A Randomized Controlled Trial of Dexamethasone for Dyspnea in Cancer Patients

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This study proposal was submitted the National Institutes of Health and received a score of 12 (i.e. top 2 percentile). National Cancer Institute is considering it for funding.

A. Objectives

Primary Objective: Compare the intensity of dyspnea (numeric rating scale [NRS]) in the dexamethasone arm with that in the placebo arm at week 1.
Our working hypothesis is that dexamethasone will improve dyspnea compared with placebo in patients with cancer.

Secondary Objective #1: Compare the effects of dexamethasone with those of placebo in terms of personalized dyspnea response (based on a personalized dyspnea goal), unpleasantness of dyspnea, other symptoms, health-related quality of life, respiratory physiologic function, and adverse effects at week 1 and week 2, as well as the intensity of dyspnea at week 2.
Our working hypothesis is that short-term, high-dose dexamethasone will improve personalized dyspnea response, unpleasantness of dyspnea, symptom burden, health-related quality of life, and respiratory physiologic function, with limited adverse effects.

Secondary Objective #2: Identify predictive markers of dyspnea response to dexamethasone.
Our working hypothesis is that baseline inflammatory response (interleukin [IL]-1β, IL-6, IL-8, IL-10, IL-6:IL-10 ratio, and tumor necrosis factor-α [TNF-α] levels) and certain patient characteristics (e.g., high baseline dyspnea and restrictive lung disease pattern) are associated with increased treatment response.

Secondary Objective #3: Determine the association between adverse event (AE) development (i.e. G3+ AEs, hospitalizations, specific adverse events) and the dose/duration of dexamethasone. *Our working hypothesis is that longer duration and higher dose is associated with greater AEs.*

Secondary Objective #4: Examine the similarities and differences between CTCAE and PRO-CTCAE reporting. *We will identify where CTCAE and PRO-CTCAE overlap and how they differ from each other.*

B. Background

B.1. Dyspnea. Dyspnea is defined by the American Thoracic Society as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity… dyspnea sensations also vary in their unpleasantness and in their emotional and behavioral significance" (Parshall et al. 2012). Dyspnea occurs in approximately 10-70% of cancer patients and is one of the most feared symptoms (Solano et al. 2006). It is particularly common in patients with advanced cancer and those with intrathoracic malignancies (Hui *et al.* 2015a, Tishelman *et al.* 2007). Dyspnea that "persists at rest or with minimal activity and is distressful despite optimal therapy of advanced lung or heart disease" is considered to be refractory

(Mahler *et al.* 2010). Several large studies reported that 30-50% of patients with cancer suffer from refractory dyspnea in the last few months of life, and the symptom increases in both frequency and intensity as death approaches (Currow *et al.* 2010, Dudgeon *et al.* 2001, Seow *et al.* 2011). More recently, a prospective study revealed that up to 70% of patients with advanced cancer reported dyspnea in the last week of life despite intensive palliation in an acute palliative care unit (Hui *et al.* 2015a). Importantly, dyspnea is associated with decreased daily function, quality of life, and survival (Cuervo Pinna *et al.* 2009, Maltoni *et al.* 2005, Reddy *et al.* 2009). Because of its high prevalence and impact on quality of life, dyspnea presents a major public health concern for patients living with cancer. Multiple professional organizations, including the Institute of Medicine and National Hospice and Palliative Nurses Association, identified dyspnea as a priority for research (Board 2001, Buck *et al.* 2015).

B.2. Pathophysiology. Over the years, understanding of the pathophysiologic pathways contributing to dyspnea has improved (Figure 1), which may allow development of better therapies for this devastating symptom (Mahler 2011, Manning and Schwartzstein 1995). The sensory cortex receives afferent input from various peripheral and central stimuli, generating the sensation of breathlessness (Mahler 2011, Parshall *et al.* 2012). Parenchymal metastasis, lymphangitic carcinomatosis, airway obstruction, pleural effusion, pneumonia, pulmonary embolism, and atelectasis may cause dyspnea in the context of progressive cancer—all of which are associated with an inflammatory response.

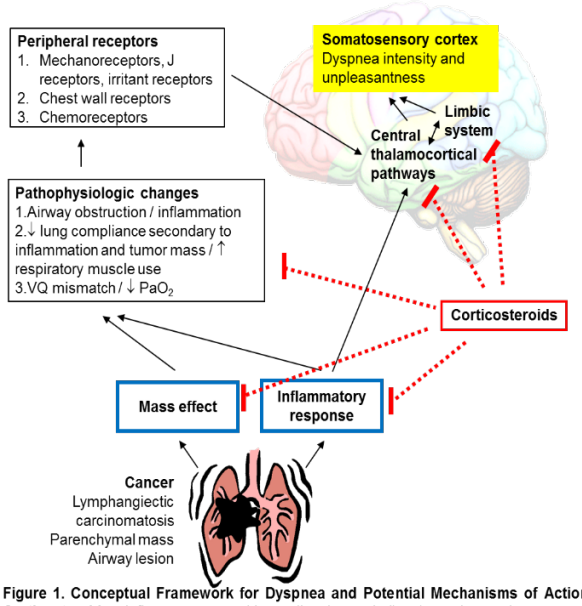

Figure 1. Conceptual Framework for Dyspnea and Potential Mechanisms of Action of Corticosteroids. Inflammatory cytokines directly or indirectly activate chemoreceptors, mechanoreceptors, J receptors, irritant receptors, and chest wall receptors peripherally and modulate of the thalamocortical pathway centrally, contributing to the sensation of dyspnea in the somatosensory cortex. Corticosteroids may mediate their effects by reducing inflammation peripherally and centrally, thus decreasing the sensation of dyspnea.

