groups across time (i.e., baseline, follow-up 1, follow-up 2).

Chapter 3: Results

Aim 1

Preliminary Analyses

Sociodemographic characteristics, NSCLC disease and treatment characteristics, psychiatric diagnoses upon enrollment, and psychiatric history for the ABC treatment sample (*n*=19) and patients who signed consent only (*n*=11) are provided in Tables 3 and 4. For the full sample (*N*=30), the mean age was 65.1 years old (*SD*=8.71, range 46-85). The sample was mostly female (60%), White (90%), married (47%), and disabled/retired (79%), with a former smoking history (57%). The modal education level was a high school diploma (*n*=9), and most participants (71%) reported an annual household income between $15,000 and $50,000. The only significant sociodemographic difference between the ABC treatment sample (*n*=19) and patients who signed consent only (*n*=11) was race; the treatment sample was more racially diverse than the consent-only group.

Regarding disease and treatment characteristics, the majority (95%) of the sample (*N*=19 patients engaged in the study after informed consent) had adenocarcinoma, the most prevalent histologic type of NSCLC. Patients' sites of metastatic disease included brain (*n*=12, 63%), bone (*n*=8, 42%), and other, such as liver, pancreas, or lymph nodes (*n*=17, 90%). Treatment type happened to be proportionally distributed in the sample (21% chemotherapy only, 21% chemotherapy plus immunotherapy, 5% chemotherapy plus targeted therapy, 21% immunotherapy only, 21% targeted therapy only, 11% no active treatment). Eleven patients

(58%) were receiving their first line of cancer treatment, ten of whom were within the first year since initial cancer diagnosis (53% of sample).

Primary Analyses

Feasibility. Regarding accrual, the goal of 30 patients enrolled was met; 19 of 30 (63.3%) engaged in study activities beyond consent. Adherence to treatment, including dropout due to patient decision vs. morbidity/mortality, is depicted in Figure 2. Of the 19 patients, the mean number of sessions completed was 5.11 (*SD*= 4.83, range= 1-14 sessions). Nine of 19 patients (47.4%) completed at least 5 of 10 sessions. With respect to retention, 11 patients (57.9%) participated in study activities for 12 weeks or longer. Between-session homework completion (dichotomized as yes [completed $\geq$50% of homework for the week] vs. no [completed <50% of homework for the week]) is represented in Figure 3 (55%-73% completion in sessions 1-5; 50%-100% completion in sessions 6-10).

Tolerability. Table 5 provides the mean PHQ-9 and GAD-7 scores at each time point. Both depressive and anxiety symptoms decreased (i.e., did not worsen) from baseline to follow-up. Examining individual patient trajectories, none experienced worsening of depressive or anxiety symptoms across time. Dependent samples *t*-tests determined that the overall improvement in symptoms was statistically significant, with large effect sizes (two-sided p=.002, d=1.29 for PHQ-9; two-sided p=.005, d=1.07 for GAD-7). The improvements in depressive and anxiety symptoms were clinically significant (see below).

Acceptability. Eleven patients completed the Patient Satisfaction Survey at their final study session. The mean score was 3.44 (*SD*= 0.22) out of 4.00, which is above the 3.00 threshold representing treatment acceptability. Moreover, all individual scores were above 3.00

(minimum = 3.10, maximum = 3.75), indicating that each of these patients rated the intervention as acceptable.

Aim 2

SCID-5 assessments to determine psychiatric diagnoses at study enrollment found 6 of 19 patients (32%) met criteria for both MDD and GAD, 2 (11%) for MDD alone, 2 (11%) for GAD alone, and 6 (32%) for adjustment disorder. Three individuals (16%) did not meet criteria for a psychiatric diagnosis. These data show that the PHQ-9 and GAD-7 were appropriate measures for screening. Considering psychiatric history, the majority denied prior psychiatric diagnosis or psychotherapy (79% and 84%, respectively). However, most patients (58%) endorsed former or current use of medications to address mood, nerves, or sleep quality.

Descriptive analyses evaluated remission of MDD and/or GAD over the course of the ABC intervention. The patients who met criteria for MDD at baseline (n=8) had a mean PHQ-9 score of 15.5, indicating moderately severe depressive symptoms. At follow-up 1, the remaining patients from this subset (n=4) had a mean PHQ-9 score of 7.3, indicating mild depressive symptoms. The patients who met criteria for GAD at baseline (n=8) had a mean GAD-7 score of 12.8, indicating moderate anxiety symptoms. At follow-up 1, the remaining patients from this subset (n=4) had a mean GAD-7 score of 5.8, indicating mild anxiety symptoms.

Primary Analyses

Table 5 provides descriptive statistics (mean, median, minimum, maximum, standard deviation) for the following Aim 2 primary outcomes at all time points: depressive symptoms (PHQ-9), anxiety symptoms (GAD-7), cancer-specific stress (IES-R), physical symptoms (LC-13), and markers of systemic inflammation (NLR, PLR, PAR, and ALI). In preface, the table

indicates the statistical significance and effect size of change for each outcome from baseline to follow-up 1, according to paired-samples *t*-tests.

Depressive Symptoms. The mean PHQ-9 score for ABC patients at baseline was 11.68, indicating moderate severity of depressive symptoms. At the two follow-ups, mean scores were 4.55 and 3.67, respectively, which fall below the cutoff (5.0) for mild severity and thus represent minimal depressive symptoms. The RCI for the PHQ-9 was 4.51, indicating that a reduction of at least 5 points would be considered clinically significant. Thus, according to the RCI, and considering the immediate and long-lasting benefits of reducing distress, a clinically significant change in depressive symptoms was observed for the ABC patients.

A random intercept model was used to test the effect of time on depressive symptoms measured by the PHQ-9. The longitudinal mixed-effects model used 3 data points (baseline, follow-up 1, follow-up 2). Age was included as a covariate based on a significant Spearman's correlation with depressive symptoms (PHQ-9) at baseline ($p = .045$, $r = -.466$). Fit statistics for this model and all other mixed-effects models are shown in Table 6. Using a significance level of 0.05, results indicate that depressive symptoms significantly decreased over time ($F[2,13] = 23.37$, $p < .001$). Pairwise comparisons indicated a significant decrease between baseline and follow-up 1 (95% CI = [4.71, 10.03], $p < .001$), and between baseline and follow-up 2 (95% CI = [5.21, 12.20], $p < .001$), but not between follow-up 1 and follow-up 2 (95% CI = [-4.83, 2.15], $p = .433$). A random slope model was also performed, indicating significant variation between patients in the effect of time on depressive symptoms ($F[3,21] = 15.31$, $p < .001$). The model selection criteria for the two models were nearly equivalent (i.e., AIC = 197.58 for random intercept; AIC = 196.12 for random slope). As the random intercept model was 0.482 times as probable as the random slope model to minimize information loss (exp[(196.12-197.58)/2]=

0.482), the random intercept model was selected. Figure 4 represents mean PHQ-9 scores at each of the three assessment time points.

Depressive symptoms were also measured by the CES-D in each ABC session. The mean CES-D score at ABC session 1 was 17.67; by ABC session 10 the mean score was 4.75. Since higher CES-D scores indicate worse symptomatology, and a cut score of 16 is commonly used to denote significant depression, the scores suggest that, on average, ABC patients were depressed at the start of their study participation and experienced a notable improvement in symptoms over the course of the intervention. The RCI for the CES-D was 10.25, indicating that a reduction of at least 11 points would be considered clinically significant. Thus, a clinically significant change in CES-D depressive symptoms was observed for the ABC patients.

To evaluate change in depressive symptoms from session to session, longitudinal linear mixed modeling was performed using CES-D scores collected at 14 time points (descriptive statistics for this outcome provided in Table 7). Employment (currently employed vs. disabled/retired) and treatment line (first vs. later) were included as covariates based on significant Spearman's correlations with depressive symptoms (CES-D) at baseline ($p = .033$, $r = -.617$ and $p = .024$, $r = .643$, respectively). The random intercept model indicated an overall time effect on depressive symptoms measured by the CES-D ($F[13,67] = 3.66$, $p < .001$). Pairwise comparisons (detailed in Table 8) indicated a significant decrease in depressive symptoms between Session 1 and Session 4 (95% CI = [3.33, 11.83], $p < .001$), and between Session 1 and Sessions 5 through 10 (all ps $< .001$). A random slope model was also performed, indicating significant variation between patients in the effect of time on depressive symptoms ($F[13,75] = 3.53$, $p < .001$), but model selection criteria (Table 6) showed this to be a poor fit in comparison to the random intercept model. Figure 5 illustrates mean CES-D scores at each ABC session.

Anxiety Symptoms. Following a trajectory similar to the depressive symptoms measured by the PHQ-9, ABC patients' anxiety symptoms measured by the GAD-7 began in the moderate severity range (*M*=9.37) at baseline and decreased to the minimal symptom range (*M*=3.27, 2.00) at the two follow-ups. The RCI for the GAD-7 was 4.89, indicating that a reduction of at least 5 points would be considered clinically significant. Thus, a clinically significant change in GAD-7 symptoms was observed for the ABC patients. Reviewing the structure of the GAD-7 measure allows us to further highlight the clinical significance of this symptom reduction. A patient scoring a 9 or 10 on the GAD-7 may have been experiencing three to four anxiety symptoms (e.g., feeling unable to stop or control worrying, physical and mental restlessness, increased irritability) "nearly every day" over the past two weeks. Conversely, a score of 2 on the GAD-7 indicates that the patient reported experiencing two anxiety symptoms on "several days" or only one symptom "more than half the days" over the past two weeks. This relationship with worry is fully normal, and qualitatively demonstrates the absence/resolution of anxiety psychopathology.

A random intercept model was used to test the effect of time on anxiety symptoms measured by the GAD-7. The longitudinal mixed-effects model used 3 data points (baseline, follow-up 1, follow-up 2). Sex (male vs. female), education (high school diploma or less vs. some college or more), and income (coded 0 ["$15,000 or less"] to 9 ["more than $250,000"]) were included as covariates based on significant Spearman's correlations with anxiety symptoms at baseline (p = .049, r = -.457; p = .022, r = -.521; and p = .027, r = -.535, respectively). Results indicate that anxiety symptoms significantly decreased over time (F[2,11] = 9.48, p = .004). Following the same pattern as the PHQ-9, pairwise comparisons indicated a significant decrease between GAD-7 scores at baseline and follow-up 1 (95% CI = [2.93, 9.58], p = .001), and between baseline and follow-up 2 (95% CI = [1.58, 10.23], p = .013), but not between follow-up

1 and follow-up 2 (95% CI = [-3.81, 4.51], p = .861). A random slope model indicated significant variation between patients in the effect of time on anxiety symptoms (F[2,15] = 8.42, p = .004), but the model selection criteria for the two models were nearly equivalent (see Table 6). As the random intercept model was 0.44 times as probable as the random slope model to minimize information loss (exp[(136.42-138.06)/2]= 0.440), the random intercept model was selected. Figure 4 represents mean GAD-7 scores at each of the three assessment time points.

Cancer-Specific Stress. IES-R scores of 24 or higher indicate that post-traumatic stress disorder may be a clinical concern, with individuals scoring in this range likely to have full or partial symptoms of PTSD related to their cancer (McCabe, 2019; Weiss, 2007). The mean IES-R score for ABC patients at baseline was 24.5, suggesting that they were experiencing a trauma-like response to their lung cancer diagnosis and/or treatments. ABC patients' scores decreased to 14.9 at the first follow-up, and 10.3 at the second follow-up, suggestive of "routine life stress" (Weiss, 2007). The RCI for the IES-R was 15.13, suggesting that ABC patients' scores nearly reached the threshold for clinically significant change.

