Document Coversheet

Study Title: Phase II Investigation of Use of CNS Active Pembrolizumab and Chemotherapy for Asymptomatic Brain Metastasis From Non-small Cell Lung Cancer (NSCLC)

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Phase II Investigation of Use of CNS Active Pembrolizumab and Chemotherapy for Asymptomatic Brain Metastasis from NSCLC

Short Title: CNS Active Pembro+Chemo in Asymptomatic Brain Mets from NSCLC

PROTOCOL FACE PAGE FOR MCC INTERVENTIONAL THERAPEUTIC PROTOCOL

ROLE	*NAME*	*DEPARTMENT/DIVISION*
Principal Investigator	John Villano, MD, PhD	Professor, Director of Neuro-oncology Department of Medicine, Division of Oncology
Co-Investigators:	Reinhold Munker, MD	Internal Medicine, Oncology, Hematology
	Alexander Kreimer, PharmD	Clinical Pharmacist, Markey Cancer Center
	Heidi Weiss, PhD	Statistician
	Susanne Arnold, MD	Internal Medicine, Medical Oncology
	Ralph Zinner, MD	Internal Medicine, Medical Oncology
	Zhonglin Hao, MD	Internal Medicine, Medical Oncology
	William St Clair, MD, PhD	College of Medicine, Radiation Medicine
	Tom Pittman, MD	College of Medicine, Neuro-Surgery
Collaborators:	Leigh Anne Faul, PhD	Director, Investigator-Initiated Trials Office
	April Bramel	Senior IITs Project Manager, IITs Office
	Jennifer Land	Senior Clinical Data Manager

Study Site: Markey Cancer Center

Funding Source: Markey Cancer Center CCSG internal research grant and supplemental funding from Markey IIT Executive Steering Committee (PI, Villano)

FDA Status: Study Exempt from IND Requirements per 21 CFR 312.2(b).

Commercial Agents:
Pembrolizumab (Merck)
Carboplatin
Pemetrexed
Paclitaxel
Nab-paclitaxel

Investigational Agent: None (study is evaluating the timing of systemic therapy in advanced CNS-involved NSCLC)

Protocol Type / Version # / Version Date: Amendment / Version 1 / 15 December 2021
Amendment / Version 2 / 8 February 2022

Protocol Development History – Original Version to Current Version, w/ major Summary of Changes noted	
Original 1/20/2021	Original protocol for concept review, version date 20JAN2021.
1/29/2021	PRMC Review of concept. *Resolution:* Conditional approval, pending edits.
2/8/2021	FRC full review of Original protocol version date 20JAN2021. *Resolution*: One edit and a few clarifications requested by FRC.
Revision 1 2/16/2021	Protocol revised in response to PRMC and FRC reviews. New Version date 16FEB2021.
3/8/2021	PRMC Approval
5/11/2021	IRB Approval
Revision 2 9/10/2021	Protocol version date 16FEB2021 was revised. Revisions comprisie the following: Clarification of correlatives as 4 collections; clarification of Pembro vs. Pembro maintenance; added MOCA and QOL to calendar (corrected their omission); clarified PFS window as 6-mos in study calendar. New protocol version date 10SEP2021.
12/07/2021	**Open to Accrual**
Amendment 1 12/15/2021	Administrative changes only.
Amendment 2 02/08/2022	*The 15DEC2021 protocol was modified; Revised protocol version date, 02/08/2022.* *Protocol edits comprise the following: clarified pts whose mutation status is unknown are eligible (3.1.5, 3.2.1); expanded eligibility to include select pts with nonmeasurable disease (delete 3.2.2; add new 3.1.2); moved other inclusion criteria re: lesions (size, count) up to appear beneath new 3.1.2; Section 12.0: Patients with nonmeasurable disease by traditional RANO-BM enrolled on-study will be assessed by RANO-BM UK MOD.*
Amendment 3 *Add date*	*Placeholder for a future amendment*

PROTOCOL ABBREVIATIONS	
ABC	ATP Binding Cassette
ALK	Anaplastic lymphoma kinase
BOIN	Bayesian optimal interval
CA125	Cancer Antigen 125
DFS	Disease free survival
EGFR	Epidermal growth factor receptor
FDA	U.S. Food and Drug Administration
IND	Investigational New Drug
Mg	Milligrams
MTD	Maximum tolerated dose
NSCLC	Non-small cell lung cancer
OS	Overall Survival
P-gp	P-Glycoprotein
RANO	Response assessment in neuro-oncology
ROS-1	ROS Proto-Oncogene 1
RP2D	Recommended Phase 2 Dose
TKI	Tyrosine Kinase Inhibitors

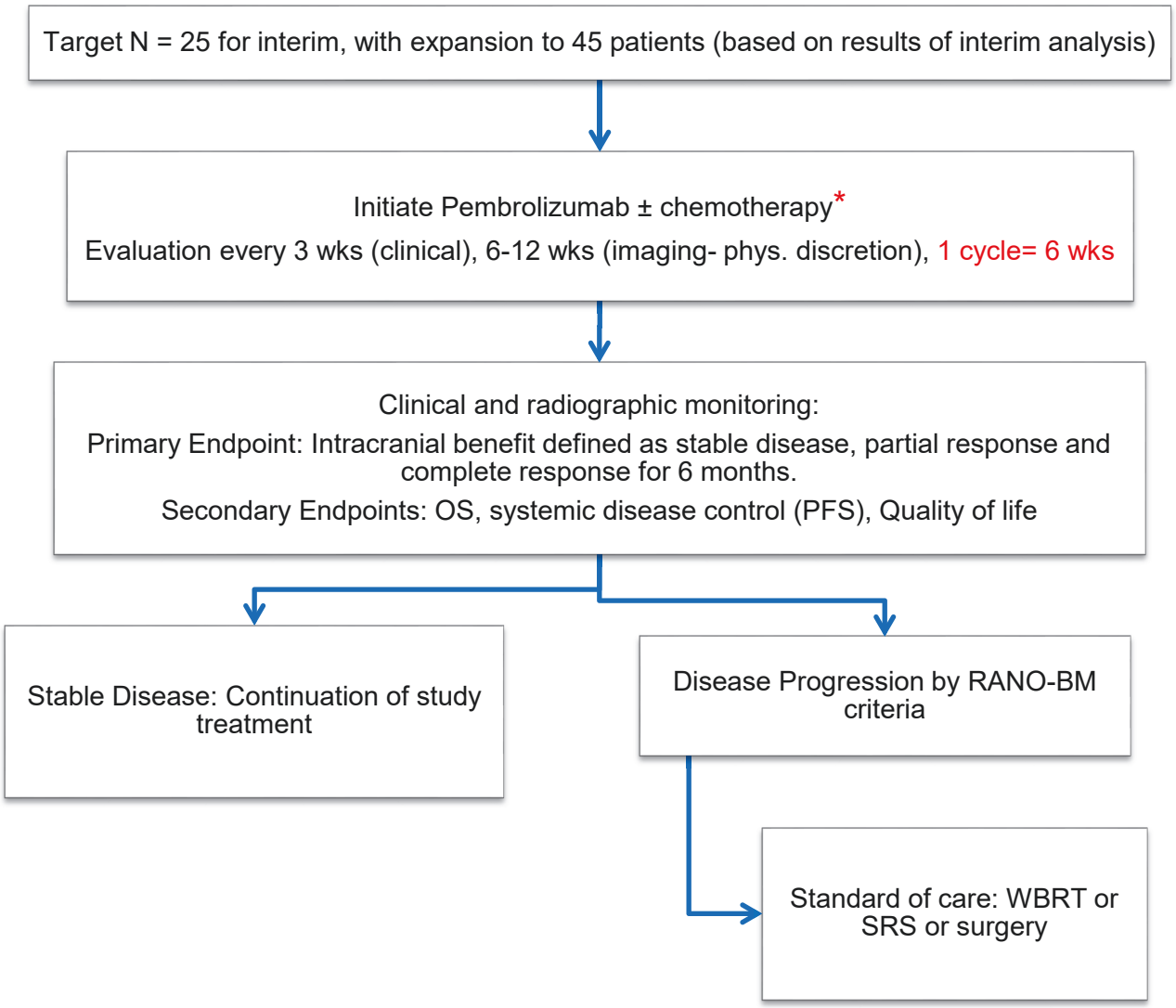
SCHEMA

Single-arm, Phase II trial
NSCLC w/ untreated asymptomatic brain metastasis, lacking *known* EGFR, ALK & ROS mutations
Major Inclusion criteria: ages 18 - 85