B.3. Role of inflammation in dyspnea. Cytokines drive the inflammatory response, and dysregulation of cytokines is seen with chronic inflammation and cancer (Marrugal *et al.* 2016). COPD, as a disease model for dyspnea, is characterized by a substantial inflammatory component, including elevated serum IL-6 and TNF-α (Falk *et al.* 2008). In patients with asthma, increased levels of IL-1β and IL-6 predicted increased perception of dyspnea (Carpio *et al.* 2016). In patients with restrictive lung disease, serum IL-1β and TNF-α levels were correlated with the severity of lung injury (Bauer *et al.* 2000). De Brito *et al*. (De Brito *et al.* 2016) recently found elevated serum IL-6 in patients with pneumonia; IL-6 levels were correlated with dyspnea ($r = 0.61$, $P = 0.012$) in patients with severe pneumonia, as was the ratio between systemic levels of IL-6 and IL-10 (i.e., IL-6:IL-10), an anti-inflammatory cytokine that serves as a biomarker for the severity of pneumonia—a decreased ratio indicated response to treatment. Few studies have examined the relationship between inflammatory biomarkers and dyspnea in cancer patients. In one study that included 1466 patients with advanced cancer, levels of C-reactive protein (CRP), a marker of acute inflammation, >10 mg/L were associated with increased levels of dyspnea (35 mg/L compared with 27 mg/L for CRP < 10 mg/L; $P < 0.001$)

(Laird et al. 2013). Collectively, the literature indicates that selective inflammatory biomarkers (i.e., IL-1β, IL-6, IL-8, IL-10, and TNF-α) play a role in the pathogenesis of dyspnea, indicating that further research is needed in the oncology setting.

B.4. Treatment options for dyspnea. Because of the paucity of research on dyspnea, there are currently no US Food and Drug Administration (FDA)-approved therapies for dyspnea. Contemporary management of dyspnea involves treatment of any reversible causes and supportive measures to minimize the sensation of dyspnea. Medications such as opioids, bronchodilators, and benzodiazepines offer moderate benefits (Barnes *et al.* 2016, Ben-Aharon *et al.* 2008, Cranston *et al.* 2008, Jennings *et al.* 2002). Given the important role of inflammation in cancer-related dyspnea, corticosteroids show promise as a therapeutic option, although few studies have examined this option (Table 1).

C. Rationale

C.1. Role of corticosteroids in dyspnea. Steroids have been shown to modulate the inflammatory response and improve dyspnea in patients with obstructive lung disorders (Calverley et al. 2003, Lapperre et al. 2009). In systematic reviews, systemic corticosteroids have been shown to reduce respiratory symptoms, improve FEV1, and shorten hospitalization in acute exacerbations of COPD (Falk et al. 2008, Walters et al. 2009, Wood-Baker et al. 2007). Inhaled steroids have also been demonstrated to improve various clinical outcomes in patients with COPD, including reducing the number of physician visits and decreasing airway hyperreactivity (Calverley et al. 2007, Lung Health Study Research 2000, Yang et al. 2007). These findings from non-cancer populations may or may not apply to patients with cancer. On the one hand, restrictive lung diseases are predominant in the oncology setting instead of obstructive lung disorders, secondary to inflammation, infiltration, fibrosis, effusion, or respiratory muscle weakness. On the other hand, cancer is known to induce host inflammatory response and often produces cytokines with both systemic and peripheral effects (Wang et al. 2010), raising the possibility that corticosteroids may also be effective for the management of dyspnea among patients with cancer.

C.2. Limited research on the effect of corticosteroids on cancer-related dyspnea. A handful of studies show that systemic corticosteroids may be effective for the management of dyspnea in patients with cancer. However, all studies to date were hypothesis-generating, including four small retrospective case reports/series, two randomized controlled trials in which dyspnea was only an exploratory outcome, and one randomized trial that was only a feasibility study and not adequately powered. This lack of confirmatory data has contributed to substantial variations in how corticosteroids are prescribed in practice (Denton and Shaw 2014a, Gannon and Mcnamara 2002, Matsuo *et al.* 2012). Some clinicians see value in a therapeutic trial of corticosteroids on the basis of anecdotal evidence, particularly given that few other options currently exist. Others are less certain about the benefits of corticosteroids and hesitate to prescribe them out of concerns about adverse effects (Denton and Shaw 2014b, Hougardy *et al.* 2000). Those who prescribe corticosteroids for dyspnea struggle to decide which corticosteroids to use and what would be the optimal dose, schedule, duration, and tapering scheme. Understandably, multiple systematic reviews of dyspnea concluded that high-quality randomized controlled trials are needed to examine the efficacy of corticosteroids (Simon et al. 2012, Viola et al. 2008).