Mixed effects modeling utilizing the same 3 data points tested the effect of time on cancer-specific stress (IES-R). Education (high school diploma or less vs. some college or more) was included as a covariate based on its significant Spearman's correlation with cancer-specific stress at baseline (p = .022, r = -.551). The random intercept model indicated there was not a statistically significant decrease in this outcome over time (F[2,11] = 2.98, p = .093). Pairwise comparisons indicated a significant decrease from baseline to follow-up 2 (95% CI = [2.00, 27.75], p = .026), but not between baseline and follow-up 1 (95% CI = [-1.66, 22.29], p = .086), or between follow-up 1 and follow-up 2 (95% CI = [-15.43, 6.31], p = .359). A random slope model was also performed, indicating no significant variation between patients in the effect of

time on cancer-specific stress (F[2,14] = 2.55, p = .114); model selection criteria are represented in Table 6.

Physical Symptoms. LC-13 scores can range from 0 to 42, with higher scores indicating greater frequency of physical symptoms and/or greater severity of those symptoms. The mean score for ABC patients at baseline was 9.56, suggesting that, on average, patients were experiencing three to four symptom categories (e.g., pain, cough, dyspnea) with high intensity or a larger number of symptoms with moderate intensity. Of note, LC-13 scores at baseline ranged from 2 to 32, indicating a wide variety of experience with symptoms related to lung cancer and its treatments. At the two follow-up time points, mean LC-13 scores remained comparable to baseline (9.64 and 7.83, respectively).

Mixed effects modeling tested the effect of time on physical symptoms related to lung cancer (LC-13). Line of treatment (first vs. later) was included as a covariate based on its significant Spearman's correlation with physical symptoms at ABC baseline (p = .027, r=.520). The random intercept model indicated no significant worsening (or improvement) of physical symptoms across time (F[2,14] = 0.77, p = .482). There were no significant pairwise comparisons for this outcome (all ps > .244). A random slope model was also performed, indicating no significant variation between patients in the effect of time on physical symptoms (F[3,20] = 1.09, p = .377). Model selection criteria are represented in Table 6.

Systemic Inflammation Markers. Each of the four markers of inflammation followed a different trajectory over the course of the ABC study. At baseline, the NLR value (4.9) was slightly below the cutoff (5.0) for higher mortality, whereas the PLR, PAR, and ALI baseline values (288, 8.9, and 29, respectively) were indicative of worse overall survival. At the follow-up time points, PLR (254, followed by 301) and ALI (24, followed by 14) continued to reflect

high systemic inflammation, NLR increased above its 5.0 cutoff to values (9.0, then 7.4) predictive of worse overall survival, and PAR decreased below its 8.6 cutoff to values (5.7, then 6.1) associated with better overall survival.

To evaluate change/stability in markers of inflammation over the course of the study, linear mixed modeling was performed for each of the four biomarker outcomes. Based on Spearman's correlations with the outcomes at baseline, the following covariates were included: education (high school diploma or less vs. some college or more) with NLR (p = .019, r=.661); race (White vs. Black/Native American) with PLR (p = .025, r=.640); brain metastases (yes vs. no) with PAR (p = .014, r= -.684); and other metastases (yes vs. no) with ALI (p < .001, r= -.859). All four random intercept models indicated no significant changes in the inflammation biomarkers across time (NLR: F[2,7] = 1.29, p = .334; PLR: F[2,17] = 0.32, p = .731; PAR: F[2,7] = 1.55, p = .274; ALI: F[2,7] = 1.18, p = .362). There were no significant pairwise comparisons for these outcomes (all ps > .132). For each outcome, random slope models showed no significant variation between patients in the effect of time on inflammation (NLR: F[2,17] = 1.06, p = .367; PLR: F[2,24] = 0.29, p = .750; PAR: F[2,8] = 1.47, p = .284; ALI: F[2,17] = 1.28, p = .305). For each outcome, the model selection criteria between the random intercept model and random slope model were nearly equivalent (Table 6).

Secondary Analyses

Table 5 provides descriptive statistics (mean, median, minimum, maximum, standard deviation) for the following Aim 2 secondary outcomes at all time points: social network (SNI), social support (NIH-SS), functional status (EQ-5D-5L), and rating of overall health (EQ-VAS). Additionally, the table indicates the statistical significance and effect size of change in each outcome from baseline to follow-up 1, according to paired-samples t-tests. Results demonstrate a

statistically significant increase in perceived social support from baseline to follow-up 1, as measured by the NIH Social Support scale (p = .004, d = 1.11). At baseline, the ABC patients reported a mean NIH-SS score of 46 out of 64 points, which may represent perceptions of generally adequate social support, while acknowledging areas for improvement. At follow-up, the mean scores were 57 and 59, nearly reaching the maximum possible score. This suggests that ABC patients felt increasingly satisfied with the social support domains assessed by this measure: emotional support, instrumental support, friendship, and minimal loneliness and rejection.

For all other secondary outcomes, change from baseline to follow-up 1 was not statistically significant (ps > .076). SNI scores at all three time points (M=9.1, 10.0, 11.3 out of 15 possible points) indicated that ABC patients had moderately sized social networks which remained mostly stable over time. EQ-5D-5L scores showed that ABC patients were able to engage in self-care behaviors such as showering and dressing oneself (M=3.6, 3.3, 3.6 out of 4.0), were mostly able to maintain baseline levels of mobility (M=3.0, 3.3, 3.0), and experienced a slight decline in ability to complete one's usual daily activities (M=3.0, 2.9, 2.8). On the EQ-VAS at each time point, patients rated their current overall health as 57-68 on a scale from 0 (worst health) to 100 (best health).

Exploratory Aim 3

Matching

ABC patients and BLCIO patients were matched on the following variables: baseline PHQ-9 score, sex (male vs. female), partner status (present vs. absent), and treatment type (e.g., chemotherapy vs. immunotherapy). The two sample sizes were equivalent (each N=19).

Preliminary Analyses

The "success" of the matching procedure was evaluated. Baseline PHQ-9 scores for the ABC and BLCIO groups were equivalent (M=11.68, SD=4.99; M=11.42, SD=4.51, respectively). Independent samples t-tests confirmed no significant difference on this baseline measure between groups: d=.055, p=.866. Descriptive statistics comparing the two groups on baseline values of other matching variables (sex, partner status, treatment type) also showed no significant differences. Both groups consisted of 13 females (68%) and 6 males (32%). The ABC group consisted of 10 unpartnered (53%) and 9 partnered (47%) individuals, and the BLCIO group consisted of 11 unpartnered (58%) and 8 partnered (42%). The number of patients receiving each type of cancer treatment within the ABC and BLCIO groups, respectively, was as follows: chemotherapy only: 4, 3; chemotherapy plus immunotherapy: 4, 5; chemotherapy plus targeted therapy: 1, 0; immunotherapy only: 4, 5; targeted therapy only: 4, 3; no active treatment: 2, 3. Table 9 provides comparisons between the two groups on all other relevant baseline variables (age, race, smoking status, education, employment status, annual household income, time since cancer diagnosis, cancer treatment line, prior psychiatric diagnosis, and GAD-7 score).

Primary Analyses

Table 10 provides descriptive statistics (mean, standard deviation) for primary outcomes (depressive symptoms [PHQ-9], anxiety symptoms [GAD-7], cancer-specific stress [IES-R], physical symptoms [LC-13], and markers of systemic inflammation [NLR, PLR, PAR, and ALI]) for the ABC and BLCIO groups at all time points.

Depressive Symptoms. A random intercept model was used to test for a group by time interaction in depressive symptoms (PHQ-9). The longitudinal mixed-effects model (and all

models described below) utilized the study's three data points (baseline, follow-up 1, follow-up 2). Age was included as a covariate based on its significant Spearman's correlation with depressive symptoms at baseline. Results indicate a significant group by time interaction in depressive symptoms (F[2,45] = 3.91, p = .027), such that depressive symptoms decreased at a more rapid rate in the ABC group compared to the BLCIO group. Post-hoc pairwise comparisons of estimated marginal means tested all group and time differences and revealed large effects from baseline to follow-up 1 (Cohen's d = 0.92) and from baseline to follow-up 2 (d = 0.85) in the ABC group as compared to the BLCIO group. See Figure 6.

Anxiety Symptoms. A random intercept model was used to test for a group by time interaction in anxiety symptoms (GAD-7). There was no significant interaction between group and time (F[2,40] = 1.34, p = .273), indicating that the anxiety symptom trajectory did not significantly differ between ABC and BLCIO groups. See Figure 6.

Cancer-Specific Stress. A random intercept model was used to test for a group by time interaction in cancer-specific stress (IES-R). There was no significant interaction between group and time (F[2,26] = 0.45, p = .508), indicating that the trajectory of cancer-specific stress did not significantly differ between ABC and BLCIO groups. See Figure 6.

Physical Symptoms. A random intercept model was used to test for a group by time interaction in physical symptoms related to lung cancer (LC-13). There was no significant interaction between group and time (F[2,39] = 0.99, p = .381), indicating that the trajectory/stability of physical symptoms did not significantly differ between ABC and BLCIO groups. See Figure 6.

Systemic Inflammation Markers. Linear mixed modeling was performed to test for a group by time interaction in the following markers of inflammation: neutrophil-to-lymphocyte

ratio (NLR), platelet-to-lymphocyte ratio (PLR), platelet-to-albumin ratio (PAR), and advanced lung cancer inflammation index (ALI). In each of the four random intercept models, there was no significant interaction between group and time (NLR: $F[2,50] = 0.40$, $p = .673$; PLR: $F[2,55] = 0.36$, $p = .699$; PAR: $F[2,37] = 1.95$, $p = .157$; ALI: $F[2,31] = 0.82$, $p = .452$), indicating that the trajectory/stability of inflammation did not significantly differ between ABC and BLCIO groups (see Figure 6). It is relevant to consider these findings in the context of those described above, specifically that there was no time effect for the inflammation biomarkers. Of note, when data from follow-up 2 were excluded and a model was conducted to test for a group by time interaction from baseline to follow-up 1 in PAR, the model trended toward statistical significance ($F[1,32] = 3.37$, $p = .076$). A larger *n* at follow-up 2 may have enabled detection of a significant group by time effect in PAR across the duration of the study.

Chapter 4: Discussion

A Phase IIa study examined the effectiveness of A Biobehavioral/Cognitive (ABC) treatment in improving psychological and physical outcomes for patients with advanced NSCLC. Over the course of the ABC intervention, patient-reported depressive and anxiety symptoms significantly decreased. Additionally, patients reported a significant increase in social support. Lung cancer-specific physical symptoms remained stable. There were no statistically significant changes in cancer-specific stress, systemic inflammation, functional status, or rating of overall health. In comparing the ABC group with matched controls, there was a significant group by time interaction in depressive symptoms, such that depressive symptoms decreased at a more rapid rate for the ABC group compared to the controls. Group by time interactions were not found for the study's other primary outcomes. The clinical significance of the findings, as well as their contributions to advancing knowledge and improving clinical practice, are discussed.

Effectiveness of ABC: Depressive and Anxiety Symptoms

Depressive and anxiety symptoms significantly decreased when ABC was delivered. Declines occurred between baseline and the first follow-up, and effects were maintained through the second follow-up. Moreover, the changes were clinically significant. At baseline, the average depressive and anxiety scores were indicative of "moderate" symptom severity, for which psychotherapy is recommended and higher levels of systemic inflammation are expected (Andersen, Lacchetti, et al., 2023; Andersen, Myers, et al., 2023; Kroenke, 2021; Kroenke & Spitzer, 2002). At both follow-up time points, scores were indicative of "minimal" depressive

and anxiety symptom severity, which is below the threshold for ongoing surveillance or repeated assessment, and is not linked with heightened immune response.

Session-by-session assessment of depressive symptoms using the CES-D supports the finding of a reduction in depressive symptoms as measured by the PHQ-9 at baseline, follow-up 1, and follow-up 2. From ABC session 1 to session 10, the mean CES-D score decreased from 18 to 5 on a 60-point scale. Although the CES-D was not developed for diagnostic purposes, a score of 16 has been identified as the cutoff for identifying a "depressive case" (Eaton et al., 2004). In the ABC study, the initial mean CES-D score was above this cutoff, and subsequent scores dropped considerably below it (from 15 in session 2, to 5 in session 10), suggesting a resolution of "depressive cases" within the study.