- Absence of neurological symptoms; ECOG Performance Status 0-2 and ≥ 3 months life expectancy
- Measurable disease per RANO, OR presence of 3 lesions that can be followed, OR Presence of one lesion measuring ≥5 mm PLUS a second lesion that can be followed
- Less than 10 intracranial lesions; no lesion larger than 3cm

Major Exclusion criteria:

- Midline shift; known leptomeningeal involvement
- Lesions located within 10mm of optic chiasm or optic nerve, or within the brainstem
- Not eligible for Pembrolizumab; TKI-sensitive tumors are excluded



Legend from Schema (figure on previous page):

* Pembrolizumab ± chemotherapy at investigator's discretion will select one of the following:
    a. Squamous NSCLC receives carboplatin plus paclitaxel/nab-paclitaxel plus pembrolizumab for 4 treatments and then pembrolizumab maintenance to continue
    b. Adenocarcinoma lung receives carboplatin plus pemetrexed plus pembrolizumab for 4 treatments and then pemetrexed plus pembrolizumab maintenance to continue
    c. If PDL1 Tumor Proportion Score ≥50%, may receive single agent pembrolizumab (up to 2 yrs)

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1. OBJECTIVES

1.1 Primary Objective

Single-arm, Phase II single arm non-inferiority trial to assess intracranial benefit of systemic therapy with pembrolizumab, with or without chemotherapy, defined as disease control rate (DCR) which includes stable disease (SD), partial response (PR), and complete response (CR) at 6 months.

1.2 Secondary Objectives

1.2.1 Evaluate Overall Survival at 12-months post study enrollment

1.2.2 Evaluate systemic disease control (6-month systemic Progression-Free Survival).

1.2.3 Assess changes in quality of life, via patient self-report on validated measures (FACT-Cog, FACT-Brain Cancer and FACIT-F Fatigue questionnaires) every 3 mos.

1.2.4 Evaluate changes in patients' neurocognitive functioning, via repeated assessment using the Montreal Cognitive Assessment (MoCA) pre- and 1-, 3-, 6-, 9- and 12-mos.

1.2.5 Assess changes in performance status as rated by physician – defined as latency to increase in ECOG performance status greater than 2 and scores on the Montreal Cognitive Assessment (MoCA)

1.3 Exploratory/Correlative Endpoint

Evaluation of immune based biomarker activity: e.g., PD-1 expression and activation of cytotoxic T-cells.

2. BACKGROUND

2.1 Non-Small Cell Lung Cancer

Lung cancer is the leading cause of cancer mortality in the United States (U.S.). More than 80 percent of lung cancers are classified as non-small cell lung cancer (NSCLC) and include adenocarcinoma, squamous cell, bronchioalveolar and adenosquamous histologies.

When metastatic, the disease is treated palliatively and cure is generally not an option. The goal of treatment is to prolong survival and preserve quality of life while minimizing the side effects due to treatment. When oncogenic driver mutations like EGFR, ALK, ROS1, BRAF mutations are present in metastatic NSCLC, targeted specific inhibitors are the preferred treatment option.[1] In tumors lacking known oncogenic drivers, NSCLC treatment includes Pembrolizumab with or without chemotherapy based on PDL1 expression status.

2.2 Brain Metastasis and Current Treatment

The incidence of metastatic lesions to the brain is increasing.[2,3] The estimated incidence is as high as 200,000 metastatic cancers to the brain per year in the United States and lung cancer represents 40-50% of these.[4] The increasing frequency of metastatic lesions to the brain is attributable to earlier detection using superior imaging modalities and to patients living longer with more effective treatment of systemic disease.

Current care for patients with metastatic disease to the brain for the majority of cancers remains focused on symptom management and/or therapeutic strategies. Symptomatic therapies include the use of corticosteroids and, if needed, antiepileptic medications, as well as supportive care.

Therapeutic measures include the use of radiation therapy administered as whole brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS) and possibly surgery for single metastatic lesions.[5] WBRT involve repeated administration of small doses of radiation to the whole brain to achieve killing of tumor cells. However, administration of WBRT is associated with an increased risk of decline in neurocognitive function. Stereotactic radiation surgery delivers single or very limited number of fractions of high-dose radiation directed specifically at the tumor while avoiding normal tissue. The Gamma Knife System is a commonly used technique of SRS, employing an array of radioactive sources to target the tumor with increased accuracy.

Due to the high risk of decline in cognitive function with WBRT, SRS is currently preferred in patients with 1 to 3 brain metastases.[6] Prospective non-randomized data in patients with newly diagnosed brain metastases have expanded the use of SRS to up to 10 brain lesions.[7] Despite the reduced dose outside target tissue with SRS, close proximity to cranial nerves can often lead to radiation neurotoxicity.

Median survival is in the range of 2.4–4.8 months with treatment via whole-brain radiation therapy (WBRT) alone and do not offer survival benefit compared to optimal supportive care.[8,9] The two-year relapse rates at initial and new sites range from 59% and 42% respectively with surgery, and 31% and 48% with SRS alone.[10] Median overall survival for patients with 2-4 brain metastasis who received SRS was 6.4 months.[11]

2.3 **Pembrolizumab and Systemic Chemotherapy in NSCLC**

Multiple resistance mechanisms, including systemic dysfunction in T-cell signaling[12-15] and exploitation of immune checkpoints[16] evolve in tumors, helping them evade specific immune responses despite the presentation of tumor antigens to the immune system. Recent understanding of these host-tumor immune interactions has given rise to novel antibodies directed against immune checkpoint proteins.[17,18]

Pembrolizumab is also a human immunoglobulin (Ig) G4 programmed cell death (PD) 1 immune checkpoint inhibitor antibody via intravenous infusion with FDA approval in numerous cancers. The drug is involved in PD1 (ligand) and PDL1 (receptor) signaling. PDL1 is a transmembrane protein that binds to its receptor, PD-1, found on activated T cells, B cells, and myeloid cells to modulate activation or inhibition during particular events such as pregnancy, tissue allografts, autoimmune disease and severe infections. Drugs targeting PD1 and PDL1, checkpoint inhibitors, are associated with fewer high-grade treatment-related adverse events than systemic cytotoxic chemotherapy.

Pembrolizumab as a single agent showed significant PFS/OS benefit in a subset of frontline NSCLC patients [as determined as a tumor proportion score (TPS) >50% staining of tumor cells for PDL1] relative to standard of care. When TPS score is 0-50%, Pembrolizumab is used in conjunction with carboplatin and pemetrexed in non-squamous histologies and carboplatin and paclitaxel (or nab-paclitaxel) in squamous histology.

2.4 **Pembrolizumab**

Pembrolizumab is a highly selective anti-PD-1 humanized monoclonal antibody which inhibits PD-1 activity by binding to the PD-1 receptor on T-cells to block PD-1 ligands from binding. Blocking the PD-1 pathway inhibits the negative immune regulation caused by PD-1 receptor signaling. This reverses T-cell suppression and induces anti-tumor responses. Pembrolizumab is given at a dose of 200mg IV over 30 minutes once on Day 1 every 3 weeks or 400mg IV over 30 minutes once on Day 1 every 6 weeks. Selection of q3 weeks or q6 weeks dosing will be at the discretion of the treating physician, while all subjects will be seen in clinic every 3 weeks. Administration every 3-weeks versus every 6-weeks will be based on patient/physician preference and insurance approval. Pembrolizumab administration every 6 weeks was granted accelerated FDA approval in April 2020 based on pharmacokinetic modeling and exposure-response analyses in the KEYNOTE-555 trial.[19]

Pembrolizumab is cleared from the circulation through non-specific catabolism and no studies were done on routes of elimination. There are no clinically important effects on the clearance based on age, sex, race, renal impairment, mild hepatic impairment, or tumor burden. The impact on moderate or severe hepatic on the pharmacokinetics of pembrolizumab is unknown. No metabolic drug interactions are expected.