C.3. Dexamethasone for cancer-related dyspnea (Hui *et al.* 2016a). We recently completed a double-blind, randomized, controlled trial to examine the effect of dexamethasone on dyspnea. Cancer patients with dyspnea were randomized to receive either dexamethasone (8 mg twice daily for 4 days, then 4 mg twice daily for 3 days) or placebo for 7 days, followed by an open-label phase for 7 days. We documented the within-arm changes in dyspnea (according to the dyspnea NRS), spirometry measures, quality of life, and toxic effects. Forty-one patients were randomized and 35 (85%) completed the blinded phase. As shown in Table 2, dexamethasone was associated with a significant reduction in dyspnea by day 4 (average change in dyspnea NRS score -1.9, 95% confidence interval [CI] -3.3 to -0.5, P = 0.01) and by day 7 (average change in dyspnea NRS score -1.8, 95% CI -3.2 to -0.3, P = 0.02). In contrast, placebo was associated with an average change in dyspnea NRS score of -0.7 (95% CI -2.1 to 0.6, P = 0.38) by day 4 and -1.3 (95% CI -2.4 to -0.2, P = 0.03) by day 7. This preliminary study was not powered to detect the between-arm difference. Dexamethasone was well tolerated with no significant toxicities. This pilot study provided important preliminary data for the current proposed trial. First, it showed that a double-blind, randomized, controlled trial of dexamethasone was feasible, with a low attrition rate. We expect to be able to enroll patients and successfully complete the proposed trial because the eligibility criteria are similar. Second, the study showed that dexamethasone was associated with a rapid within-arm improvement in dyspnea and may potentially represent an improvement over the placebo arm. Third, the moderate effect size for a single-modality intervention is encouraging given that there are currently no FDA-approved therapies for dyspnea. Confirmation of the benefit of dexamethasone in the proposed study will pave the way for future studies examining combination therapies that may result in a greater effect size. Finally, dexamethasone, at a dose of 8 mg twice daily for 4 days, was well tolerated with no significant adverse effects; thus, it is reasonable to consider extending this same dose for a total of 7 days. Based on the findings from this preliminary study, we propose a larger confirmatory trial to definitively assess the efficacy of dexamethasone for dyspnea, with the potential to greatly improve patients' symptom burden, function, and quality of life.

Table 1. Change in dyspnea in the dexamethasone and placebo arms (statistically significant values in boldface type)

	Dexamethasone			Placebo			Mean difference between arms (95% CI)
Variable	N	Mean (SD)	Mean change from baseline (95% CI)	N	Mean (SD)	Mean change from baseline (95% CI)	
ESAS dyspnea (average over the past 24 hours)							
Baseline	19	5.0 (2.1)	-	19	4.7 (1.5)	-	-
Day 4	15	3.3 (1.8)	**-1.9 (-3.3 to -0.5), P = 0.01**	15	3.7 (2)	-0.7 (-2.1 to 0.6), P = 0.38	-1.2 (-3 to 0.6)
Day 7	16	3.6 (2.6)	**-1.8 (-3.2 to -0.3), P = 0.02**	14	3.3 (2.1)	**-1.3 (-2.4 to -0.2), P = 0.03**	-0.5 (-2.2 to 1.2)
EORTC Quality of Life Questionnaire-C30 Dyspnea (over the past week)							
Baseline	19	57.9 (29.1)	-	19	49.1 (20.4)	-	-
Day 4	15	46.7 (16.9)	**-15.6 (-29.3 to -1.8), P = 0.04**	15	46.7 (24.6)	0 (-14 to 14), P > 0.99	-15.6 (-33.5 to 2.3)
Day 7	16	47.9 (17.1)	-10.4 (-21.1 to 0.3), P = 0.08	13	43.6 (16)	-5.1 (-19 to 8.8), P = 0.69	-5.3 (-21.2 to 10.6)

D. Experimental Approach

D.1. Overall Study design. This is a parallel, two-arm, double-blind, randomized, placebo-controlled trial of dexamethasone for cancer patients with dyspnea (Figure 2). We plan to enroll 201 patients (134 in the dexamethasone group and 67 in the placebo group, Section D.1.11.1), with a target enrollment rate of five to six patients per month. The eligibility criteria are shown in Table 2. After providing written informed consent, enrolled patients will complete baseline questionnaires to assess the severity of their dyspnea. Study drug may be mailed to participants. At MD Anderson, sometimes patients do not have time to pick up study medication after enrollment and do not start the study until a few days later. For HHS/LBJ, patients will get their medication via MD Anderson pharmacy so their medications will also need to be mailed to them. On the basis of our experience, we believe that the proposed study is feasible and will not add an undue burden for patients. The rationale for the proposed study design is as follows.

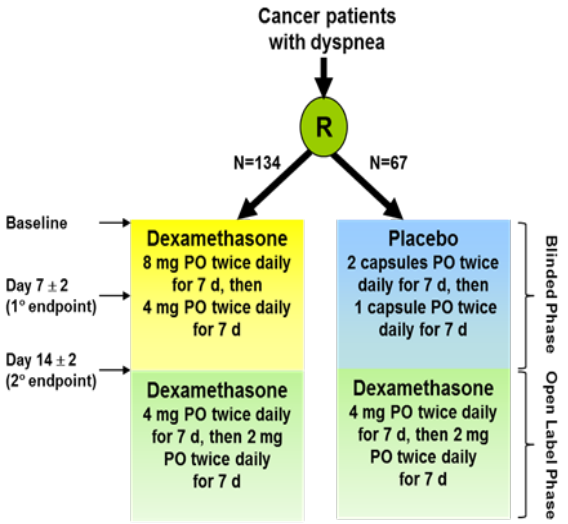

Figure 2. Study Flow Chart

D.1.1. Dexamethasone. Dexamethasone was chosen over other corticosteroids because it is a synthetic, long-acting, potent corticosteroid with minimal mineralocorticoid activity. It is commonly used in the oncology setting for management of fatigue, pain, anorexia, and nausea and vomiting (Chow *et al.* 2015, Hesketh *et al.* 2016, Yennurajalingam *et al.* 2013). Moreover, dexamethasone demonstrated promising activity in our preliminary trial (Hui *et al.* 2016a) (Section D.1.1.3).

D.1.2. Oral route. The oral route was selected instead of the inhaled route because dexamethasone is expected to exert its effect both peripherally and centrally. Absorption of inhaled corticosteroid may be less reliable. The oral route is also more convenient than the intravenous route in the ambulatory setting. Furthermore, our preliminary data (Section D.1.1.3) suggest that oral dexamethasone was associated with dyspnea improvement.