Thus, two methods show that ABC patients experienced a statistically and clinically meaningful reduction in depressive symptoms. By addressing the psychological health of patients with advanced lung cancer, in combination with medical treatments focusing on their physiological health, the ABC intervention enables the multidisciplinary team to treat the whole patient. This form of integrated approach has been shown to improve general quality of life (Fernando, 2020). Moreover, there are benefits specific to advanced cancer. As depression in known to impede motivation and energy levels (Grahek et al., 2019), cancer patients with depression may delay or avoid medical help-seeking behaviors, such as attending appointments or adhering to medication regimens (Signorelli et al., 2020). By addressing depression, interventions such as ABC may support patients in progressing toward treatment goals, with implications for health and overall survival.

The level of detail provided by the CES-D data is valuable when considering the ideal treatment length for future iterations of the ABC study. Since statistically and clinically

significant depressive symptom reduction was found in four to six sessions, there is now empirical support for shortening the ABC intervention. This would be consistent with similar psychosocial interventions in advanced cancer settings, among which the most common treatment length is four ("brief intervention") to eight sessions (Warth et al., 2020).

Effectiveness of ABC: Cancer-Specific Stress and Physical Symptoms

The decrease in cancer-specific stress over the course of ABC treatment was not statistically significant, but nearly reached the threshold for clinically significant change per the RCI. The mean IES-R score at baseline (24.5) suggested that, on average, patients were experiencing a trauma-like response to their lung cancer diagnosis and/or treatments. This score indicates that patients were likely facing full or partial symptoms of PTSD, which may include intrusive memories, avoidance of thoughts or behaviors relevant to the stressor, and/or negative cognitions about the self or the world. By the second follow-up, the mean score (10.3) was suggestive of "routine life stress" (Weiss, 2007). The reduction from pathological to normative stress levels is meaningful, considering what is known about the psychological and physiological impacts of stress in the context of advanced cancer (Andersen et al., 1998; Brothers et al., 2011).

We hypothesized that ABC patients would show no significant worsening of lung cancer-specific physical symptoms over the course of the ABC intervention; this stability of symptoms was achieved. This consistency is notable, considering that physical symptoms, particularly cough, shortness of breath, chest pain, and fatigue, typically worsen over time in the context of lung cancer, especially when treated with chemotherapy (Bradley et al., 2019). Of note, while immunotherapies and targeted therapies have drastically improved overall survival, current research is indicating that these treatments are not associated with significant symptom improvement in stage IV disease.

The benefits of preventing symptom exacerbation are extensive, including improved quality of life, reduced frequency of emergency department visits and hospital bills, and lower likelihood of cancer treatment delays due to adverse events. It is possible that specific components of the ABC intervention (e.g., regular or intermittent use of PMR, assertive communication with the medical team, light physical activity) contributed to preventing a worsening of symptoms. It is also possible that repeated assessment of symptoms supported their stability over time, as previous studies have shown that web-based symptom monitoring during treatment, as compared to routine surveillance, can lead to reduced symptom burden and increased survival in individuals with lung cancer (Denis et al., 2019).

Effectiveness of ABC: Systemic Inflammation

In examining the effects of ABC on systemic inflammation, we explored changes across time in the biomarkers NLR, PLR, PAR, and ALI. Overall, systemic inflammation remained stable, with no statistically significant change over time in each cell ratio outcome. It is important to consider the findings in relation to their established cutoff scores. For these patients, the mean baseline NLR value (4.86) was slightly below the cutoff (5.0) for worse overall survival in NSCLC (Platini et al., 2022). NLR values at the two follow-up time points (9.0 and 7.4, respectively) rose to levels typically associated with worse survival, but did not drastically increase. We could speculate whether ABC played a protective role in this regard, meaning that in its absence NLR values might have increased more rapidly. However, there are very few studies in which markers of systemic inflammation are reported longitudinally. One study reported that change in NLR over time was a non-linear predictor of outcomes for patients with advanced cancer treated with immunotherapy (Li et al., 2019). Patients with a moderate decrease in NLR during cancer treatment were found to have the longest survival, whereas a dramatic

decrease or increase in NLR was associated with shorter survival. These findings emphasize that both the direction of change in inflammatory biomarkers and the speed at which they change are relevant factors in this domain.

The ABC patients' PLR and ALI values indicated high systemic inflammation at each time point during the study. PAR values followed a more favorable trajectory, with baseline values above the cutoff corresponding to worse overall survival, and follow-up values decreasing below the cutoff. This discrepancy may point to PAR as a more targetable measure of inflammation, which would advance knowledge related to improving survival in NSCLC. We may consider whether PAR could have a mediating effect, such that a reduction in PAR then contributes to reduction in other markers of inflammation. If this were the case, perhaps additional assessments in ABC would have revealed later decreases in inflammation per PLR and ALI. Such reflections present considerations for future research.

It is interesting to consider this study's inflammation-related findings in the context of other current studies. Although recent investigations (Andersen, Myers, et al., 2023) have demonstrated a strong association between systemic inflammation biomarkers and depressive symptoms in lung cancer, the ABC patients maintained overall stability in inflammation while depressive symptoms decreased across time. It is possible that ABC's sample size did not allow for significant changes in biomarkers, particularly PAR, to be detected.

Effectiveness of ABC: Secondary Outcomes

The following outcomes were also examined to assess for patterns of change over the course of the ABC intervention: social network (SNI), social support (NIH-SS), functional status (EQ-5D-5L), and rating of overall health (EQ-VAS). Of these, only the NIH Social Support scale demonstrated a statistically significant change over time: ABC patients reported a significant

increase in social support from baseline to follow-up. This increase was reflected in items assessing both emotional support (e.g., “I feel there are people I can talk to if I’m upset”) and task support (e.g., “I have someone to help me if I’m sick in bed”).

The literature indicates that support within a patient-provider relationship is associated with increased positive affect and sense of belonging (Shen et al., 2016). Thus, ABC’s design (i.e., connecting each patient with a supportive study therapist) may have improved perceptions of social support. Moreover, the reported increase in task support suggests that the change was not simply a reflection of being in therapy. It is plausible that the perceived increase in support was a product of engagement with the ABC material on identifying/enhancing social support, communication skills, and problem-solving.

The other measure examining social support, the Social Network Index, also showed increases over the course of the study, but on a smaller scale. The relative stability of SNI scores is logical, considering the typical consistency over time in the items assessed by this measure, e.g., “with how many other individuals do you live” and “do you belong to any religious, social, or professional groups?”

The EQ-5D-5L measured three functional status domains: mobility, ability to engage in self-care (i.e., personal hygiene), and ability to complete one’s usual daily activities. The EQ-VAS measured patients’ perceptions of their overall health at present. On average, these items did not change over the course of engagement with ABC. It is likely that missing data for the follow-up time points impacted these conclusions; the patients who dropped out of the study prior to completing one or both follow-up assessments were likely experiencing greater limitations in functional domains, and thus would rate their overall health more poorly than patients who remained on study.

Comparing ABC to BLCIO Matched Controls

Comparison of the ABC and BLCIO groups across time provided evidence that improvements in depressive symptoms in the ABC group were not simply due to the passage of time. The BLCIO sample was appropriate for such comparison, as it was comprised of patients with the same diagnosis (stage IV NSCLC), receiving the same cancer treatment options. The ABC and BLCIO samples were successfully matched on baseline PHQ-9 score, sex, partner status, and treatment type. Additionally, the two groups completed the same assessments and blood draws at comparable time points.

Results indicated a significant group by time interaction in depressive symptoms, such that depressive symptoms decreased at a more rapid rate for the ABC group compared to the controls. Both groups began in the moderate severity range. The ABC group's mean depressive score decreased by 7 points, reaching the 'minimal' symptom range, whereas the BLCIO group's score decreased by 3 points, falling just below the cutoff (10) for moderate symptoms. The greater decline in the ABC group as compared to the BLCIO group suggests that we may rule out the most plausible rival hypothesis (i.e., that symptoms naturally decreased over time) for the effect of ABC on depressive symptoms.

Since it is well-known that depressive symptoms, even in the moderate range, can impact ambition and ability to complete daily tasks (Grahek et al., 2019), it is possible that the distinct ABC and BLCIO depression levels at follow-up could differentially predict attendance to medical appointments, adherence to at-home medication regimens, and consistency with other health-promoting behaviors (Avancini et al., 2020; Signorelli et al., 2020). Further, as depression severity has been associated with lowered tolerance of lung cancer symptoms and treatment

adverse effects, the difference in depression across time between groups may impact long-term capacity to continue potentially curative cancer treatments (Morrison et al., 2017; Sung et al., 2017). The reduction in depressive symptoms made possible by psychosocial interventions in the lung cancer setting may provide benefit that improves quality of life and overall survival (Andersen et al., 2022).

We predicted that the ABC group's changes over time in the other primary outcomes (anxiety symptoms, cancer-specific stress, physical symptoms, and systemic inflammation markers) would also be significant as compared to the control group's trajectories. However, across these analyses examining group by time interactions, the results were not significant. There may be several reasons for this. It is likely that the study was not adequately powered to detect these effects, and that a larger sample size would have provided more precise estimates. An *a priori* power analysis suggested a sample size of 30 would yield an estimated power greater than or equal to 0.80. The present study's attrition rate was a barrier to completing treatment and collecting data from all 30 patients enrolled.

It is also possible that the difference between groups in time since diagnosis (M=442 days for ABC group vs. 50 days for BLCIO group) and thus the difference in current line of treatment (58% first-line treatment for ABC vs. 100% for BLCIO) impacted the findings of these analyses, particularly for the inflammatory biomarkers. Existing research suggests that inflammatory biomarker values are associated with disease progression and development (Singh et al., 2019). Although all patients in both groups had stage IV non-small cell lung cancer, the longer amount of time since diagnosis for the ABC group may have been indicative of more advanced disease, thus influencing levels of inflammation at ABC study baseline, as well as the biomarkers' ability or likelihood to respond to treatment.

Of note, when comparing the groups' platelet-to-albumin (PAR) trajectories from baseline to first follow-up, the model trended toward statistical significance (p=.076), illustrated by a reduction in PAR value for the ABC group but no change in PAR for the BLCIO group. This finding, in combination with null findings for the NLR and PLR comparisons, invited us to consider whether there are specific biological attributes of PAR inflammation that could be targeted by psychosocial interventions. Albumin reflects systemic inflammation status in cancer because inflammation increases capillary permeability and escape of serum albumin, leading to an increased volume of albumin which then undergoes a shortening of half-life, decreasing total albumin mass (Soeters et al., 2019). Although deliberations about targeting one representation of inflammation over another are beyond the scope of the present project, we recommend that future research studying inflammation in the lung cancer setting includes PAR in addition to NLR and PLR measurements.

Feasibility, Tolerability, and Acceptability

In the context of the findings related to treatment effectiveness, the feasibility, tolerability, and acceptability of the ABC intervention can be considered. In short, ABC was found to be tolerable, acceptable, and mostly feasible. The study's feasibility aim included patient accrual, adherence to treatment, retention over time, and between-session homework completion. The accrual goal to enroll 30 patients was met. Of the 615 patients screened, 46 were eligible per lung cancer histology, disease stage, treatment type, and endorsement of depressive/anxiety symptoms. Thus, 65.2% (30 out of 46) of eligible patients were accrued. Of the 16 eligible patients who declined, 8 reported that they were not interested in services, 6 reported interest but deferred enrollment due to feeling overwhelmed with lung cancer and its

treatments, and 2 reported an inability to participate due to lack of home internet and limitations in traveling to the hospital on a weekly basis.

Nineteen of the 30 enrolled patients (63.3%) engaged in study activities beyond signing consent. Reasons for dropout included mortality, transition to hospice, decline in performance status, and change in availability (e.g., recovering from surgery or moving to a new home). For the 19 patients, the average number of sessions completed was 5 sessions, with 9 of 19 patients (47.4%) completing at least 5 of 10 sessions. In examining 12-week study retention (i.e., signing consent, completing the SCID-5 and baseline assessment, and then participating in treatment sessions and follow-up assessments), 57.9% met this retention target. When conceptualizing the study, we defined treatment adherence as 75% of patients completing 5 of 10 sessions, and retention as 70% of patients engaging with the study for at least 12 weeks. Thus, the study did not meet the adherence and retention goals originally specified. Of note, ABC's retention rate was similar to other psychosocial interventions in advanced cancer, ranging from 35-100% (Teo et al., 2019). The retention rate of 58% is notable, given the challenges inherent in advanced lung cancer, e.g., multiple medical appointments and a high prevalence of moderate to severe symptoms.