Pembrolizumab safety and efficacy has been proven in multiple clinical trials in various cancers. In an open-label, phase 3 trial pembrolizumab was compared with standard of care platinum-based chemotherapy for patients with previously untreated advanced NSCLC with PDL1 expression on at least 50% of tumor cells and no sensitizing mutation of the EGFR or ALK gene. At the time of first analysis, median PFS was 10.3 months for the pembrolizumab arm versus 6 months for the chemotherapy arm. Estimated median OS at 6 months was also improved, 80.2% vs. 72.4%, respectively. Safety evaluation also favored the pembrolizumab arm.[20] At a median follow up of 24.2 months, the updated analysis continued to demonstrate benefit with pembrolizumab monotherapy with an OS of 30 months vs. 14.2 months for the chemotherapy arm.[21]

The safety and efficacy of Pembrolizumab in combination with pemetrexed and platinum chemotherapy was investigated in KEYNOTE-189, a randomized, multicenter, double-blind, active controlled trial in patients with metastatic nonsquamous NSCLC, regardless of PDL1 tumor expression status, who had not previously received

systemic therapy for metastatic disease and in whom there were no EGFR or ALK genomic tumor aberrations. The addition of pembrolizumab to standard chemotherapy (pemetrexed plus a platinum-based drug) resulted in significantly longer survival and progression-free survival than chemotherapy alone with similar frequency of adverse events.[22] At a median follow-up of 24.1 months, median OS was 22 months in the pembrolizumab-combination arm versus 10.7 months in the placebo-combination arm and median PFS was 9 months vs. 4.9 months, respectively. OS and PFS benefits were observed regardless of the PDL1 expression. Similar benefit for OS and PFS was also seen in patients with or without brain metastases.[23]

The safety and efficacy of pembrolizumab in combination with carboplatin and investigator's choice paclitaxel or paclitaxel protein-bound was investigated in KEYNOTE-407, a randomized, multicenter, double-blind, placebo controlled trial in patients with metastatic squamous NSCLC, regardless of PDL1 tumor expression status, who had not previously received systemic therapy for metastatic disease. The addition of pembrolizumab to standard chemotherapy (carboplatin plus paclitaxel or paclitaxel protein-bound) resulted in significantly longer OS and PFS than chemotherapy alone with similar frequency of adverse events.[24] At a median follow-up of 14.3 months, median OS was 17.1 months in the pembrolizumab combination arm versus 11.6 months in the placebo-combination arm and median PFS was 8 months vs. 5.1 months, respectively. OS and PFS benefits were observed regardless of PDL1 expression.[24]

2.5 **Concurrent Carboplatin-plus Regimens that are FDA approved**

2.5.1 Carboplatin with Pemetrexed

Carboplatin is a platinum compound alkylating agent which covalently binds to DNA and interferes with the function of DNA by producing interstrand DNA cross-links. Carboplatin is apparently not cell-cycle specific. Per standard of care carboplatin can be used in combination pemetrexed with/without pembrolizumab for non-squamous histologies.

Pemetrexed is an antifolate agent that disrupts folate-dependent metabolic processes essential for cell replication. Pemetrexed inhibits thymidylate synthase, dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, and aminoimidazole carboxamide ribonucleotide formyltransferase, the enzymes involved in folate metabolism and DNA synthesis, resulting in inhibition of purine and thymidine nucleotide and protein synthesis. Per standard of care and FDA approval pemetrexed is used in combination with carboplatin for non-small cell lung cancer with non-squamous histology. Standard of care supplementation with folic acid, vitamin B12, and corticosteroids are used to help reduce toxicities from pemetrexed.[25] In a phase III trial, carboplatin and pemetrexed were compared against a standard of care regimen for advanced non-small cell lung cancer, docetaxel and carboplatin. Carboplatin and pemetrexed combination was found to have improved survival without treatment-emergent grade 3/4 toxicity and similar overall survival.[26] Another phase III study looked at combination therapy with pemetrexed/carboplatin versus standard of care, gemcitabine/carboplatin. Pemetrexed/carboplatin combination was found to have similar health-related quality of life and survival when compared to the standard regimen for advanced non-small cell lung cancer.[27] These studies utilized standard of care dosing, intravenous pemetrexed 500mg/m2 plus carboplatin area under the curve (AUC) of 5 on day 1 of an every 3 week cycle. Treatment delays and dose-reductions for toxicities were based on standard of care recommendations.

2.5.2 Carboplatin with Paclitaxel or Nab-paclitaxel

Paclitaxel is a taxane derivative that promotes microtubule assembly by enhancing the action of tubulin dimers, stabilizing existing microtubules, and inhibiting their disassembly, interfering with the late G2 mitotic phase, and

inhibiting cell replication. Per standard of care, paclitaxel can be used in combination with carboplatin for non-small cell lung cancer with squamous cell histology. Due to risk of hypersensitivty reactions with paclitaxel, premedications based on standard of care must be given to reduce the risk of reactions. Efficacy with carboplatin/paclitaxel was compared in a randomized trial with standard of care cisplatin/paclitaxel and two other regimens, cisplatin/gemcitabine and cisplatin/docetaxel. Carboplatin/paclitaxel found to have a similar response rate and survival when compared to the other regimens with a lower rate of toxic effects.[28]

Nab-paclitaxel is a taxane derivative that is an albumin-bound paclitaxel nanoparticle formulation with a mechanism similar to paclitaxel. Due to the protein binding, drug delivery is optimized by utilizing the reversible binding affinity of paclitaxel to promote transport across the endothelial cell and concentrates the drug within the tumor cell. Per standard of care nab-paclitaxel can be used in combination with carboplatin for advanced non-small cell lung cancer with squamous cell histology. Nab-paclitaxel can be utilized first line or substituted for paclitaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel despite premedication or if standard premedications are contraindicated. Efficacy of nab-paclitaxel/carboplatin was shown in a phase 3 trial comparing against standard paclitaxel/carboplatin. Nab-paclitaxel was found to have significantly improved objective overall response rate with significantly less grade 3 toxicities, specifically neuropathy. Progression free survival and overall survival were non-inferior and comparable to historical results in non-small cell lung cancer patients. This study utilized standard of care dosing for these agents. Nab-paclitaxel was administered intravenously (IV) 100mg/m2 over 30 minutes on days 1, 8, and 15 followed by carboplatin IV AUC 6 on day 1 of an every 3 week cycle. Paclitaxel was administered IV 200mg/m2 over 3 hours on day 1 followed by carboplatin IV AUC 6 on day 1 of an every 3 week cycle. Treatment delays and dose-reductions for toxicities were based on standard of care recommendations.[29]

2.6 **Rationale**

Although WBRT, SRS and surgery are established in the treatment for those patients with symptomatic brain metastases, the management of asymptomatic or controlled brain metastases is not as straight forward. Radiation therapy confers significant side effects, especially the potential risk of cognitive decline.[30] Brain radiation necrosis can also cause significant toxicities, generally occurring from 6 months to several years after treatment.[31] With regards to patients with NSCLC with brain metastatic disease with poorer performance status for surgery or stereotactic radiosurgery (SRS), the non-inferiority QUARTZ phase III trial evaluated dexamethasone and supportive care with or without WBRT and found no overall survival difference (HR 1.06) as well as no overall quality of life difference.[32] This suggests that this population may derive minimal benefit from WBRT.