D.1.3. Dosing. In our preliminary study, dexamethasone was given at a dose of 8 mg orally twice daily for 4 days, followed by 4 mg twice daily for 3 days, and the peak effect was reached within 4 days. We observed no significant adverse effects in the dexamethasone group at this dose compared with placebo. Thus, we would like to extend the use of dexamethasone at a dose of 8 mg twice daily to 7 days to evaluate its longer-term effects. This dose is justified because high-dose prednisone (i.e., 100 mg daily, which is equivalent to 16 mg of dexamethasone) is often given in the oncology setting as part of cancer treatment.

D.1.4. Tapering. The tapering schedule is designed according to routine clinical practice, which reduces the dexamethasone dose to half (4 mg twice daily, then 2 mg twice daily) before stopping to minimize cortisol deficiency due to hypothalamic-pituitary-adrenal axis suppression. Given that the total duration of treatment with dexamethasone is 2-4 weeks, we do not expect substantial adverse effects.

D.1.5. Study duration and endpoint. The duration to the primary endpoint will be 7 ± 2 days of high-dose dexamethasone/placebo. This was carefully chosen over longer time frames because (1) dyspnea is highly distressing and rapid symptomatic relief is essential; and (2) prolonged use of high-dose dexamethasone may result in greater side effects. We will assess the longer-term use of dexamethasone at lower doses for up to 4 weeks as part of our secondary analysis.

D.1.6. Open label phase. This will offer all patients the opportunity for a trial of the active agent, which may enhance the rate of recruitment. It will also allow us to taper the corticosteroid dose slowly and to explore longer-term use of corticosteroids beyond 2 weeks.

D.1.7. Placebo control. The use of placebo control is justified because definitive evidence to suggest that dexamethasone is superior to placebo remains lacking (i.e., clinical equipoise). Patients in either study arm will have access to other contemporary treatments if already scheduled (e.g., opioids, bronchodilators). Because the primary outcome measure is a patient-reported outcome, placebo control is essential. Indeed, our previous research studies have consistently shown that a placebo offers clinically significant benefits with minimal harm (Bruera *et al.* 1993, Bruera *et al.* 2007).

D.1.8. Randomization in 2:1 ratio. The 2:1 ratio was elected to maximize the number of patients available for response predictor analysis (Aim 2) and to help to improve our chances of recruitment. On the basis of our preliminary data favoring dexamethasone, we believe this ratio is justified.

D.1.9. Selection of putative predictive markers.

D.1.9.1 Inflammatory biomarkers. Dexamethasone is hypothesized to modulate the inflammatory response to help treat dyspnea. We have selected IL-1β, IL-6, IL-8, IL-10, and TNF-α for their specific relevance to dyspnea on the basis of our literature review.

D.1.9.2. Pulmonary function. A large proportion of patients with cancer have restrictive lung disease (Hui *et al.* 2016a). In the fibrotic interstitial lung disease setting, there is evidence to support the use of corticosteroids for dyspnea (Bajwah *et al.* 2013). Thus, restrictive lung disease may be a predictive marker. Cachexia, a common syndrome in patients with advanced cancer, is associated with decreased respiratory muscle function (Coats 2002, Remels *et al.* 2013, Roberts *et al.* 2013), which in turn may be associated with dyspnea (Chiu *et al.* 2004, Travers *et al.* 2008). Indeed, short-term corticosteroids have been reported to have a positive impact on muscle strength in patients with various inflammatory disorders (Manzur *et al.* 2008, Sunderkotter *et al.* 2016). Mechanistically, a positive association between dyspnea response to dexamethasone and pulmonary function (i.e., baseline or change) would suggest that the therapeutic effect of corticosteroids on dyspnea is mediated peripherally, and a lack of association may imply more a central effect.

D.1.9.3. Baseline dyspnea function. Studies from our group and others consistently demonstrated that a high baseline symptom score is associated with a greater likelihood of response to both active intervention and placebo (De La Cruz *et al.* 2010, Hui *et al.* 2015b). Thus, the randomization scheme will stratify by this variable. We will also adjust for this variable in our statistical analysis.

D.2. Eligibility criteria (Table 2). We designed these criteria to maximize the study's generalizability. We will be stratifying by baseline dyspnea intensity and study site. We also

considered stratifying by other factors such as pulmonary function and inflammatory markers, but no other factors have been consistently found to be predictive markers at this time in cancer patients.

Table 2. Study eligibility criteria

Inclusion criteria

1. Diagnosis of cancer
2. Dyspnea with an average intensity ≥4 on the dyspnea NRS (range 0-10) over the past week
3. Seen at an outpatient clinic at MD Anderson Cancer Center or LBJ Hospital General Oncology Clinic
4. Able to communicate in English or Spanish
5. Karnofsky performance status ≥30%
6. Age 18 years or older

Exclusion criteria

1. Delirium (i.e., score >13 on the Memorial Delirium Assessment Scale; range 1-30)
2. Oxygen saturation <90% despite supplemental oxygen >6 L/minute
3. Previous allergic reactions to dexamethasone
4. Diagnosis of diabetes mellitus uncontrolled with oral hypoglycemic agents or insulin
5. Postsurgical open wound that has not healed at the time of enrollment
6. Any infection requiring antibiotics at the time of study enrollment
7. Major surgery within the past 2 weeks
8. Megestrol use at the time of study enrollment
9. Neutropenia (absolute neutrophil count $<1.0 \times 10^9$/L) at the time of study enrollment (bloodwork is not required if patient did not have chemotherapy within past 2 weeks)
10. Currently receiving or expected to start cytotoxic chemotherapy or immunotherapy within 1 week of study enrollment and additional dexamethasone cannot be used concurrently as per attending oncologist
11. Severe anemia (hemoglobin <8 g/L) not corrected prior to study enrollment (bloodwork is not required if patient did not have chemotherapy within past 2 weeks)
12. COPD exacerbation at the time of study enrollment
13. Heart failure exacerbation at the time of study enrollment
14. Expected to undergo therapeutic thoracentesis in the next 2 weeks
15. High anxiety score (≥15/21) on the Hospital Anxiety and Depression Scale (HADS)
16. Chronic systemic corticosteroid use (>14 days) at the time of study enrollment
17. Any expected corticosteroid use during study enrollment at higher doses than will be used in this study