Between-session homework completion ranged from 50% to 100%. For example, of the 12 patients who completed both session 1 and session 2, eight of 12 patients (66.7%) completed the homework assigned for the week between the two sessions. The lowest rate of homework completion (50%) occurred in the week after session 7, which asked patients to increase social support by contacting individuals with whom contact is typically less frequent, and/or engaging with a lung cancer support group/online forum. The highest rates of homework completion occurred after session 6 (87.5%, 7 of 8 patients), which asked patients to advocate for their

support needs by communicating with their closest family and friends, and session 10 (100%, 5 of 5 patients), which asked patients to continue practicing PMR, physical activity, and social support skills. ABC's rates of homework completion were similar to other pilot studies testing the feasibility of psychosocial interventions in advanced cancer, which reported 58-88% homework completion (Badr et al., 2015, 2019; Reb et al., 2020). Some pilot programs in the cancer setting have reported difficulty achieving high rates of homework completion, noting that "few members routinely completed homework between sessions" (Hall et al., 2020). This is an important target for future interventions, especially those involving older adults experiencing a high symptom burden, as research indicates that completion of homework is directly related to increased improvements in treatment outcomes (Mausbach et al., 2010).

The ABC study exceeded the established threshold representative of treatment tolerability. The intervention was considered tolerable if depressive and anxiety symptoms did not worsen over the course of treatment. Since both depressive and anxiety symptoms improved in a statistically (ps < .005) and clinically (according to reliable change indices and established cutoffs for symptom severity) significant manner throughout the study, tolerability was achieved.

Additionally, ABC met its treatment acceptability goal of a 3.00 or higher average score on the Patient Satisfaction Survey (PSS). The intervention's average PSS score of 3.44 out of 4.00 indicates that patients were "mostly satisfied" with the study. Of note, the satisfaction survey was completed by a subset of the study sample (11 patients) at the conclusion of their study participation. It is likely that the satisfaction scores would be lower for patients who dropped out of the study or declined completion of this survey, which would impact the overall average score. Although the PSS did not formally solicit qualitative feedback, a number of

patients verbally reported gratitude for the supportive, skills-based intervention, and also described a preference for the intervention to be shorter (i.e., lower number of sessions in total).

Lessons Learned and Future Directions

Conducting this pilot study revealed valuable insights into the implementation of a psychosocial intervention for patients with advanced lung cancer. The ultimate lesson learned was that the ABC intervention was longer than needed. Although modern lung cancer treatments are enabling prolonged survival and reduced symptom burden, the lung cancer experience remains unpredictable and physically and psychologically challenging. Medical treatments may get delayed due to adverse events, procedures or surgeries may be scheduled unexpectedly, symptom severity tends to fluctuate in irregular patterns, and functional capacity may deteriorate at any moment. When enrolling for a study, patients cannot foresee their ability to participate over 6 months. In accordance with the present study's feasibility data, future iterations of the ABC intervention would be condensed to 5 sessions in total.

The consolidated ABC intervention would incorporate another lesson learned from the present study: each session should include components of both BBI and CBT. Patients who left the study early did not learn cognitive skills central to CBT. Thus, the 5-session ABC protocol might be structured as follows. Session 1: psychoeducation about BBI/CBT, plus an introduction and practice of PMR; Session 2: assertive communication skills and identifying automatic thoughts; Session 3: enhancing social support and identifying problematic thinking patterns; Session 4: addressing dyspnea, increasing/maintaining physical activity, and generating alternative thoughts; and Session 5: practice/review of skills and goal-setting. This structure considers patients' informal descriptions of the most impactful topics from the current protocol.

Future versions of ABC would continue to offer the telehealth format, as patients noted its many benefits, including the ability to remain at home when symptomatic and immunocompromised, avoiding logistical barriers (e.g., limited access to transportation; the inconvenience/cost of parking at an academic medical center), and greater flexibility with scheduling sessions.

An additional element to inform future directions is shown within the study's flow diagram: a large proportion of screened patients (340 of 615) were excluded from ABC due to eligibility criteria regarding disease stage/histology. For the present study, accrual was limited to patients with stage IV NSCLC to enable clear comparisons to the BLCIO cohort. In future studies, ABC could be offered to – and would be appropriate for – individuals with lower-stage disease and other histology (e.g., small cell lung cancer). Broadening the eligibility criteria for the ABC intervention would expedite accrual, increase access to psychological care, and allow the sample to be more representative of clinical practice. We aim to integrate each of the lessons learned from the present study into the development of a randomized controlled trial, which would include and evaluate the ABC intervention as its treatment arm.

Strengths of the Study

The study has several strengths. First, the ABC intervention is grounded in two empirically supported treatments: the Biobehavioral Intervention (Andersen et al., 1994; Brothers et al., 2011) and Cognitive Behavioral Therapy (Carpenter et al., 2018; Etzelmueller et al., 2020; Lopez-Lopez et al., 2019; van Dis et al., 2020). Consistent with the American Society of Clinical Oncology's newly updated guidelines for the management of depression and anxiety in adult cancer survivors, the ABC treatment integrates the use of cognitive and behavioral skills

to address moderate to severe symptoms. As a manualized intervention, ABC treatment fidelity was made possible.

Research design elements strengthened the contributions that could be made with a Phase IIa study. The collection of process data – measuring depressive symptoms with the CES-D in every session – was important. If assessments had been less frequent, the extent to which depressive symptoms improved early in the treatment course may have gone unrecognized. Inclusion of the PHQ-9 in the assessments at baseline and two follow-ups enabled additional confirmatory evidence of a reduction in depressive symptoms. Further, the comparison of ABC patient outcomes to those of a matched control group that completed measure- and time-equivalent assessments was a significant strength.

Rarely included in a pilot of this type is the retrieval and analysis of inflammatory biomarkers. By including these elements, the ABC study contributes to a growing literature on the connections between systemic inflammation, psychological functioning, and lung cancer survival. Additionally, as this study involved treatment with immunotherapies and targeted therapies, in contrast to most existing lung cancer studies involving chemotherapy only, the ABC study's findings are a timely addition to a limited knowledge base surrounding current treatments for advanced lung cancer.

Limitations of the Study

Limitations are noted. Although the study's sample size was appropriate for a pilot and sufficient to detect effects on important outcomes, a larger sample size would provide more precise estimates and would better represent the population of patients with advanced NSCLC. Compared to national data for patients with lung and bronchus cancers, the ABC sample was less

racially diverse (90% White, whereas the national incidence is highest among Black individuals at 76.1 per 100,000, followed by 69.7 per 100,000 White individuals), slightly younger (mean age 65; national median age 71), and included a higher percentage of females (60% female; national incidence higher for males, with reported sex ratios varying from 1.5 to 20; Siegel et al., 2023; Stabellini et al., 2022).

Further, the rate of attrition over the course of the study is a limitation. Although attrition (up to 65%; Teo et al., 2019) is to be expected in a sample of patients with an illness as demanding and symptomatic as advanced lung cancer, dropout from ABC baseline to follow-up (especially second follow-up) impacted analytical procedures by potentially introducing bias (Dumville et al., 2006). A key consideration related to dropout is the extent to which it affects the generalizability of findings, i.e., whether participants who complete the full treatment differ on certain characteristics from those who drop out (Feng et al., 2012). Monitoring attrition was a critical component in evaluating the feasibility of ABC for this patient population. Studying the percentage of patients who completed each treatment session provided valuable data about the most suitable length of treatment in this context.

Conclusion

This study adapted and delivered an empirically supported psychosocial treatment to patients with advanced lung cancer, finally giving this cancer group the attention and support it deserves. This work was conducted in the context of leading medical treatments such as immunotherapies and targeted therapies, thus contributing novel findings to the modern era of cancer treatment.

In sum, this study evaluated the feasibility and effectiveness of A Biobehavioral/ Cognitive (ABC) treatment for patients with advanced NSCLC, and further compared ABC outcomes with those of a matched control group. Results indicate that the intervention was tolerable, acceptable, and mostly feasible, although a briefer intervention would better serve this patient population. From baseline to follow-up time points, ABC patients experienced statistically and clinically significant reductions in depressive and anxiety symptoms, stability in systemic inflammation and physical lung cancer symptoms, and an increase in perceived social support. In comparison to the group of matched controls, ABC patients' depressive symptoms decreased at a significantly more rapid rate across time, and reached the 'minimal' symptom classification while controls remained moderately depressed at follow-up.

Overall, the findings suggest that it would be a worthwhile endeavor to develop the ABC intervention into a randomized controlled trial, applying the lessons learned from the present study. With further exploration, ABC has the potential to become widely accepted as the first evidence-based, manualized psychosocial treatment for addressing depression and anxiety, reducing systemic inflammation, and potentially prolonging survival for patients with advanced lung cancer.

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Appendix A: Figures

Figure 1

CONSORT diagram demonstrating screening, recruitment, and retention rates (May 19, 2021 to June 7, 2022).

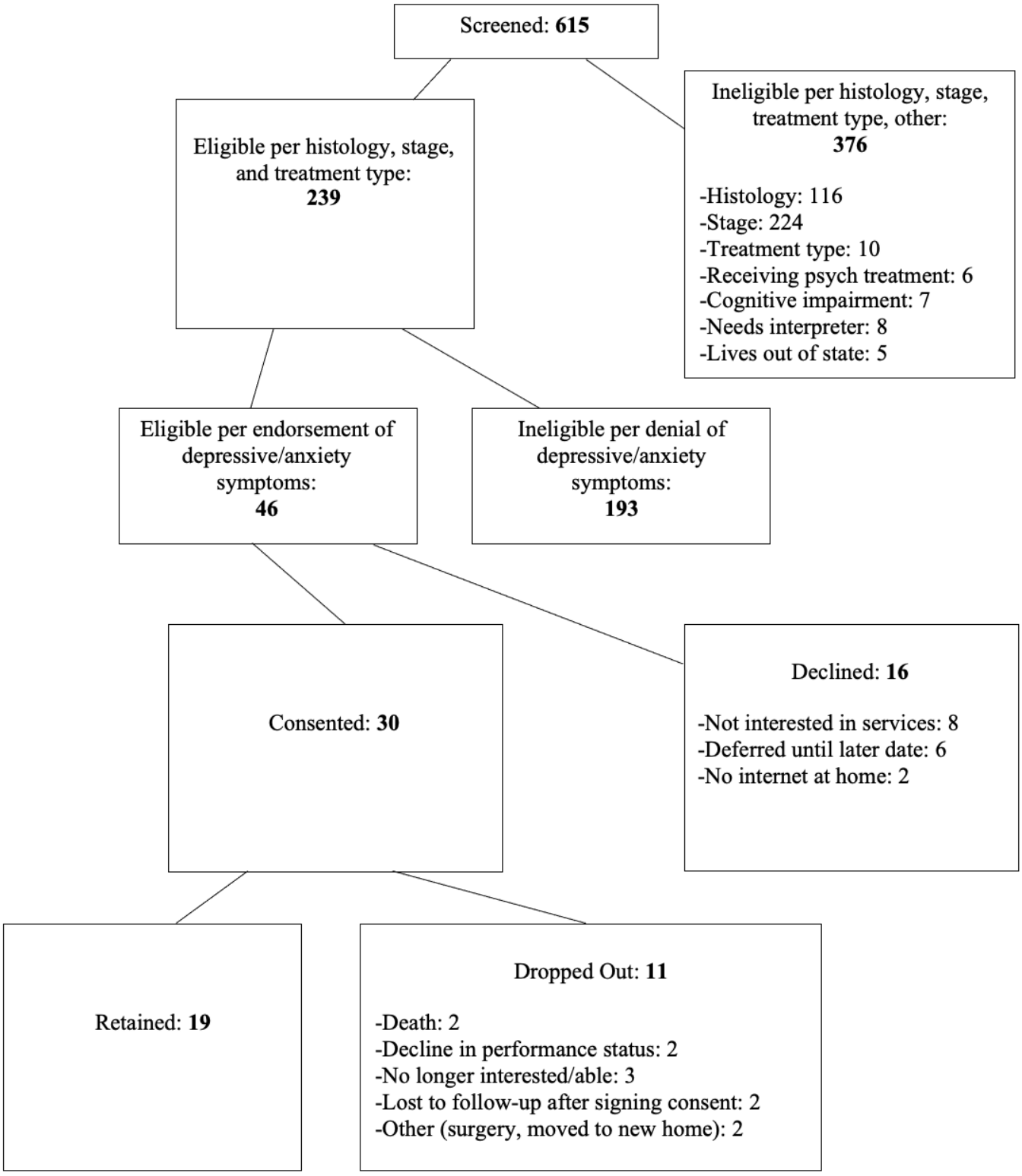


Figure 2

*Number of patients (*N*=19) completing ABC sessions. Mean number of sessions completed was 5.11 (*SD*= 4.83, range= 1-14).*