In the treatment of CNS metastases, chemotherapy was previously thought to be inferior to radiation and/or surgery due to concerns of poor penetration of systemic agents via the blood-brain barrier.[33] Gerstner et al. established that tumor neovasculature is similar to extracranial vessels in relation to permeability.[34] Further, due to improvement in systemic therapy, there is evidence to support efficacy in treating brain metastasis from NSCLC with systemic therapy. Lee et al. described a similar response rate between NSCLC patients with absent or controlled neurologic symptoms treated with primary chemotherapy versus WBRT administered as initial therapy. There was no statistically significant difference in overall response rate which was 28% vs 39%, progression-free survival, 3.6 months vs 4.4 months, and overall survival, 9.1 months vs 9.9 months.[35] Further, in the WBRT-first arm, grade 3 or 4 neutropenia was more frequent (79% vs 40%) during chemotherapy and 4 patients (17.4%) did not receive further chemotherapy because of early death or worsening performance status after WBRT. Robinet et al examined early versus delayed WBRT in NSCLC in phase III trial where 86 patients who had chemotherapy alone had RR of 27% and those with chemotherapy with WBRT had RR of 33%.[36] An additional trial examined 26 chemotherapy -naïve patients with metastatic NSCLC

to brain who received cisplatin/paclitaxel and either vinorelbine on D1 and D15 or gemcitabine D1 and D8 and found that 38% had intracranial responses.[37]

With the advent of immunotherapy for the treatment of metastatic non-small cell lung cancer, improved disease response in regard to CNS metastases has been observed. Crino et al. included 409 of 1588 patients with asymptomatic or controlled brain metastases in their non-squamous NSCLC study evaluating the use of Nivolumab as subsequent therapy. The disease control rate was 39% among these patients. However, of these 409 patients, 118 were receiving corticosteroids and 74 were undergoing concomitant radiotherapy.[38] A phase III trial completed by Brahmer, et al. demonstrated the effect of Nivolumab, an anti-PD-1 monoclonal antibody, on patients with CNS disease from NSCLC. This trial included 37 patients with treated and stable brain metastases. The disease control rate was 49% among patients with CNS metastasis and the objective response rate was 7/37 (19%). Further the overall survival rate at 12 months was 35% for CNS metastatic patients compared to 39% for all patients.[39] Two phase II trials evaluated the use of Pembrolizumab in untreated non-small cell with brain metastases. The first study included 18 NSCLC patients without associated neurologic symptoms or need for steroids and tissue demonstrating PDL1 expression (>1%). Brain metastasis response rate was 33% for patients with NSCLC with durable response, ranging from 3 to 7 months.[40] The second study enrolled 42 patients with similar characteristics and were treated with pembrolizumab 10mg/kg every 2 weeks. On median follow up of 8.3 months, 29.7% of patients with PD-L1 expression ≥1% achieved brain metastatic response indicating pembrolizumab has activity in brain metastasis.[41] Borghaei et al found that Nivolumab improved overall survival versus docetaxel in advanced non-squamous non-small cell lung cancer after failure of platinum therapy (12.2 months for nivolumab versus 9.4 months for docetaxel [HR 0.73, p=0.002]). However, of those with CNS metastases (n=68) the hazard ratio did not favor nivolumab.[42]

Given the risks of brain radiation and the above data that supports brain metastasis response to systemic chemotherapy and immunotherapy, we propose a trial providing up-front therapy for non-mutated EGFR, ALK and ROS1 (wild-type) NSCLC patients with asymptomatic brain metastases using Pembrolizumab +/- chemotherapy (Carboplatin/Pemetrexed for nonsquamous and Carboplatin/Paclitaxel or Nab-paclitaxel for squamous). It is reasonable that the initial treatment of CNS metastasis with systemic chemotherapy and immunotherapy will have similar disease control to lung disease alone. This study would add onto the Goldberg investigation, but include the improved benefit of allowing chemotherapy to improve disease control, and hopefully improved clinical outcomes with early systemic treatment.[40]

2.7 **Correlative Studies**

This exploratory study assesses the T-cell subsets and monitors PD-1 expression along with activation and will correlate with therapy. Multiplex immunofluorescence will be used to evaluate spatial relationships between immunologic factors in the tumor microenvironment. The study is based on peripheral blood to assess immune activation. The following steps for processing and cryopreservation of blood samples will be performed in Flow Cytometry and Immune Monitoring (FCIM) SRF. FCIM SRF provides flow cytometric analysis and cell sorting as well as human immune monitoring services. These services include blood processing and cryopreservation of PBMC.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Non-small cell lung cancer with untreated asymptomatic brain metastases

3.1.2 Measurable disease as defined by as defined by the Response Assessment in Neuro-Oncology (RANO) group criteria. Per RANO, Measurable disease is defined as at least one brain lesion that can be accurately measured in at least one dimension with the longest recorded diameter ≥10 mm.

OR

Presence of 3 lesions that can be followed*

OR

Presence of one lesion measuring ≥5 mm PLUS a second lesion that can be followed*

*RANO criteria considers these "*nonmeasurable*" leasions, which is terminology used in sections 9.2 and 12

3.1.3 Presence of fewer than 10 intracranial lesions

3.1.4 Each lesion measures 3cm or less.

3.1.5 Absence of <u>known</u> oncogenic driver mutations, i.e., EGFR, ALK, or ROS-1.

NOTE: *IF* a mutation is discovered after the patient enrolls to this trial, then the patient will be taken off-study and considered "non-evaluable" for analysis.

3.1.6 Absence of new onset neurological symptoms (includes increased intracranial pressure, uncontrolled nausea or vomiting, Grade 3 headache, epilepsy, or focal motor deficit attributed to the metastatic lesions).

3.1.7 Eligible for treatment with immune checkpoint inhibitor. Note that no limit is placed on prior systemic treatment.

3.1.8 Ages 18-85 years.

3.1.9 ECOG performance status ≤ 2 (see **Appendix A**).

3.1.10 Life expectancy of ≥3 months.

3.1.11 Patients must have adequate organ and marrow function as defined below:

- absolute neutrophil count ≥1,000/mm^3
- platelets ≥75,000/mm^3
- total bilirubin ≤ 1.5 x ULN
- AST and ALT if no hepatic metastasis ≤ 2.5 × ULN
- AST and ALT with hepatic metastasis ≤ 5 x ULN
- Creatinine ≤ 1.5 x ULN and Requires CrCl ≥ 40ml/min (per 24-hr urine collection or calculated via Cockcroft-Gault formula, see **Appendix B**)

3.1.12 Steroid dose maintenance is allowed, however no more than 10 mg of prednisone or equivalent per day or inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day.

3.1.13 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.1.14 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.15 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.16 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.1.17 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

3.1.18 The effects of Pembrolizumab on the developing human fetus are unknown. The other chemotherapy agents used in this trial are known to be teratogenic. Hence, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 120 days after completion of Pembrolizumab administration.

3.1.19 Ability to understand and the willingness to sign a written informed consent document.

3.2 **Exclusion Criteria**

3.2.1 Presence of <u>known</u> oncogenic driver mutations, such as EGFR, ALK and/or ROS-1, at study pre-screening.

3.2.2 Measurable lesion located within 10mm of the optic chiasm or optic nerve, or within the brainstem.

3.2.3 Known leptomeningeal involvement.

3.2.4 Midline shift.

3.2.5 Pregnant and/or lactating women expecting to conceive or father children within the projected duration of the study, starting with the screening visit and extending through 120 days after the last dose of the trial treatment. Female subjects of childbearing potential must not be pregnant at screening. Female subjects are considered to be of childbearing potential unless one of the following criteria is met in **Appendix C**.

3.2.6 Active clinically serious infection > CTCAE Grade 2.

3.2.7 Serious non-healing wound, ulcer or bone fracture.

3.2.8 Baseline inability to participate or complete neurocognitive testing, e.g. having developmental disabilities.

3.2.9 Ineligible for immune checkpoint inhibitors based on package insert of the chosen immune checkpoint inhibitor (e.g., uncontrolled immunologic disorders, active hepatitis, active colitis, active pneumonitis, uncontrolled/active hormone gland problems - including thyroid, pituitary, adrenal glands and pancreas).

3.2.10 Major surgical procedure (including craniotomy and open brain biopsy) or significant traumatic injury within 14 days prior to registration.

3.2.11 Receipt of a non-CNS minor surgical procedure (e.g. core biopsy or fine needle aspiration) within 3 days prior to registration. There is no waiting period for central line placement.

3.2.12 History of allergic reactions attributed to monoclonal antibodies (mAb), compounds of similar chemical or biologic composition to Pembrolizumab. Severe hypersensitivity to Pembrolizumab or any of its excipients.

3.2.13 Clinically significant cardiovascular disease, for example cerebrovascular accidents (less than 6 months, CVA) /stroke, myocardial infarction (also less than 6 months), unstable angina pectoris, New York Heart Association class 3 or 4 congestive heart failure, or serious cardiac arrhythmia requiring medication.