D.3. Recruitment. The research staff will screen patients in the outpatient setting to identify potential candidates. For patients who are eligible on the basis of chart review, our research staff will approach them either in-person, or through remote methods for permission to conduct further screening for eligibility. Remote methods will consist of phone or vetted video-conferencing platforms (WebEx, Skype, FaceTime, or Zoom) to call potential participants to explain the study and gauge interest. If the participant wishes to participate, MyChart or e-mail will be used to send the consent form and research staff will obtain consent through this method.

A 2-step consent process will be used. A verbal script is provided in the Appendix. First, a verbal consent will be obtained by the study staff to proceed with screening of potential participants for eligibility and to characterize their dyspnea. Eligible patients will then be formally enrolled onto the study after they have signed the informed consent indicating a willingness to participate in the trial. The number of patients screened, approached, eligible and enrolled will be documented. Reasons for refusal for eligible patients will also be captured.

The outpatient supportive care clinic alone has more than 7000 patient visits per year, with approximately 50 new consultations per week. Patients at the thoracic medical oncology and radiation oncology clinics will also be enrolled. To augment recruitment and study generalizability, we will also enroll patients from the General Medical Oncology Clinic at The Harris Health System (LBJ), a county hospital in Houston. In 2015, the program had approximately 500 new consultations and 9500 total patient visits. Our team has successfully recruited from this clinic for other supportive care trials (Yennurajalingam *et al.* 2013).

To improve retention, we also plan to offer participants $50 gift cards for completion of day 7 and day 14 in-person or phone assessments, for a total of up to $100, to compensate them for their time and the costs associated with transportation. The research staff will also provide $15 valet parking vouchers to MD Anderson patients upon completion of in-person assessments at Baseline, day 7, and day 14 for a total of up to $45. LBJ patients will receive $6 parking vouchers for Day 7 and Day 14. A $6 Target gift card will be provided to LBJ patients at Baseline.

D.4. Randomization and stratification. After patient enrollment, randomization will be conducted by a pharmacist using permuted blocks and an institutional Clinical Trial Conduct (CTC) website. To minimize the possibility that imbalance in baseline dyspnea levels will affect measurement of the primary outcome, we will stratify patients by baseline dyspnea NRS score at enrollment (4-6 and 7-10) and study site (MDA vs. LBJ). Only the pharmacists preparing the study medications will have access to the treatment assignment. We will maintain allocation concealment.

D.5. Study interventions. Dexamethasone is a commonly used medication in cancer patients. It is approved by the US Food and Drug Administration for treatment of multiple indications, including allergic disorder (including asthma), cerebral edema associated with primary or metastatic brain tumor, craniotomy, or head injury, collagen disease, disorder of ear, disorder of endocrine system, disorder of eye, disorder of gastrointestinal tract, disorder of hematopoietic structure, disorder of respiratory system (treatment of berylliosis, fulminating or disseminated pulmonary tuberculosis (when used concurrently with appropriate antituberbulosis therapy), idiopathic eosinophilic pneumonias and symptomatic sarcoidosis, Loeffler's syndrome not manageable by other means and aspiration pneumonitis), disorder of skin, exacerbation of multiple sclerosis, hypercalcemia of malignancy, idiopathic thrombocytopenic purpura, inflammatory disorder of musculoskeletal system, macular retinal edema, mycosis fungoides, neoplastic disease, palliative management of leukemias and lymphomas, nephrotic syndrome, Idiopathic or due to lupus erythematosus without uremia, non-infectious posterior uveitis, trichinosis with neurologic or myocardial involvement, tuberculosis of meninges with subarachnoid block or impending block when used concurrently

with antituberculosis therapy. However, it has not been specifically approved for management of dyspnea.

Our study proposes to use oral dexamethasone for the management of dyspnea. Based on our preliminary data, the intervention arm will receive dexamethasone at a dose of 8 mg given orally twice daily for 7 days, then 4 mg given orally twice daily for 7 days. We do not plan to seek FDA approval for the new indication of dyspnea.

The control arm will receive placebo capsules prepared by a compounding pharmacy (e.g. Greenpark Pharmacy) identical in appearance to dexamethasone 4 mg capsules, and will be instructed to take two capsules twice a day for 7 days, followed by one capsule twice a day for 7 days.

In the open label phase, patients assigned to either arm will be asked to take dexamethasone 4 mg orally twice a day for 7 days, then 2 mg orally twice a day for 7 days. Both dexamethasone and placebo capsules used throughout this study will be dispensed by Investigational Pharmacy at MD Anderson. Dexamethasone/placebo capsules and open-label tablets will be provided free of charge to patients during the study period.

We will keep track of adherence by pill count. Patients will receive daily phone calls or other remote contact for reminders and assessments. They can take it as soon as possible if they forget a dose.

D.6. Blinding. Both patients and the research staff conducting the assessment will be blinded to the treatment assignment. Placebo capsules identical to dexamethasone 4mg capsules in appearance and taste will be manufactured by a compounding pharmacy, and both will be dispensed by Investigation Pharmacy at MD Anderson. At the end of the blinded phase, we will assess blinding by asking patients which study arm they believe they have been randomized to.

To minimize bias during statistical analyses, we will also blind the biostatisticians to the group assignment (groups A/B instead of dexamethasone/placebo) until they have completed the analyses pre-specified in the statistical analysis section after completion of study enrollment.