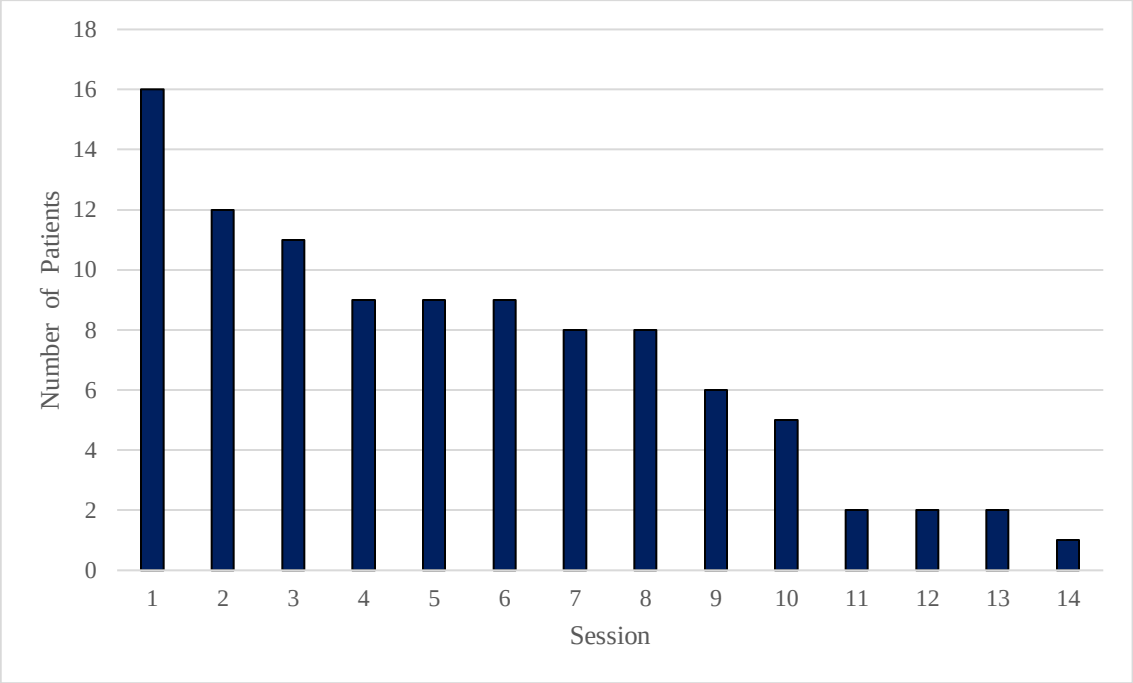


Figure 3

Percentage of patients completing homework per session, by available n. *Homework completion was dichotomized as yes (completed ≥50% of homework for week) vs. no (completed <50% of homework for week).*

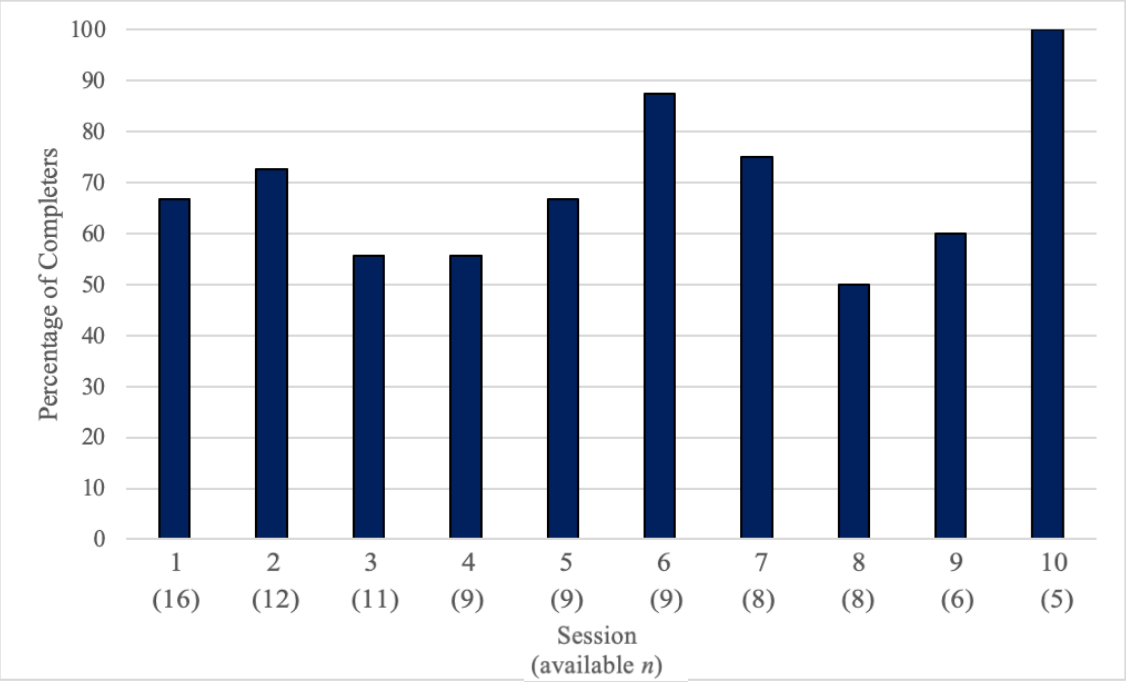


Figure 4

Mean depressive symptoms (Patient Health Questionnaire-9) and anxiety symptoms (Generalized Anxiety Disorder-7) for the ABC sample at baseline, follow-up 1 (week 5), and follow-up 2 (week 10).

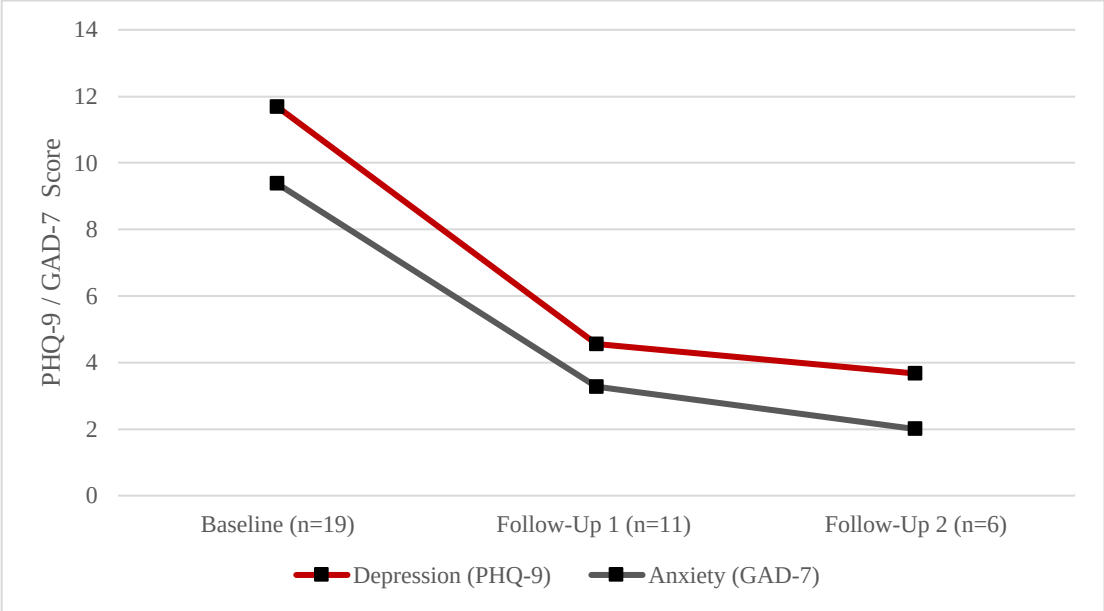


Figure 5

Mean depressive symptoms reported at each ABC session via the Center for Epidemiological Studies Depression (CES-D) scale.