3.2.14 Uncontrolled hypertension defined as sustained blood pressure (BP) > 150 mm Hg systolic or > 90mm Hg diastolic despite optimal antihypertensive treatment.

3.2.15 QT interval calculated by the Fridericia formula (QTcF) > 480 ms per electrocardiogram (ECG) within 14 days before first dose of study treatment.

Note: If a single ECG shows a QTcF with an absolute value > 500 ms, two additional ECGs at intervals of approximately 3 min must be performed within 30 min after the initial ECG, and the average of these three consecutive results for QTcF will be used to determine eligibility (i.e., if the average is ≤ 500ms the patient is eligible).

3.2.16 Patients with uncontrolled intercurrent illness.

3.2.17 Patients with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.18 Patients who received prior radiation (WBRT, SRS or Stereotactic radiotherapy) within the past 3 years at the discretion of the treatment team.

3.2.19 Patients who have a RET or MET driver mutation that can be targeted with an FDA-approved TKI (tyrosine kinase inhibitor) that is expected to generate a high response.

3.3 **Inclusion of Women and Minorities**

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.

4. INVESTIGATOR REQUIREMENTS AND REGISTRATION PROCEDURES

4.1 Trial Registration required by National Cancer Institute

The National Cancer Institute requires that interventional treatment trials be registered in clinicaltrials.gov and on NCI's CTRP (Clinical Trials Reporting Program) prior to patient enrollment. The Regulatory Group within MCC's Clinical Research Office and Investigator-Initiated Trials Office at Markey will provide assistance in completing these required registrations/renewals.

4.2 Protocol Review and Monitoring Committee and Institutional Review Board

Before implementing this study, the protocol must be reviewed by the Markey Cancer Center's Protocol Review and Monitoring Committee (PRMC). Additionally, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by the University of Kentucky Institutional Review Board (IRB). A signed and dated UK IRB initial review approval memo must be maintained in the Markey Cancer Center Clinical Research Office (MCC CRO) regulatory binder. Any amendments to the protocol, other than administrative ones, must be reviewed and approved by the PRMC, and UK IRB.

4.3 Investigator and Research Associate Registration with MCC Enrollment Guidelines

All investigators must be qualified by education, training and experience to assume responsibility for the proper conduct of human subject research. Investigators are responsible for being able to provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation and training per institutional, state and federal guidelines. All investigators conducting MCC trials will register with the MCC Clinical Research Office and complete all requisite training and registrations per MCC SOPs.

4.3.1 Delegation of Tasks Log (DTL)

All MCC studies require a Delegation Task Log which is maintained by the MCC Regulatory Unit of the Clinical Research Office. The DTL for this study has training requirements as follows: In order to be added to the DTL for a given study, each staff member must have appropriate training to conduct assigned duties including but not limited to protocol specific training. The DTL log will identify the protocol version on which each staff member was trained when being added to a study.

The Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Principal Investigator and Statistician have access to the study data at all times through OnCore. All decisions regarding dose modifications require consultation with the Principal Investigator.

4.4 **Overview and Informed Consent Guidelines**

4.4.1 Brief Overview of Enrollment Process

Eligible patients will be identified by the principal investigator and co-investigators of this study. Potentially eligible patients will be screened in the University of Kentucky Markey Cancer Center clinics by the investigators and study personnel with oversight by the Principal Investigator (PI). The consenting professional will explain in detail the study to the patient and will review the informed consent with the patient (Section 4.4.2). Broadly, patients will be made aware of the protocol, its specific aims and objectives, and the potential risks and benefits the patient may incur. A copy of the signed informed consent form is provided to the patient. Upon obtaining consent, study staff will register potentially eligible patients in the trial's database in OnCore, Markey's Clinical Trials Management System. During the screening and enrollment process, registering individuals (study staff and PI) will be required to complete a protocol-specific Eligibility Checklist for each patient. The PI or treating physician signing the Eligibility Checklist is confirming whether or not the patient is eligible to enroll in the trial. Upon confirmation of eligibility, the patient will be enrolled into the study as a participant via the entry of an on-study date. See Section 4.5 for details.

4.4.2 Informed Consent

The goal of the informed consent *process* is to provide people with sufficient information so they can make informed choices about whether to begin or continue participation in clinical research. The process involves a dynamic and continuing exchange of information between the research team and the participant throughout the research experience. It includes discussion of the study's purpose, research procedures, risks and potential benefits, and the voluntary nature of participation.

The informed consent *document* provides a summary of the clinical study and the individual's rights as a research participant. The document acts as a starting point for the necessary exchange of information between the investigator and potential research participant. Also, research participants and their families may use the consent document as an information resource and reference throughout participation in the trial. The informed consent *document* is often considered the foundation of the informed consent process; it does not, however, represent the entirety of the process. Nor is the informed consent document a risk-management tool for the investigator and/or institution.

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained. The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with the protocol at the time of IRB review.

4.4.3 Screening and Enrollment Guidelines

Prior to any study-required tests, subjects must first provide written informed consent to participate in this study.

4.5 **Eligibility Confirmation and Enrollment**

The following information should be reviewed by the Clinical Research Nurse (CRN) / Clinical Research Associate (CRA) with the study physician per MCC SOPs to confirm eligibility:

- Copy of required laboratory tests
- Pathology reports
- Physician dictations
- Imaging reports
- Signed patient consent form and HIPAA authorization form
- Referring physician records as available
- Other required screening procedures when applicable
- Eligibility Checklist

Once eligibility is confirmed, the CRN/CRA will complete subject enrollment to the trial in the OnCore database. To complete the enrollment process, the CRN/CRA will complete the OnCore on-study form, which comprises the following:

- assignment of a patient study number
- enter diagnosis and date of diagnosis
- enter histology
- enter the on-study date in OnCore

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Timepoint	Specimen	Send Specimens To:
Baseline (pre-treatment)		
	• *15 mL blood in whole blood tube w/ anticoagulant , BD Vacutainer™ CPT™ Tube with Sodium Citrate (mandatory)*	*Markey FCIM*
6 weeks after treatment initiation (±2-weeks)		
	• *15 mL blood in whole blood tube w/ anticoagulant , BD Vacutainer™ CPT™ Tube with Sodium Citrate (mandatory)*	*Markey FCIM*
12 weeks after treatment initiation (±2-weeks)		
	• *15 mL blood in whole blood tube w/ anticoagulant , BD Vacutainer™ CPT™ Tube with Sodium Citrate (mandatory)*	*Markey FCIM*
18 weeks after treatment initiation (±2-weeks)		
	• *15 mL blood in whole blood tube w/ anticoagulant , BD Vacutainer™ CPT™ Tube with Sodium Citrate (mandatory)*	*Markey FCIM*

5.2 Specimen Collection and Processing

All samples cryopreserved by FCIM are then banked and managed by Biospecimen and Tissue Procurement (BSTP) SRF until all samples for a subject have been collected. Once all samples are collected, all stored samples for a subject will be thawed and analyzed simultaneously by FCIM to obtain correlative endpoints as described above. Data analysis will be performed by Dr. Cohen with members of his laboratory along with review and discussion of data with Drs. Subbarao Bondada, Val Adams, and John L. Villano.

The correlative studies are based on peripheral blood to assess immune activation. The following steps for processing and cryopreservation of blood samples listed below are to be performed in Flow Cytometry and Immune Monitoring (FCIM) SRF. FCIM provides flow cytometric analysis and cell sorting as well as human immune monitoring services. These services include blood processing and cryopreservation of PBMC. All samples cryopreserved by FCIM are then banked and managed by Biospecimen and Tissue Procurement (BSTP) SRF until all samples for a subject have been collected. Once all samples are collected, all stored samples for a subject will be thawed and analyzed simultaneously by FCIM to obtain correlative endpoints as described below. Data analysis will be performed by Dr. Don Cohen with members of his FCIM laboratory along with review and discussion of data with Drs. Subbarao Bondada, Val Adams, and John L. Villano.

At each time-point, 15 ml of blood will be collected from patients at indicated times (Whole Blood tube w/ Anticoagulant, BD Vacutainer™ CPT™ Tube with Sodium Citrate). This collection is performed in clinics and handed to Markey FCIM. There will be a total of 4 collection times as mentioned and should yield approximately 16 million PBMCs for each blood draw that will be analyzed by flow cytometry.