D.7. Study assessments. See Table 3 for a detailed description of study assessments. Study assessments will be conducted either in-person, by phone, or other remote methods as previously detailed (vetted platforms consisting of WebEx, Skype, FaceTime, or Zoom) during the course of the study.

D.7.1. Baseline characteristics. We will collect the following information to characterize the study population: date of birth, sex, race, education, marital status, cancer diagnosis, comorbidities, cause(s) of dyspnea, medications (e.g., scheduled and as-needed opioids, bronchodilators), and Karnofsky Performance Status (Schag *et al.* 1984).

D.7.2. Dyspnea NRS. The dyspnea NRS score will be the primary study outcome measure. The dyspnea NRS is an 11-point categorical scale validated for rating the average intensity of dyspnea over the past 24 hours, ranging from 0 (no dyspnea) to 10 (worst dyspnea) (Dorman *et al.* 2007, Gift and Narsavage 1998, Powers and Bennett 1999). It has been extensively validated and translated into multiple languages, including Spanish (Carvajal *et al.* 2011, Chang *et al.* 2000, Moro *et al.* 2006, Nekolaichuk *et al.* 2008, Paiva *et al.* 2015, Rees *et al.* 1998, Richardson and Jones 2009, Vignaroli *et al.* 2006, Watanabe *et al.* 2012, Zeng *et al.* 2011). Dyspnea NRS

score was chosen as the primary outcome measure instead of the modified Borg scale score because the dyspnea NRS was more responsive to change in our preliminary study (Hui *et al.* 2016a). Specifically, the dyspnea NRS has good discriminatory performance, with area under the receiver-operating characteristic curve of 0.71 for improvement and 0.79 for deterioration (Hui *et al.* 2015b). The MCID was 1 point for improvement and 1 point for deterioration (Hui *et al.* 2015b). In addition to intensity, we will assess the affective component (unpleasantness associated with dyspnea) using the same scale as one of the secondary measures.

D.7.3. Personalized dyspnea goal and personalized dyspnea response. The personalized dyspnea goal is determined by asking the patient, "At what level of shortness of breath intensity would you feel comfortable?" Personalized dyspnea response is defined as dyspnea NRS score ≤ personalized dyspnea goal. Thus, personalized dyspnea response provides a simple yet individualized therapeutic "target" and allows for intra-patient determination of a symptom response that is both practical and meaningful (Section D.2.1.1). However, because personalized dyspnea goal has never been tested in randomized, controlled trials, we will consider personalized dyspnea response only as a secondary outcome.

D.7.4. Unpleasantness associated with dyspnea. We will ensure that each patient understands the differences between intensity and unpleasantness of breathlessness by providing clear instructions as follows: "Intensity refers to the pure level or magnitude of the sensation. It is like a physical measure: for example, 'how much do you weigh in pounds?' Intensity does not contain any pleasantness or unpleasantness, like or dislike, or measure of how terrifying the experience is to you. Unpleasantness describes how much you like or dislike something or feel terrified by it. High unpleasantness indicates that your breathing feels very bad or terrifying regardless of whether the intensity is high or low."

D.8. Medication use during study and cointerventions. During the 2-week blinded phase, patients may continue their usual treatments for dyspnea, including opioids, supplemental oxygen, and bronchodilators. These treatments will be documented and adjusted for in the analysis. Our eligibility criteria are designed to specifically exclude patients who have reversible causes of acute dyspnea, such as pleural effusions, COPD exacerbations, or pneumonia.

D.9. Research staff training. An orientation will be held with research staff involved in this study to introduce them with the study design, and standardize the provision of each intervention. We will also conduct principal investigator research meetings 2-4x/month.

D.10. Patient Safety, Monitoring, and Confidentiality. Prior to study initiation, all research staff participating in this study will receive an orientation to the devices and forms in this study to ensure consistent assessments. During the study, trained research staff will be performing study assessments and monitoring the patient carefully throughout the study period. In addition to daily phone calls, or contact through other remote methods, patients will be given the contact information of the research staff in case they develop any significant adverse effects, and will be treated as they arise as per clinical practice. The study may be discontinued at the discretion of the treating physician or study principal investigator. Regulatory monitoring will be provided by the principal investigator, the Institutional Review Board, and the Data Safety

and Monitoring Board. Patient confidentiality will be ensured by use of patient initials, secure storage of clinical data, and anonymous reporting.

Table 3. Study assessments

Assessment	Baseline (in person)	Days 0-6 (phone or remote contact)	Day 7±2 (in person[11])	Days 8-13 (phone or remote contact)	Day 14±2 (in person[11])	Day 28±2, Day 42±2 (phone or remote contact)
Screening (Appendix A, B)	✓					
Demographics (Appendix C)	✓					
Dyspnea NRS score (primary outcome: intensity; secondary: unpleasantness; assessment requires <1min)[1] (Appendix D)	✓	✓	✓	✓	✓	✓
Personalized dyspnea goals (<1min)[2] (Appendix I)	✓				✓	
Biomarkers (blood draw, 15min)[3] (Appendix J)	✓		✓		✓	
Physiologic measures (i.e., spirometry, vital signs, maximal inspiratory pressure [MIP]; 20min)[4] (Appendix J)	✓		✓		✓	
Edmonton Symptom Assessment System (<3min)[5] (Appendix E)	✓		✓		✓	
HADS (<5min)[6] (Appendix H)	✓		✓		✓	
EORTC Quality of Life Questionnaire (QLQ)-C30 (<10min)[7] (Appendix F)	✓		✓		✓	
Adverse effects (10min)[8] (Appendix K)	✓		✓		✓	✓
Global assessment (<1min)[9] (Appendix G)			✓		✓	
Pill count and check of blinding (<1min)[10] (Appendix L)			✓		✓	

[1]The dyspnea NRS is a categorical scale ranging from 0 (no dyspnea) to 10 (worst dyspnea), validated for rating the average intensity of dyspnea over the past 24 hours (Dorman *et al.* 2007, Gift and Narsavage 1998, Powers and Bennett 1999). It is part of the ESAS (Bruera *et al.* 1989). The MCID is 1 point (Hui *et al.* 2015b). We will ask patients to rate the unpleasantness of dyspnea over the past 24 hours as well using the same NRS (i.e., ranging from 0 to 10).