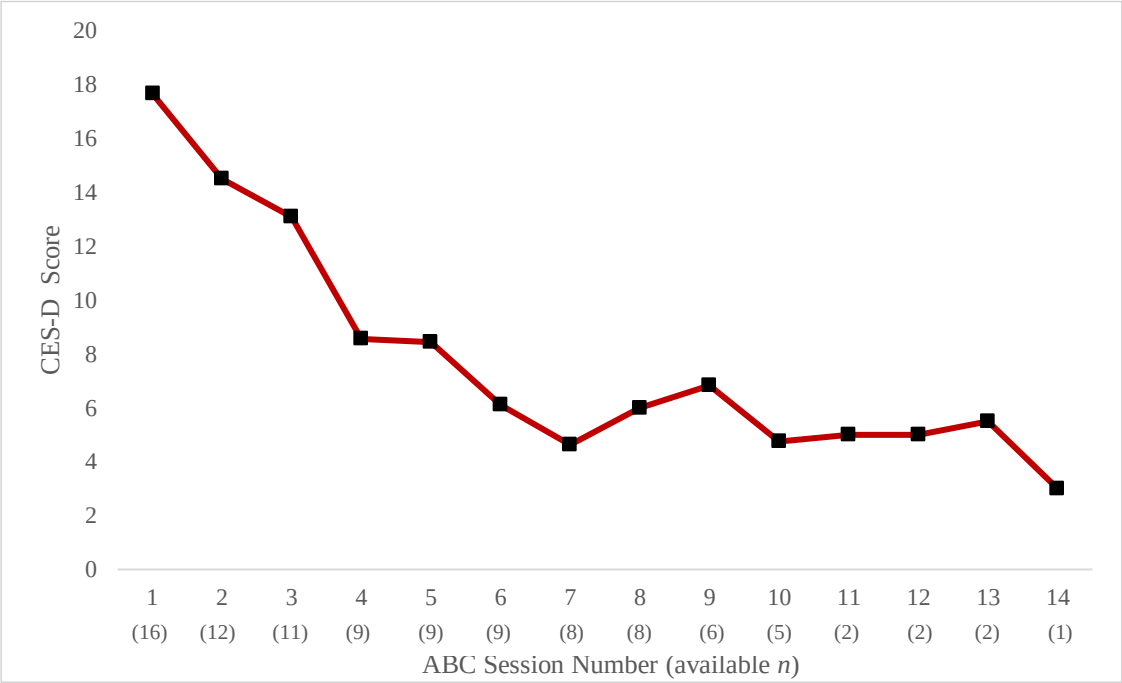
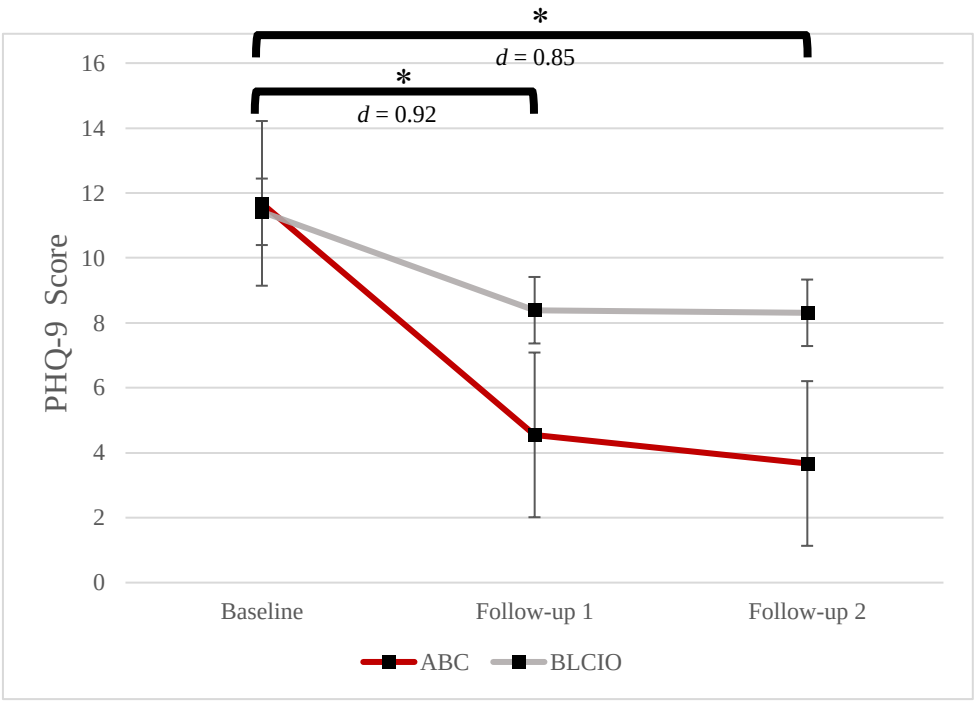
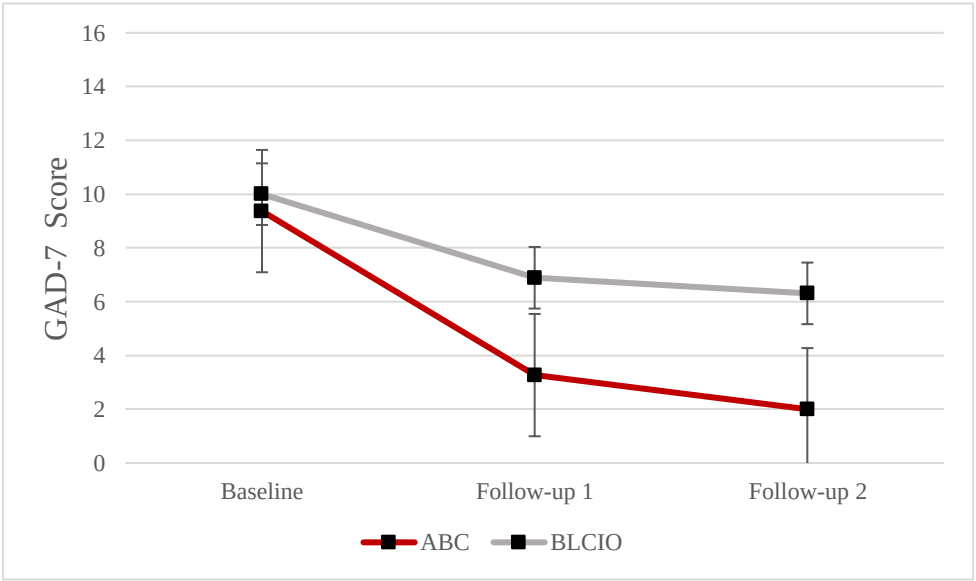
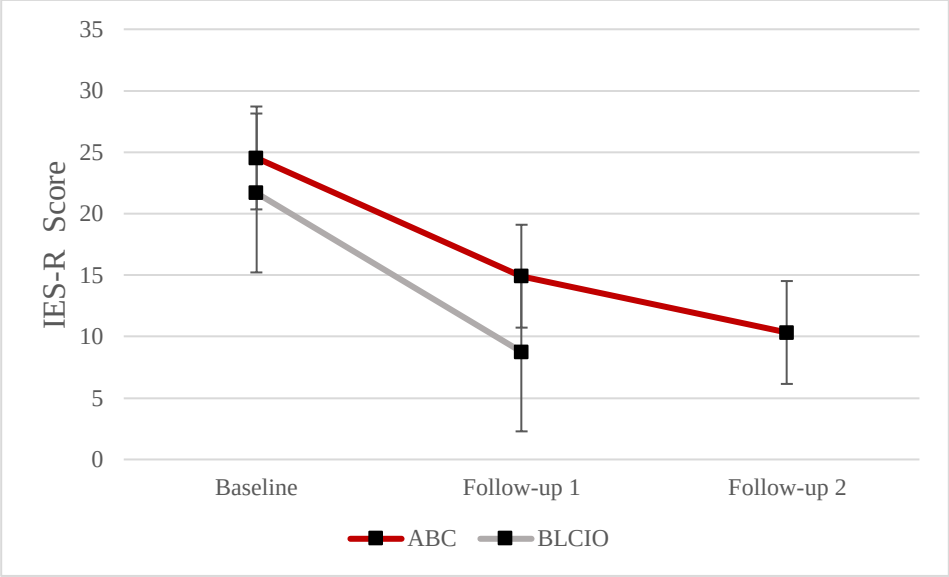


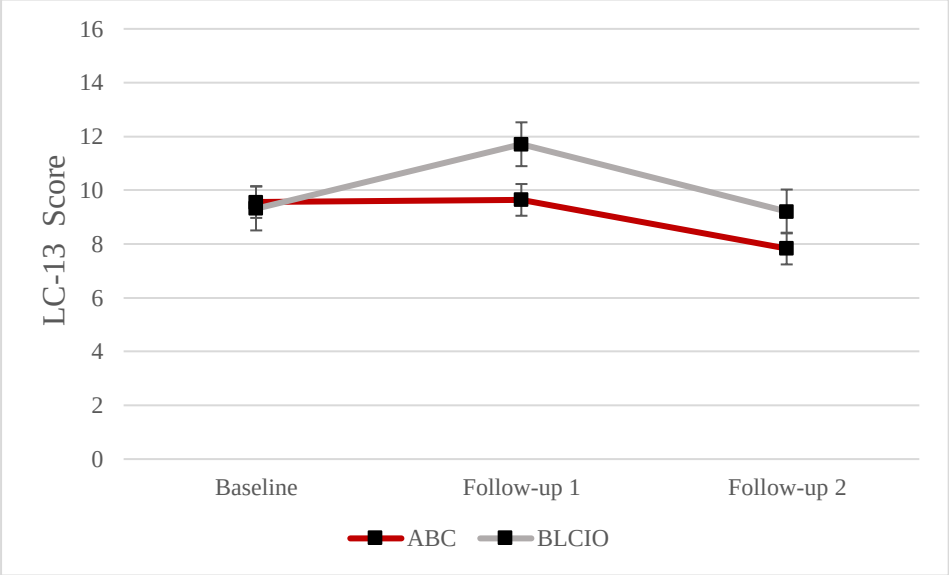
Figure 6

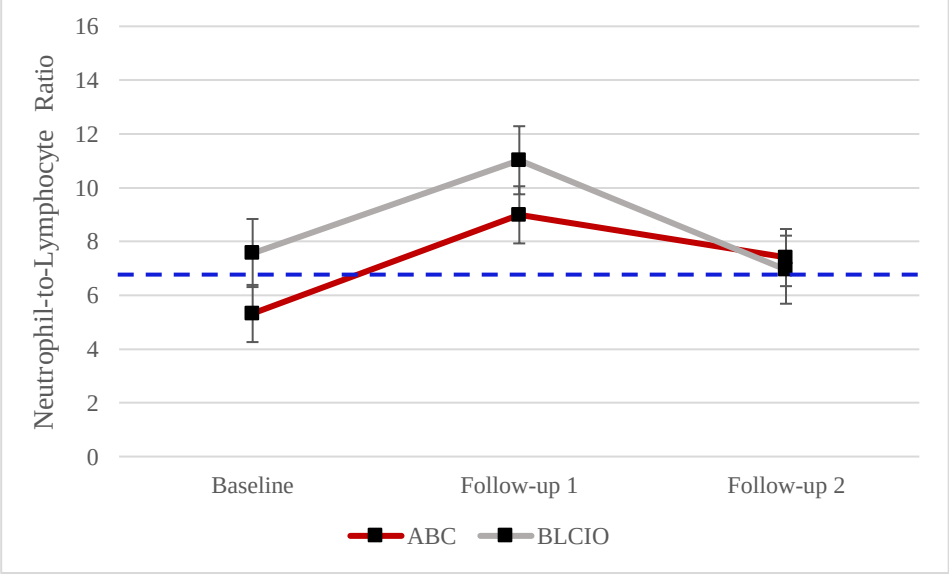
Plots of estimated marginal means for all primary outcomes from tests of group by time interactions between ABC and BLCIO groups. At baseline, N*=19 for both groups. At follow-up 1 (week 5),* N*=11 for ABC, 18 for BLCIO. At follow-up 2 (week 10),* N*=6 for ABC, 13 for BLCIO. Blue dashed lines represent cutoffs indicating high systemic inflammation.*