Lab manual for processing of the liquid specimen is provided in Appendix D.

6. TREATMENT PLAN

Prior to any study-required tests, subjects must first provide written informed consent to participate in this study. Section 11 (Study Calendar) details windows for completion of baseline scans and labs to verify eligibility.

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

6.1 Overview of Pembrolizumab and Concurrent Chemotherapy Regimens

6.1.1 Pembrolizumab with Carboplatin/Pemetrexed Regimen

Carboplatin/Pemetrexed/Pembrolizumab Regimen Description (C1-4)					
Agent	**Premedications; Precautions; Postmedications**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Pembrolizumab	Monitor for hypersensitivity reactions (refer to section 6.1.1) Give prior to chemotherapy	200 mg (diluted in 100mL 0.9% sodium chloride)	IV over 30 minutes with 0.22 micron filter	Day 1, Q3 weeks	21 days (3 weeks)
Carboplatin	Aprepitant 130mg IV, Ondansetron 16mg PO, Dexamethasone 8mg IV (if PO dexamethasone has not been administered at home) prior to chemotherapy on day1 Dexamethasone 4mg BID day before chemotherapy and on days 1, 2, and 3	AUC 5 (diluted in 250mL 0.9% sodium chloride)	IV over 30 minutes	Day 1, Q3 weeks	21 days (3 weeks)
Pemetrexed		500 mg/m2 (diluted in 100mL 0.9% sodium chloride)	IV over 10 minutes	Day 1, Q3 weeks	21 days (3 weeks)
Pembrolizumab/Pemetrexed Maintenance (after C1-4)					
Pembrolizumab	Monitor for hypersensitivity reactions (refer to section 6.1.1) Give prior to chemotherapy	200 mg (diluted in 100mL 0.9% sodium chloride)	IV over 30 minutes with 0.22 micron filter	Day 1, Q3 weeks	21 days (3 weeks)
Pemetrexed	Anti-emetics per institutional guidelines	500 mg/m2 (diluted in 100mL 0.9% sodium chloride)	IV over 10 minutes	Day 1, Q3 weeks	21 days (3 weeks)

6.1.2 Pembrolizumab with Paclitaxel and Carboplatin Regimen

Carboplatin/Paclitaxel/Pembrolizumab Regimen Description (C1-4)					
Pembrolizumab	Monitor for hypersensitivity reactions (refer to section 6.1.1) Give prior to chemotherapy	200 mg (diluted in 100mL 0.9% sodium chloride)	IV over 30 minutes with 0.22 micron filter	Day 1, Q3 weeks	21 days (3 weeks)
Carboplatin	Aprepitant 130mg IV, Dexamethasone 12mg PO, Ondansetron 16mg PO, Cetirizine 10mg PO, Famotidine 20mg PO prior to chemotherapy on day 1 Dexamethasone 8mg PO once daily on days 2,3,4 Give paclitaxel prior to carboplatin Monitor for hypersensitivity reactions *See additional precautions below	AUC 6 (diluted in 250mL 0.9% sodium chloride)	IV over 30 minutes	Day 1, Q3 weeks	21 days (3 weeks)
Paclitaxel		200mg/m2 (diluted in 500mL 0.9% sodium chloride) Non-PVC tubing with 0.22 micron filter	IV over 3 hours	Day 1 Q3 weeks	21 days (3 weeks)
Maintenance Pembrolizumab (After C1-4)					
Pembrolizumab	Monitor for hypersensitivity reactions (refer to section 6.1.1) Give prior to chemotherapy	400 mg (diluted in 100mL 0.9% sodium chloride)	IV over 30 minutes with 0.22 micron filter	Day 1, Q6 weeks	42 days (6 weeks)

6.1.3 Pembrolizumab with Nab-Paclitaxel and Carboplatin Regimen

Carboplatin/Nab-Paclitaxel/Pembrolizumab Regimen Description (C1-4)					
Pembrolizumab	Monitor for hypersensitivity reactions (refer to section 6.1.1) Give prior to chemotherapy	200 mg (diluted in 100mL 0.9% sodium chloride)	IV over 30 minutes with 0.22 micron filter	Day 1, Q3 weeks	21 days (3 weeks)
Carboplatin	Aprepitant 130mg IV, Dexamethasone 12mg PO, Ondansetron 16mg PO prior to chemotherapy on day 1 Dexamethasone 8mg PO on days 2,3,4 Ondansetron 16mg PO prior to chemotherapy on day 8 and 15 Give nab-paclitaxel prior to carboplatin on day 1 Monitor for hypersensitivity reactions	AUC 6 (diluted in 250mL 0.9% sodium chloride)	IV over 30 minutes	Day 1, Q3 weeks	21 days (3 weeks)
Nab-paclitaxel		100mg/m2 (undiluted)	IV over 30 minutes	Day 1, 8, 15 Q3 weeks	21 days (3 weeks)
Maintenance Pembrolizumab (After C1-4)					
Pembrolizumab	Monitor for hypersensitivity reactions (refer to section 6.1.1) Give prior to chemotherapy	400 mg (diluted in 100mL 0.9% sodium chloride)	IV over 30 minutes with 0.22 micron filter	Day 1, Q6 weeks	42 days (6 weeks)

6.1.4 Pembrolizumab Alone Regimen

Pembrolizumab Regimen Description					
Pembrolizumab	Monitor for hypersensitivity reactions (refer to section 6.1.1) Give prior to chemotherapy	400 mg (diluted in 100mL 0.9% sodium chloride)	IV over 30 minutes with 0.22 micron filter	Day 1, Q6 weeks	42 days (6 weeks)

6.1.5 Pembrolizumab Administration

Pembrolizumab Infusion Requirements and Guidance	
<u>First</u> Infusion	**Subsequent Infusions:**
• No premedication is permitted. • Vital signs (blood pressure, respiratory rate, pulse, and temperature) should be recorded within 60 min prior to the infusion. • Pembrolizumab should be infused over 30 min (-5 min/+10 min). • If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 min (± 5 min for all time points) during the infusion and at 30 (± 10) min after the infusion. • Subjects should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their physician	• If the subject experienced an infusion-related reaction with any previous infusion, premedication with antihistamines, antipyretics, and/or analgesics may be administered for subsequent doses at the discretion of the investigator. • Vital signs should be recorded within 60 min prior to the infusion. • Pembrolizumab should be infused over 30 (± 15) min if the previous infusion was tolerated without an infusion-related reaction, or 60 (± 15) min if the subject experienced an infusion-related reaction with the previous infusion. • If the subject experienced an infusion-related reaction with the previous infusion or if clinically indicated, vital signs should be recorded during the infusion and at 30 (± 5) min after the infusion.

6.1.6 Administration of Other Commercial Agents

6.1.6.1 Carboplatin Administration

- Premedications per institutional standard
- Administer after pembrolizumab and chemotherapy (pemetrexed, paclitaxel, nab-paclitaxel) on day 1

- For dosing please refer to institution carboplatin dosing guideline
    - Calvert Formula
        - Carboplatin dose (mg) = (Target AUC) X (GFR + 25)
            - Maximum GFR of 125 ml/min
    - Cockcroft-Gault to estimate GFR
        - CrCl (ml/min) = $\frac{(140\text{-age}) \times \text{Actual* Body Weight (kg)}}{\text{Serum Creatinine (mg/dL)} \times 72}$
            - Obese patients (BMI ≥ 25) use Adjusted Body Weight
            - Multiply by 0.85 if female
            - Minimum SCr of 0.7 mg/dL
    - Adjusted Body Weight (If BMI ≥ 25)
        - Estimate Ideal body weight (IBW)
            - Males: IBW = 50kg + 2.3kg for each inch over 5 feet
            - Females: IBW = 45.5kg + 2.3kg for each inch over 5 feet
        - Adjusted body weight: IBW + 0.4 (ABW - IBW)