[2]We will assess personalized dyspnea goals for dyspnea intensity by asking "At what level of intensity would you feel comfortable, on a scale of 0 to 10 where 0 = no shortness of breath and 10 = worst possible?" (Hui *et al.* 2016b). As an exploratory measure, we will also assess the personalized dyspnea goal for unpleasantness related to dyspnea: "At what level of unpleasantness would you feel comfortable, on a scale of 0 to 10 where 0 = no unpleasantness related to shortness of breath and 10 = worst possible?" Personalized dyspnea response is defined as dyspnea NRS ≤ personalized dyspnea goal. To assess the stability of personalized dyspnea goals, we will ask participants to provide this on day 14 ± 2 as well.

[3]A blood sample (~10 mL) will be obtained using sterile venipuncture techniques between 1200 and 1600 to control for potential diurnal variation at designated data points. Samples obtained in EDTA-containing Vacutainers will be transported on ice in a secure cooler to the bioscience laboratory at the University of Texas. Samples will be centrifuged for 15 minutes at 3000 rotations per minute within 24 hours and plasma will be aliquoted into cryovials for storage at -80°C until batch processing. Following standardized protocols of specific enzyme-linked immunosorbent assays for each biomarker (R&D Systems, Minneapolis, MN), inflammatory biomarkers (IL-1β, IL-6, IL-8, IL-10, and TNF-α) will be assessed in duplicate by the same trained person. Intra- and interassay coefficients of variation will be calculated to check precision. This type of bioassay has been routinely performed in this laboratory with high precision.

[4]The MicroLoop Spirometer (Micro Direct Inc, Lewiston, ME) will be used at baseline, day 7, and day 14. It is approved by the American Thoracic Society and the US FDA. Various spirometry parameters will be obtained, such as forced expiratory volume (FEV1), forced vital capacity (FVC), FEV1/FVC, peak inspiratory flow, and peak expiratory flow. Respiratory rate and oxygen saturation will be assessed in person. We will also assess MIP using the NS 120-TRR NIF Monitor (Instrumentation Industries Inc., Bethel Park, PA) according to the American Thoracic Society Guideline (Ats/Ers 2002). At least three consecutive inhalation scores will be recorded, with a 1-minute pause between each effort. We will use the average of the top three measures that varied by <20% for analysis.

[5]The ESAS is a validated questionnaire that measures 10 common symptoms in the past 4 hours (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well-being) using numeric rating scales (Bruera *et al.* 1991).

[6]The HADS consists of 14 items with 4-point numeric rating scales, including seven items on depression (HADS-D) and seven items on anxiety (HADS-A) (Zigmond and Snaith 1983). HADS has been validated for depression and anxiety in various settings. The average Cronbach alpha for HADS-A was 0.83, and 0.82 for HADS-D. Using a cutoff of 8 or greater for either subscale, the sensitivity and specificity were both approximately 80% for both HADS-A and HADS-D (Bjelland *et al.* 2002).

[7]The EORTC QLQ-C30 is a well-validated quality-of-life assessment for patients with cancer, consisting of 30 questions that encompass three symptom scales (pain, fatigue, and nausea/vomiting) and six questions about single symptoms, as well as five functional scales (physical, cognitive, role, emotional, and social) and one scale assessing global health status/quality of life. Each scale consists of two to five items, and all items have four response categories (not at all, a little, quite a bit, and very much), except for two items assessing overall health status/quality of life, which use a 7-point scale.

[8]In addition to clinician assessment of adverse effects according to CTCAE v4.03, adverse effects related to the use of dexamethasone, such as heartburn (F, S), nausea (F, S), pain in the abdomen (F, S, I), vomiting (F, S), arm/leg swelling (F, S, I), fatigue (F, I), decreased appetite (S, I), anxiety (F, SI, I), feelings that nothing could cheer you up (F, S, I), insomnia (S, I), sad or unhappy feelings (F,S, I), hiccups (F, S), hives (P), itchy skin (S), and rash (P) will be rated by patients using the PRO-CTCAE, which has recently been translated and validated in Spanish (Arnold *et al.* 2016, Basch *et al.* 2014, Bennett *et al.* 2016, Dueck *et al.* 2015). F = frequency, S = severity, I = interference with usual or daily activities, P = presence.

[9]Patients will be asked about their dyspnea (worse, about the same, or better) to compare the level of dyspnea before and after the study (Guyatt *et al.* 1993, Redelmeier *et al.* 1996).

[10]We will assess adherence by pill count on day 7 and day 14. We will also examine the success of blinding by asking patients to guess which treatment was given ("dexamethasone," "placebo," or "do not know").

[11] If patient available, otherwise, a phone call or other remote method will be conducted to administer the questionnaires.

E. Statistical Analysis

E.1. Sample size calculation. We will use 2:1 randomization as outlined in Section D.1.2.8. With a two-sided 5% alpha, normally distributed data, equal variance between treatment groups, and a within-group standard deviation of 2.0 (based on our preliminary data; Section D.1.1.3), we will need a total of 174 (116 + 58) patients to have 80% power to detect a mean difference of 1.0 between treatment groups. Assuming 15% attrition, we will need to enroll 134 patients in the dexamethasone arm and 67 in the placebo arm (201 total).