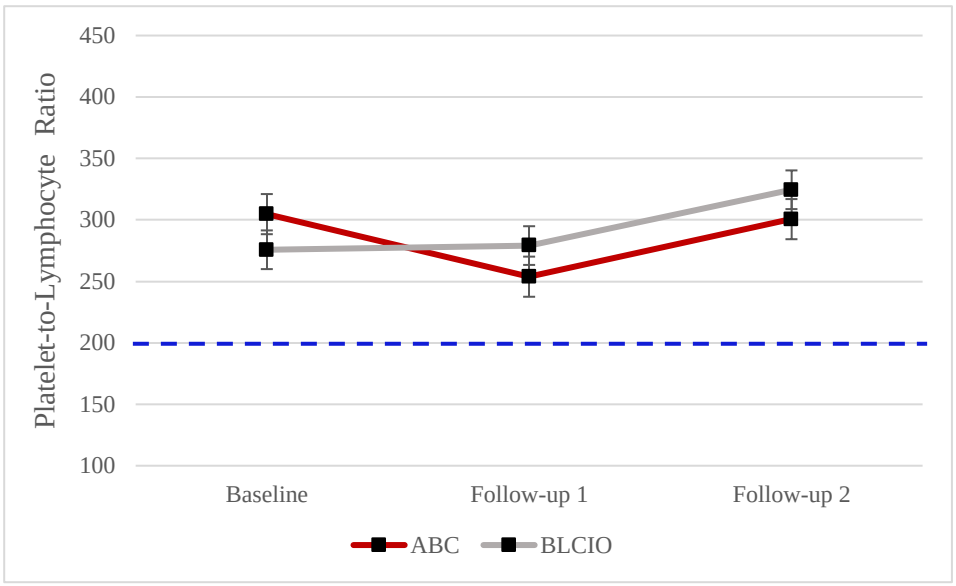


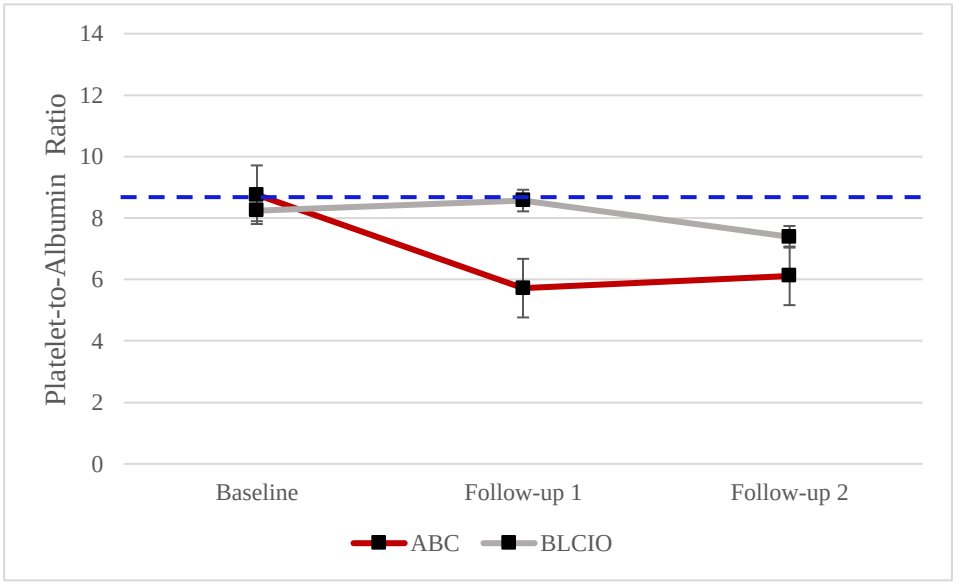


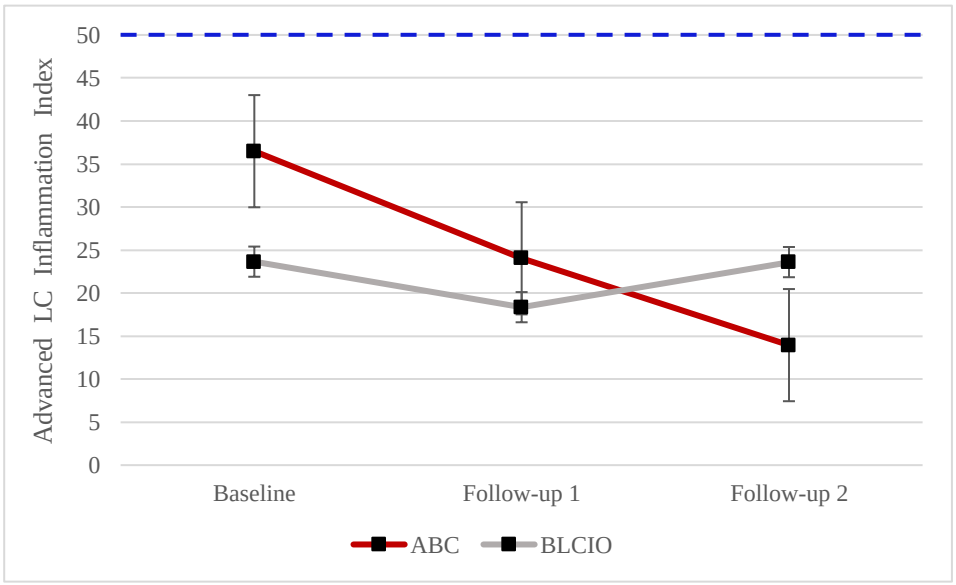

35
30
25
20
15
10
5
0
IES-R Score
Baseline
Follow-up 1
Follow-up 2
ABC
BLCIO


16
14
12
10
8
6
4
2
0
LC-13 Score
Baseline
Follow-up 1
Follow-up 2
ABC
BLCIO


16
14
12
10
8
6
4
2
0
Neutrophil-to-Lymphocyte Ratio
Baseline
Follow-up 1
Follow-up 2
ABC
BLCIO


Platelet-to-Lymphocyte Ratio
450
400
350
300
250
200
150
100
Baseline
Follow-up 1
Follow-up 2
ABC
BLCIO


Platelet-to-Albumin Ratio
14
12
10
8
6
4
2
0
Baseline
Follow-up 1
Follow-up 2
ABC
BLCIO


Advanced LC Inflammation Index
50
45
40
35
30
25
20
15
10
5
0
Baseline
Follow-up 1
Follow-up 2
ABC
BLCIO

Appendix B: Tables

Table 1

Major components of the ABC treatment, by session.

Session	Therapy Components
Biobehavioral Intervention	
1	Treatment Overview; Progressive Muscle Relaxation
2	Seeking and Asking for Disease/Treatment Information
3	Problem-Solving
4	Addressing Dyspnea and Sleep Disturbance
5	Assertive Communication
6	Identifying Social Network
7	Asking for Support
8	Enhancing Social Support
9	Physical Activity
10	Review of Skills and Setting Goals
Cognitive Behavioral Therapy	
11	Identifying Negative Thoughts and Problematic Thinking Patterns
12	Generating Alternative Thoughts
13	Behavioral Activation
14	Review of Skills and Transition to Maintenance

Table 2

Study calendar for actions and assessments by time point.

Action / Measure	Screening	Baseline	Follow-up 1	Follow-up 2
Confirm eligibility	X			
Obtain informed consent	X			
Conduct SCID-5 assessment	X			
Collect socio-demographics		X		
Assess psychiatric history		X		
Collect lung cancer disease information (histology, metastatic sites)	X	X	X	X
Collect lung cancer treatment information (treatment type, line)	X	X	X	X
Depressive symptoms (PHQ-9)	X	X	X	X
Anxiety symptoms (GAD-7)	X	X	X	X
Cancer-specific stress (IES-R)		X	X	X
Lung cancer symptoms (LC-13)		X	X	X
Abstract laboratory values for markers of inflammation		X	X	X
Social support (SNI, NIH-SS)		X	X	X
Functional status (EQ-5D-5L)		X	X	X
Overall health (EQ-VAS)		X	X	X
Depressive symptoms (CES-D)	Each ABC Session (1-14)			
Patient satisfaction survey (PSS)	Patient's final session (+/- 5 days)			

Table 3

*Sociodemographic characteristics comparing the ABC treatment sample (*n*=19) with patients who signed consent only (*n*=11).*

	ABC Treatment (*n*=19) *n* (%)	Consent Only (*n*=11) *n* (%)	*p* (*d*) [a]
Age (years)	63.6 (6.6) [b]	67.6 (11.4) [b]	.316 (0.45)
Sex			
Female	13 (68.4)	5 (45.5)	.123 (0.47)
Male	6 (31.6)	6 (54.5)	
Race			
White	16 (84.2)	11 (100.0)	**.041 (0.53)**
Black/African American	2 (10.5)	0 (0.0)	
Native American	1 (5.3)	0 (0.0)	
Marital Status			
Married/partnered	9 (47.4)	5 (45.5)	.923 (0.04)
Single, never married	2 (10.5)	4 (36.4)	
Divorced	5 (26.3)	1 (9.1)	
Widowed	3 (15.8)	1 (9.1)	
Smoking Status			
Never	4 (21.1)	3 (27.3)	.719 (0.14)
Former	10 (52.6)	7 (63.6)	
Current	5 (26.3)	1 (9.1)	
Education [c]			
No high school diploma	1 (5.3)	--	--
High school diploma/GED	9 (47.4)	--	
Some college	3 (15.8)	--	
Associate's degree	1 (5.3)	--	
Bachelor's degree	3 (15.8)	--	
Master's degree/PhD/MD	2 (10.5)	--	
Employment			
Disabled/retired	15 (78.9)	9 (81.8)	.428 (0.07)
Employed full-time	4 (21.2)	1 (9.1)	
Employed part-time	0 (0.0)	1 (9.1)	
Annual household income [c]			
$15,000 or less	5 (26.3)	--	--
$15,001-$25,000	0 (0.0)	--	
$25,001-$35,000	3 (15.8)	--	
$35,001-$50,000	4 (21.1)	--	
$50,001-$75,000	1 (5.3)	--	
$75,001-$100,000	0 (0.0)	--	
$100,001-$150,000	2 (10.5)	--	
More than $150,001	2 (10.5)	--	
Omitted	2 (10.5)	--	

[a] For continuous variables, significance and effect size determined by independent samples *t*-tests. For categorical variables, variables were dichotomized and significance and Chi-square statistic were determined by Chi-square tests. [b] Mean (standard deviation). [c] Data unavailable for consent-only group.

Table 4

*Non-small cell lung cancer (NSCLC) disease and treatment characteristics, psychiatric diagnoses according to Structured Clinical Interview for DSM-5 (SCID-5) administered at study enrollment, and psychiatric history for the ABC sample (*N*=19).*

		n (%)
Disease and Treatment		
	Type of NSCLC	
	Adenocarcinoma	18 (94.7)
	Squamous cell carcinoma	1 (5.3)
	Metastases	
	Brain [a]	12 (63.2)
	Bone	8 (42.1)
	Other (e.g., liver, pancreas)	17 (89.5)
	Treatment type	
	Chemotherapy only	4 (21.1)
	Chemotherapy + Immunotherapy	4 (21.1)
	Chemotherapy + Targeted therapy	1 (5.3)
	Immunotherapy only	4 (21.1)
	Targeted therapy only	4 (21.1)
	No active treatment	2 (10.5)
	Cancer treatment line	
	1st line	11 (57.9)
	2nd line	5 (26.3)
	3rd line	3 (15.8)
	Days between initial diagnosis and ABC consent	421 (19-1002) [b]
Diagnoses per SCID-5		
	Major Depressive Disorder [c]	8 (42.1)
	Generalized Anxiety Disorder [c]	8 (42.1)
	Adjustment Disorder	6 (31.6)
	No formal diagnosis	3 (15.8)
Psychiatric History		
	Prior psychiatric diagnosis	
	No	15 (78.9)
	Yes	2 (10.5)
	Omitted	2 (10.5)
	Prior psychotherapy	
	No	16 (84.2)
	Yes	3 (15.8)
	Medications for mood, nerves, sleep	
	No	8 (42.1)
	Yes	11 (57.9)

[a] All brain metastases were medically treated/removed prior to consent. [b] Median (range).

[c] Six of 8 met criteria for both Major Depressive Disorder and Generalized Anxiety Disorder.

Table 5

*Descriptive statistics of Aim 2 measures for the ABC sample at baseline (*n*=19), follow-up 1 (*n*=11), and follow-up 2 (*n*=6). Statistical significance (*p*-value) and effect size (Cohen's* d*) of change in outcomes from baseline to follow-up 1.*

Measure	Mean	Median	Minimum	Maximum	Standard Deviation	*p* (*d*) [a]
PHQ-9: Depressive symptoms						
Baseline	11.68	12.00	4	23	4.99	**.002 (1.29)**
Follow-up 1	4.55	5.00	0	12	3.33	
Follow-up 2	3.67	4.00	0	7	3.01	
GAD-7: Anxiety symptoms						
Baseline	9.37	10.00	1	21	5.18	**.005 (1.07)**
Follow-up 1	3.27	2.00	0	9	3.64	
Follow-up 2	2.00	1.00	0	6	2.45	
IES-R: Cancer-specific stress						
Baseline	24.53	17.00	1	70	21.31	.088 (0.44)
Follow-up 1	14.91	8.00	2	37	12.13	
Follow-up 2	10.33	9.00	1	25	8.73	
LC-13: Physical symptoms						
Baseline	9.56	8.00	2	32	7.07	.500 (0.00)
Follow-up 1	9.64	9.00	1	21	5.61	
Follow-up 2	7.83	6.50	2	16	5.04	
Systemic Inflammation: NLR						
Baseline	4.86	4.69	1.18	9.36	2.31	.169 (0.45)
Follow-up 1	8.99	6.96	1.33	27.67	8.47	
Follow-up 2	7.40	6.98	4.24	12.93	2.94	
Systemic Inflammation: PLR						
Baseline	288.14	271.58	62.24	601.82	154.97	.401 (0.26)
Follow-up 1	253.80	282.50	85.38	350.00	86.92	
Follow-up 2	300.61	301.90	137.91	442.31	108.67	
Systemic Inflammation: PAR						
Baseline	8.87	7.37	3.52	28.37	6.92	.202 (0.41)
Follow-up 1	5.72	5.51	2.88	10.10	2.13	
Follow-up 2	6.12	4.89	3.15	10.45	3.12	
Systemic Inflammation: ALI						
Baseline	29.35	19.73	7.65	102.11	26.69	.264 (0.36)
Follow-up 1	24.04	15.34	2.41	101.12	27.95	
Follow-up 2	13.95	12.47	7.76	21.07	5.54	
Social Network Index						
Baseline	9.12	9.00	4	12	2.57	.076 (0.49)
Follow-up 1	10.00	10.00	7	13	1.95	
Follow-up 2	11.33	10.00	10	15	2.16	
NIH Social Support						
Baseline	46.41	51.00	4	64	18.34	**.004 (1.11)**
Follow-up 1	56.91	62.00	30	64	10.48	
Follow-up 2	59.00	60.00	51	64	4.98	

Continued

Table 5 continued

EQ-5D-5L: Mobility						
Baseline	3.00	3.00	1	4	1.06	.338 (0.13)
Follow-up 1	3.27	4.00	2	4	0.91	
Follow-up 2	3.00	4.00	0	4	1.73	
EQ-5D-5L: Self-Care						
Baseline	3.61	4.00	2	4	0.70	.138 (0.35)
Follow-up 1	3.36	4.00	2	4	0.81	
Follow-up 2	3.60	4.00	2	4	0.89	
EQ-5D-5L: Usual Activities						
Baseline	3.00	3.50	0	4	1.24	.259 (0.20)
Follow-up 1	2.91	3.00	0	4	1.22	
Follow-up 2	2.83	3.00	2	4	0.75	
EQ-VAS: Overall Health						
Baseline	57.28	62.50	0	95	28.29	.431 (0.05)
Follow-up 1	59.73	60.00	20	90	21.07	
Follow-up 2	68.33	77.50	30	95	29.27	

Note. Appendix E provides full description of items comprising each measure. PHQ-9 = Patient Health Questionnaire-9; GAD-7 = Generalized Anxiety Disorder-7; IES-R = Impact of Events Scale-Revised; LC-13 = Lung Cancer 13-item scale; NLR = Neutrophil-to-Lymphocyte Ratio; PLR = Platelet-to-Lymphocyte Ratio; PAR = Platelet-to-Albumin Ratio; ALI = Advanced Lung Cancer Inflammation Index; NIH Social Support = National Institutes of Health Social Support scale; EQ-5D-5L = European Quality of Life 5-Dimension 5-Level questionnaire; EQ-VAS = European Quality of Life Visual Analogue Scale.