6.1.6.2 Pemetrexed Administration

- Premedications (in conjunction with carboplatin):
    - Administer aprepitant 130mg IV prior to chemotherapy on day 1 to prevent nausea
    - Administer ondansetron 16mg PO prior to chemotherapy on day 1 to prevent nausea
    - Administer dexamethasone 8mg IV (if PO dexamethasone has not been administered at home) prior to chemotherapy on day 1 to prevent nausea and rash
    - Administer dexamethasone 4mg PO BID day before chemotherapy and on days 1, 2, and 3 to prevent nausea and rash
- No NSAIDs 2 days prior, day of, and 2 days after pemetrexed
- Should not be administered in the presence of ascites or pleural effusions
- Confirm patient has taken the following:
    - Folic acid 1mg PO daily starting 7 days prior to initial dose of pemetrexed and continue until 21 days after the last dose
    - Vitamin B12 (cyanocobalamin) 1,000 mcg IV every 3 months beginning 1-2 weeks prior to pemetrexed
    - Dexamethasone 4mg PO twice daily the day prior to pemetrexed
- Administer after pembrolizumab and prior to carboplatin on day 1
- For dosing utilize actual body weight and Dubois formula for body surface area
- Monitor for hypersensitivity reactions; refer to institution hypersensitivity protocol

6.1.6.3 Paclitaxel Administration

- Premedications (in conjunction with carboplatin):
    - Administer aprepitant 130mg IV prior to chemotherapy on day 1 to prevent nausea
    - Administer dexamethasone 12mg PO prior to chemotherapy on day 1 to prevent nausea and minimize hypersensitivity reactions
    - Administer ondansetron 16mg PO prior to chemotherapy on day 1 to prevent nausea

- Administer cetirizine 10mg PO prior to chemotherapy on day 1 to minimize hypersensitivity reactions
- Administer famotidine 20mg PO prior to chemotherapy on day 1 to minimize hypersensitivity reactions
- Administer dexamethasone 8 mg PO on days 2,3, and 4 to prevent nausea

- Administer after pembrolizumab and prior to carboplatin on day 1
- For dosing utilize actual body weight and Dubois formula for body surface area
- Monitor for hypersensitivity reactions; refer to institution hypersensitivity protocol

6.1.6.4 Nab-paclitaxel Administration

- Premedications (in conjunction with carboplatin):
  - Administer aprepitant 130mg IV prior to chemotherapy on day 1 to prevent nausea
  - Administer dexamethasone 12mg PO prior to chemotherapy on day 1 to prevent nausea and minimize hypersensitivity reactions
  - Administer ondansetron 16mg PO prior to chemotherapy on day 1 to prevent nausea
  - Administer dexamethasone 8 mg PO on days 2,3, and 4 to prevent nausea
- Premedications (single agent nab-paclitaxel day 8 and 15):
  - Administer ondansetron 16mg PO prior to chemotherapy on day 8 and day 15
- Administer after pembrolizumab and prior to carboplatin on day 1
- For dosing utilize actual body weight and Dubois formula for body surface area
- Monitor for hypersensitivity reactions; refer to institution hypersensitivity protocol

6.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of Pembrolizumab with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The chemotherapy pharmacist will review all medications (concurrent use of other all other drugs, over the counter medications or alternative therapies) for interactions at the start of therapy and new medications will be reviewed if started. The study team should check a frequently updated medical reference for a list of drugs to avoid or minimize use of.

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the Pembrolizumab dose modification guidelines. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

6.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression, defined as a worsening ECOG performance status or disease-related pain or symptoms as determined by physician evaluation
- Patient non-compliance
- Pregnancy
    - All women of child-bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
    - The investigator must immediately be notified of a confirmed pregnancy in a study participant.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

6.4 Duration of Follow-Up

Survival and treatment response: Patients will be followed for at least 12 months and up to 12 months after treatment initiation or death, whichever occurs first.

Patients removed from study treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

7. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with Pembrolizumab (investigational, timing) and SOC chemotherapy (commercial agents) can be found in Section 10.

7.1 Drug Ordering and Accountability

7.1.1 *Procurement of medications:*

All of the study drugs are commercially available agents. Prescriptions for medications will be written by the treating physician, preferably the medical oncologist, using study-approved standardized Markey Cancer Center order sets. The clinical research pharmacist of the MCC-CRO will review and approve these orders per published MCC polices. Drug accountability will be maintained on a Drug Accountability Report Form (DARF).

7.2 Pembrolizumab

Consult the package insert and investigator brochure for the most current and complete information.

7.2.1 Pembrolizumab Product Dosing:

The recommended dose of KEYTRUDA in adults is either:

- 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks

or

- 400mg administered as an intravenous infusion over 30 minutes every 6 weeks

This recommended dose of Pembrolizumab is administered on the Q3 or A6 weeks schedule until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

Formulation
For injection: 50mg white to off-white lyophilized powder in a single-dose vial for reconstitution
Injection: 100 mg/4mL (25 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in single-dose vial

Reconstitution:
Add 2.3 mL of sterile water for injection, USP by injecting the water along the walls of the vial and not directly on the lyophilized powder (resulting concentration 25 mg/mL).
Slowly swirl the vial. Allow up to 5 minutes for the bubbles to clear. Do not shake the vial.

Preparation for intravenous infusion:
Visually inspect the solution for particulate matter and discoloration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.
Dilute the pembrolizumab injection (solution) or reconstituted lyophilized powder prior to intravenous administration. Withdraw the required volume from the vial(s) of pembrolizumab and transfer into an intravenous (IV) bag containing 0.9% sodium chloride injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1mg/mL to 10mg/mL.
Discard any unused portion left in the vial.

Storage:
The product does not contain a preservative.
Store the reconstituted and diluted solution from the pembrolizumab 50mg vial either:

- At room temperature for no more than 6 hours from the time of reconstitution. This includes room temperature storage of reconstituted vials, storage of the diluted solution, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of reconstitution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Store the diluted solution from the pembrolizumab 100mg/4mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration.

Discard after 6 hours at room temperature or after 24 hours under refrigeration.

Do not freeze.

Pembrolizumab Administration

Refer to the treatment section for specific administration instructions.
Administer diluted solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter.
Do not co-administer other drugs through the same infusion line.

Drug Interactions

None

Herb/Nutraceutical Interactions:

None

Pharmacokinetics

Distribution: the geometric mean value (CV%) for volume of distribution at steady state is 6L (20%).
Elimination: terminal half-life (t½) is 22 days (32%).

Excretion: Clearance: First dose 252 mL/day; steady state: 195 mL/day

7.2.2 Adverse Events for Pembrolizumab

Consult the package insert for the most current and complete information.

>10%:

Cardiovascular: Peripheral edema (11% to 15%), cardiac arrhythmia (11%)
Dermatologic: Pruritus (11% to 28%), skin rash (13% to 24%), vitiligo (13%)
Endocrine & metabolic: Hyperglycemia (19% to 59%), hyponatremia (10% to 46%), hypoalbuminemia (24% to 44%), hypertriglyceridemia (33% to 43%), hypophosphatemia (19% to 29%), hypocalcemia (15% to 27%), hyperkalemia (13% to 23%), decreased serum bicarbonate (22%), hypercalcemia (14% to 22%), hypercholesterolemia (20%), hypokalemia (15% to 20%), hypoglycemia (13% to 19%), hypothyroidism (9% to 18%), hypomagnesemia (16%), weight loss (10% to 15%)
Gastrointestinal: Diarrhea (12% to 28%), decreased appetite (15% to 25%), constipation (12% to 22%), abdominal pain (13% to 22%), nausea (11% to 22%), vomiting (11% to 19%)
Genitourinary: Hematuria (12% to 19%), urinary tract infection (12% to 19%)
Hematologic & oncologic: Lymphocytopenia (24% to 54%; grades 3/4: 1% to 25%), anemia (17% to 54%; grades 3/4: 1% to 24%), leukopenia (35%; grades 3/4: 9%), neutropenia (7% to 30%; grades 3/4: 1% to 11%), thrombocytopenia (12% to 27%; grades 3/4: 4%), increased INR (19% to 21%), hemorrhage (19%; grades 3/4: 5%), prolonged partial thromboplastin time (14%)
Hepatic: Increased serum alkaline phosphatase (17% to 42%), increased serum transaminases (27% to 34%), increased serum aspartate aminotransferase (20% to 34%), increased serum alanine aminotransferase (9% to 33%), increased liver enzymes (13%)
Immunologic: Graft versus host disease (followed by allogeneic hematopoietic stem cell transplantation: 26%)
Infection: Infection (16%)
Nervous system: Fatigue (23% to 43%), pain (22%), headache (11% to 14%)
Neuromuscular & skeletal: Musculoskeletal pain (19% to 32%), arthralgia (10% to 18%), myalgia (12%), back pain