E.2. Data analysis

E.2.1. Primary objective. The primary endpoint will be dyspnea NRS score at day 7. Primary analysis will be a linear model comparing mean day 7 scores between treatment groups while adjusting for baseline levels. We will graph the data and perform residual analyses to verify assumptions of the model and take appropriate actions if the assumptions appear to be validated (e.g., transforming the data).

We will analyze the data with modified intention-to-treat analysis, by including all patients who were randomized started the study treatment, regardless of whether they complete the study. We will perform multiple imputation to handle missing data for the primary outcome. We will also conduct sensitivity analyses with worst case scenario (assume no change if no primary outcome data) and last value carry forward approaches.

E.2.2. Secondary objective #1. We will compare treatment groups at day 7 and day 14 for the values of the outcomes listed above. For the numeric outcomes (FEV1, FVC, MIP, oxygen saturation, ESAS, HADS, EORTC QLQ-C30, PRO-CTCAE frequency/severity/interference), we will perform linear model analyses as indicated in Aim 1. For personalized dyspnea response, we will use logistic regression analysis. For clinician-rated CTCAE adverse effects, we will tabulate by grade, type, attribution, and treatment group and compare the incidence of grade 3 or higher treatment-related toxic effects between treatment groups using logistic regression. For the daily dyspnea NRS values, we will use linear mixed-effects models to compare changes in scores over time between treatment groups (for the first 7 days and for the first 14 days). For the numeric endpoints, we will have 80% power to detect an effect size (mean difference divided by within-group standard deviation) of 0.5. For personalized dyspnea response, we will have >80% power to detect a 25% difference (e.g., 10% vs. 35%).To avoid issues with multiple testing, results will be considered hypothesis-generating rather than hypothesis-testing.

E.2.3. Secondary objective #2. The primary endpoint will be the baseline to day 7 difference in dyspnea NRS (>1.0 is considered clinically significant). We will use logistic regression analysis to identify independent predictors of this outcome, including baseline dyspnea NRS, restrictive or obstructive lung disease pattern, MIP, sex, and baseline inflammatory cytokine levels (IL-1β, IL-6, IL-8, IL-10, and TNF-α). We will plot the data and use residual analyses to verify assumptions of the model and take appropriate actions if they appear to be validated (e.g., transforming the data). We will use the variance inflation factor to identify collinearity. With 116 dexamethasone-treated patients, we would have at least 80% power to detect an odds ratio of 2.5 (for a one-unit change in a normally distributed marker) if the response probability is at least 30% (assuming 5% alpha and a correlation between the marker and the other factors in the model of 0.30). As an exploratory analysis, we will perform a similar analysis to that described for the primary endpoint to determine whether patients achieved their personal goal in dyspnea improvement. We will perform a similar exploratory linear regression analysis using

the difference between the day 7 and baseline dyspnea NRS scores as the endpoint. Additional exploratory correlative analyses will be conducted for changes in inflammatory markers between day 7 and baseline.

E.2.4. Secondary objective #3. We will calculate summary statistics for duration of dexamethasone dosing and cumulative dexamethasone dose. Two-sample t-tests or Wilcoxon rank sums tests will be used to examine whether binary events, such as adverse events, are associated with higher doses or duration of dexamethasone. If number of hospital admissions follows a Poisson distribution or zero-inflated Poisson distribution, we will use the appropriate model to examine the association of number of hospitalizations with cumulative dose and duration. All patients, regardless whether they received placebo, will be used to examine dose and duration initially. In these analyses, dose and duration for patients who received placebo will be set to zero. In a second set of analyses, only those patients who received dexamethasone will be included in the analyses. All testing will be 2-sided with 5% alpha. We will consider limiting the false detection rate to 10%.

E.2.5. Secondary objective #4. We will tabulate agreement between CTCAE adverse events and adverse events collected from the PRO-CTCAE form. We will also conduct chi-squared testing or Fisher's exact tests to determine whether treatment assignment or any other potential factors affects agreement. All testing will be 2-sided with 5% alpha. We will consider limiting the false detection rate to 10%.

E.2.6 Open label phase: We will conduct descriptive analyses to summarize the findings in the open-label phase in each arm. Exploratory analyses, as appropriate, will also be conducted to examine the between-group difference for various outcomes for hypothesis-generating purposes only.

E.2.7. Interim analysis: We will conduct two interim analyses (when roughly 33% and 67% of patients have been enrolled). We will look at both superiority (efficacy) and futility using O'Brien-Fleming boundaries. For futility, the p-value boundaries are 0.980, 0.359, and 0.046. For superiority, the Z-value boundaries are +/- 3.710, +/- 2.511, +/- 1.993. Calculations were done in East 6.

F. Data Confidentiality Procedures

Health information will be protected and we will maintain the confidentiality of the data obtained from the patient's chart to the best of our ability.

Collection of identifiers: We will collect and securely store patients' identifiers (including name, medical record number, and date of birth). Each patient will be assigned a study number that will be the only identifier to figure in the analytical file and personal data will not be disclosed in any form. The key linking these numbers will be retained in a securely locked file by the investigator.

Data Storage: Protection of electronic and paper records will be maintained to the best of our ability. All electronic records will be stored on password-protected institution computers behind the institution firewall. Any paper records will be classified and stored in locked files inside a locked office.

Training of personnel: Only MDACC personnel trained in maintaining confidentiality, the principal investigator, co-investigators, and research staff will have access to study records.

Data sharing: Study data will not be shared with any individuals or entities without an IRB-approved protocol.

Final disposition of study records: PHI may be maintained indefinitely, aggregated in the future, and used for future IRB-approved research studies.

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