[a] Significance ($p < 0.05$) and effect size (Cohen's *d*) determined by paired-samples *t*-tests comparing mean values at baseline and follow-up 1.

Table 6

*Fit statistics for linear mixed models of time effect for ABC group (*N*=19).*

Outcome	Model Type	AIC	BIC
Depressive Symptoms (PHQ-9)	Random Intercept	197.58	201.98
	Random Slope	196.12	199.05
Depressive Symptoms (CES-D)	Random Intercept	497.13	501.77
	Random Slope	518.41	520.73
Anxiety Symptoms (GAD-7)	Random Intercept	138.06	141.20
	Random Slope	136.42	138.51
Cancer-Specific Stress (IES-R)	Random Intercept	224.54	229.42
	Random Slope	222.97	226.62
Physical Symptoms (LC-13)	Random Intercept	205.73	210.03
	Random Slope	204.40	207.27
Neutrophil-Lymphocyte Ratio	Random Intercept	140.99	143.98
	Random Slope	140.63	142.63
Platelet-Lymphocyte Ratio	Random Intercept	309.13	311.49
	Random Slope	307.30	308.47
Platelet-to-Albumin Ratio	Random Intercept	153.30	159.39
	Random Slope	152.07	156.94
Advanced Lung Cancer Inflammation Index	Random Intercept	207.05	210.71
	Random Slope	205.75	208.18

Note. AIC = Akaike information criterion; BIC = Bayesian information criterion; PHQ-9 = Patient Health Questionnaire-9 scale; CES-D = Center for Epidemiological Studies Depression scale; GAD-7 = Generalized Anxiety Disorder-7 scale; IES-R = Impact of Event Scale-Revised; LC-13 = Lung Cancer 13-item scale.

Table 7

Descriptive statistics for Center for Epidemiological Studies Depression (CES-D) data, measured at each ABC study session.

Session	Mean	Median	Minimum	Maximum	Standard Deviation	*N*
1	17.67	17	1	39	11.69	16
2	14.50	13	3	35	9.10	12
3	13.09	12	4	29	8.62	11
4	8.56	9	1	16	5.98	9
5	8.44	8	3	14	3.88	9
6	6.11	5	1	11	2.98	9
7	4.63	4.5	1	10	3.02	8
8	6.00	7	0	14	5.43	5
9	6.83	6.5	0	14	5.19	6
10	4.75	5	3	6	1.50	4
11	5.00	5	4	6	1.41	2
12	5.00	5	5	5	0.00	2
13	5.50	5.5	5	6	0.71	2
14	3.00	3	3	3	---	1

Table 8

Pairwise comparisons for fixed effect of time on Center for Epidemiological Studies Depression (CES-D) scores, as measured at each ABC study session.

Session	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	-													
2	.213	-												
3	.115	.714	-											
4	**.001**	**.031**	.074	-										
5	**.001**	**.028**	.068	.970	-									
6	**<.001**	**.003**	**.009**	.404	.426	-								
7	**<.001**	**<.001**	**.001**	.142	.152	.505	-							
8	**<.001**	**.014**	**.031**	.509	.530	.965	.543	-						
9	**<.001**	**.011**	**.027**	.527	.549	.909	.478	.953	-					
10	**.002**	**.025**	**.048**	.551	.571	.954	.560	.988	.969	-				
11	.081	.271	.368	.895	.877	.531	.310	.576	.597	.595	-			
12	.081	.271	.368	.895	.877	.531	.310	.576	.597	.595	1.0	-		
13	.101	.319	.424	.815	.798	.467	.265	.513	.532	.533	.936	.936	-	
14	.110	.263	.330	.838	.852	.868	.641	.890	.915	.899	.792	.792	.742	-

Table 9

*Descriptive statistics comparing the ABC group (*N*=19) and matched BLCIO group (*N*=19) at the baseline time point.*

	ABC *n* (%)	BLCIO *n* (%)	*p* (effect size) [a]
Age (years)	63.6 (6.6) [b]	67.4 (10.3) [b]	.185 (0.44)
Race			
White	17 (89.5)	18 (94.7)	.290 (1.12)
Black/African American	2 (10.5)	1 (5.3)	
Native American	1 (5.3)	0 (0.0)	
Smoking Status			
Never	4 (21.1)	1 (5.3)	.150 (2.07)
Former	10 (52.6)	15 (78.9)	
Current	5 (26.3)	3 (15.8)	
Education			
No high school diploma	1 (5.3)	1 (5.3)	.516 (0.42)
High school diploma/GED	9 (47.4)	7 (36.8)	
Some college	3 (15.8)	8 (42.1)	
Associate's degree	1 (5.3)	1 (5.3)	
Bachelor's degree	3 (15.8)	2 (10.5)	
Master's degree	1 (5.3)	0 (0.0)	
PhD/MD	1 (5.3)	0 (0.0)	
Employment			
Disabled/retired	15 (78.9)	13 (68.4)	.461 (0.54)
Employed full-time	4 (21.2)	6 (31.6)	
Employed part-time	0 (0.0)	0 (0.0)	
Annual household income			
$15,000 or less	5 (26.3)	3 (15.8)	.483 (0.24)
$15,001-$25,000	0 (0.0)	4 (21.1)	
$25,001-$35,000	3 (15.8)	4 (21.1)	
$35,001-$50,000	4 (21.1)	2 (10.5)	
$50,001-$75,000	1 (5.3)	0 (0.0)	
$75,001-$100,000	0 (0.0)	3 (15.8)	
$100,001-$150,000	2 (10.5)	0 (0.0)	
$150,001-$200,000	1 (5.3)	1 (5.3)	
More than $200,000	1 (5.3)	0 (0.0)	
Days since cancer diagnosis	442 (351.4) [b]	50 (27.5) [b]	**<.001 (1.57)**
Cancer treatment line			
1st line	11 (57.9)	19 (100.0)	**.004 (1.07)**
2nd line	5 (26.3)	0 (0.0)	
3rd line	3 (15.8)	0 (0.0)	
Prior psychiatric diagnosis			
No	15 (78.9)	18 (94.7)	.481 (0.50)
Yes	2 (10.5)	1 (5.3)	
Baseline GAD-7 score	9.4 (5.2) [b]	10.0 (6.6) [b]	.745 (0.11)

[a] For continuous variables, significance ($p < 0.05$) and effect size (Cohen's *d*) determined by independent samples *t*-tests comparing mean values for ABC and BLCIO groups. For categorical variables, variables were dichotomized and significance and Chi-square statistic were determined by Chi-square tests.
[b] Mean (standard deviation).

Table 10

Descriptive statistics for primary outcomes for the ABC group and BLCIO group at baseline, follow-up 1, and follow-up 2.

	Baseline [a] *M* (*SD*)	Follow-up 1 [b] *M* (*SD*)	Follow-up 2 [c] *M* (*SD*)
Depressive symptoms (PHQ-9)			
ABC	11.68 (4.99)	4.55 (3.33)	3.67 (3.01)
BLCIO	11.42 (4.51)	8.39 (4.60)	8.31 (6.17)
Anxiety symptoms (GAD-7)			
ABC	9.37 (5.19)	3.27 (3.64)	2.00 (2.45)
BLCIO	10.00 (6.63)	6.89 (4.69)	6.31 (4.94)
Cancer-specific stress (IES-R)			
ABC	24.53 (21.31)	14.91 (12.13)	10.33 (8.73)
BLCIO	21.68 (14.59)	8.75 (10.69)	--
Physical symptoms (LC-13)			
ABC	9.56 (7.07)	9.64 (5.61)	7.83 (5.04)
BLCIO	9.32 (4.23)	11.71 (6.27)	9.21 (5.01)
Neutrophil-to-lymphocyte ratio			
ABC	5.32 (3.77)	8.99 (8.47)	7.40 (2.94)
BLCIO	7.57 (6.41)	11.02 (20.25)	6.95 (4.46)
Platelet-to-lymphocyte ratio			
ABC	304.70 (169.37)	253.80 (86.92)	300.61 (108.67)
BLCIO	275.70 (151.23)	279.12 (120.72)	324.53 (201.45)
Platelet-to-albumin ratio			
ABC	8.76 (5.76)	5.72 (2.13)	6.12 (3.12)
BLCIO	8.25 (3.93)	8.57 (3.89)	7.39 (3.22)
Advanced LC inflammation index			
ABC	36.49 (49.62)	24.04 (27.95)	13.95 (5.54)
BLCIO	23.65 (16.68)	18.36 (9.66)	23.60 (18.61)

Note. *N*s for markers of systemic inflammation for BLCIO group: baseline = 17; follow-up 1 = 17; follow-up 2 = 16. The following cutoffs are used to indicate high systemic inflammation: NLR greater than 5, PLR greater than 200, PAR greater than 8.6, and ALI less than 50.

[a] *N*=19 for both groups. [b] *N*=11 for ABC, 18 for BLCIO. [c] *N*=6 for ABC, 13 for BLCIO.

Appendix C: Patient Recruitment Materials

Patient Recruitment Brochure, Side 1

Patient Recruitment Brochure, Side 2

You Are Not Alone

Depression and anxiety are common among people with cancer. It is normal to feel down or worry about the changes cancer brings to your life.

What is The ABC Study?

The ABC study is an online or live program for people feeling depressed, anxious or just stressed out by cancer. The program helps you manage stress, relax, communicate, and problem-solve.

What will I learn?

The program teaches short-term ways to cope with depression and long-term life skills that will help you face the future with confidence.

The program provides information on how to overcome negative thoughts—even if you've had them for a long time.

Does The ABC Study Work?

The ABC Study uses proven techniques that help improve mood. Seven out of ten people who have used the ABC Study say they feel less depressed and anxious.

You Choose the Format!

The ABC Study is available via video visits or in-person visits. You can choose the format that works best for you.

Is it right for me?

If you have a lung cancer diagnosis and experience depressed feelings, you may be eligible for the ABC Study.

What to Expect

The ABC Study is a program that helps people with lung cancer understand and manage depression and anxiety.

The program:

- Includes 10-14 weekly sessions that take about an hour each
- Provides you with a personal therapist, for sessions personalized to you
- Is interactive and helps you learn ways to adjust your behaviors and improve your mood
- Is completely confidential and free of charge

Appendix D: Study Manuals

Please see attached PDFs of ABC Therapist Manual and ABC Patient Manual.

Appendix E: Study Measures

Please see attached PDF of study measures.