(11% to 12%), asthenia (10% to 11%)
Renal: Increased serum creatinine (11% to 35%)
Respiratory: Upper respiratory tract infection (13% to 28%), cough (14% to 26%), dyspnea (10% to 23%), pneumonia (12%), flu-like symptoms (11%)
Miscellaneous: Fever (10% to 28%)

1% to 10%:
Cardiovascular: Facial edema (10%), pericarditis (4%), pericardial effusion (2%)
Endocrine & metabolic: Hyperthyroidism (3% to 10%), thyroiditis (≤2%)
Gastrointestinal: Dysphagia (8%), stomatitis (3% to 4%; grades 3/4: 1%), colitis (2%)
Hepatic: Hyperbilirubinemia (10%), hepatic sinusoidal obstruction syndrome (followed by allogeneic hematopoietic stem cell transplantation: 9%), ascites (grades 3/4: 8%), hepatitis (≤3%)
Immunologic: Antibody development (2%; neutralizing: <1%)
Nervous system: Peripheral neuropathy (2% to 10%), insomnia (7%), dizziness (5%), peripheral sensory neuropathy (1%)
Neuromuscular & skeletal: Neck pain (6%), arthritis (2%), myositis (≤1%)
Ophthalmic: Uveitis (≤1%)
Renal: Acute renal failure (2%)
Respiratory: Nasopharyngitis (10%), pneumonitis (2% to 8%)
Miscellaneous: Infusion related reaction (≤9%)

Frequency not defined:
Cardiovascular: Acute myocardial infarction, cardiac failure, cardiac tamponade, edema, pulmonary embolism, septic shock
Dermatologic: Cellulitis, dermatitis, erythematous rash, follicular rash, maculopapular rash
Genitourinary: Uterine hemorrhage
Hematologic & oncologic: Rectal hemorrhage
Infection: Candidiasis, *Clostridioides difficile* associated diarrhea, herpes zoster infection, sepsis
Nervous system: Confusion, polyneuropathy
Neuromuscular & skeletal: Osteomyelitis
Respiratory: Epistaxis, hemoptysis, pleural effusion, respiratory failure
Miscellaneous: Fistula, physical health deterioration

<1%, postmarketing, and/or case reports: Adrenocortical insufficiency, anaphylaxis, chronic inflammatory demyelinating polyneuropathy, diabetic ketoacidosis, encephalitis, Guillain-Barré syndrome, hemolytic anemia, hypersensitivity reaction, hypophysitis, myasthenia gravis, myelitis, myocarditis, nephritis, organ transplant rejection (solid), pancreatitis, sarcoidosis, subacute cutaneous lupus erythematosus, type 1 diabetes mellitus, vasculitis

Nursing Guidelines
Infuse through a 0.2 micron to 5 micron sterile, nonpyogenic, low-protein binding inline or add-on filter.
Do not infuse other medications through the same infusion line.
Assess laboratory values prior to drug administration, especially CBC, platelets, liver enzymes, creatinine
Administer antiemetic therapy pre- and post-treatment if indicated.
Monitor for signs and symptoms of hypersensitivity reactions during and post-infusion.

7.2.3 Immune-Related Adverse Events - Pembrolizumab

AEs associated with Pembrolizumab exposure may represent an immunologic etiology. These irAEs may occur shortly after the first dose or several months after the last dose of Pembrolizumab treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of Pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue Pembrolizumab and administer corticosteroids.

7.2.4 Management of Adverse Reactions to Pembrolizumab dose holds or discontinuation

As per guidelines established by FDA (package insert)

7.3 **Commercial Agents: Carboplatin, Pemetrexed, Paclitaxel and Nab-paclitaxel**

7.3.1 Carboplatin

Product description: Supplied as aqueous solution in multi-dose vials as 10mg/mL concentration (50mg/5mL, 150mg/15mL, 450mg/45mL, 600mg/60mL)

Solution preparation: refer to the package insert for standard preparation instructions

Route of administration:

- Infuse intravenously over 30 minutes per protocol
- When administered as a part of a combination chemotherapy regimen, sequence of administration may vary by regimen. Refer to specific protocol.

Agent Ordering: agent is commercially available

Expected Toxicities/Adverse Events:

- Myelosuppression (anemia, thrombocytopenia, neutropenia)
- Nausea/vomiting
- Hypersensitivity reactions
- Refer to the package insert for the comprehensive list of adverse events

7.3.2 Pemetrexed

Product description:

- Pemetrexed for injection, is a white-to-light yellow or green-yellow lyophilized powder supplied in single-dose vials for reconstitution for intravenous infusion.
- Supplied as single-dose vial: 100mg or 500mg

Solution preparation: refer to the package insert for standard preparation instructions

Route of administration:

- Infuse intravenously over 10 minutes per protocol.
- When administered as a part of a combination with platinum-based therapy (ie. carboplatin), administer pemetrexed prior to the platinum.
- When administered with pembrolizumab, administer after pembrolizumab if on the same day.

Agent Ordering: agent is commercially available
Expected Toxicities/Adverse Events:
- Fatigue
- Myelosuppression (anemia, neutropenia)
- Nausea/vomiting
- Rash
- Refer to the package insert for the comprehensive list of adverse events

7.3.3 Paclitaxel

Product description: Supplied as a nonaqueous solution intended for dilution in multidose vials at 6mg/mL concentration (30mg/5mL, 100mg/16.7mL, 150mg/25mL, 300mg/50mL)
Solution preparation: refer to the package insert for standard preparation instructions
Route of administration:
- Infuse intravenously over 3 hours per protocol.
- Infuse through a 0.22 micron in-line filter and polyethylene-lined (non-PVC) administration set.
- Ensure per protocol pre-medications are administered to reduce risk of infusion related reactions
- When administered as a part of a combination chemotherapy regimen, sequence of administration may vary by regimen. Refer to specific protocol.

Agent Ordering: agent is commercially available
Expected Toxicities/Adverse Events:
- Hypersensitivity reactions
- Myelosuppression (anemia, thrombocytopenia, neutropenia)
- Peripheral neuropathy
- Nausea/vomiting
- Alopecia
- Refer to the package insert for the comprehensive list of adverse events

7.3.4 Nab-paclitaxel

Product description: Supplied as a lyophilized powder in a single-use vial (100mg)
Solution preparation: refer to the package insert for standard preparation instructions
Route of administration:
- Infuse intravenously over 30 minutes per protocol
- When administered as a part of a combination chemotherapy regimen, sequence of administration may vary by regimen. Refer to specific protocol. If administered concurrently with carboplatin, administer nab-paclitaxel first, followed immediately by carboplatin.

Agent Ordering: agent is commercially available
Expected Toxicities/Adverse Events:
- Myelosuppression (anemia, thrombocytopenia, neutropenia)
- Peripheral neuropathy
- Nausea/vomiting
- Alopecia
- Hypersensitivity reactions
- Refer to the package insert for the comprehensive list of adverse events

8. DOSING DELAYS/DOSE MODIFICATIONS

Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines		
NCI CTCAE Grade	**Treatment**	**Premedication at Subsequent Dosing**
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of Pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug intervention.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Dose modifications and toxicity management guidelines for immune-related AEs associated with Pembrolizumab

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembro must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last Pembro treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	*Toxicity grade*	*Action with Pembro*	*Corticosteroid and/or other therapies*	*Monitoring and follow-up*
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Grade 4 or recurrent Grade 3	Permanently discontinue		
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyper-glycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyper-thyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypo-thyroidism	Grade 2, 3, or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Intolerable/persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e].		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

[a] AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 - 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM)

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

Other Grade 3 or 4 toxicities not outlined above. Hold all treatment until toxicities resolve to < Grade 2 and discuss with PI prior to restarting.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints and Sample Size/Accrual Rate

A single arm, phase II, single arm non-inferiority trial is proposed. The primary endpoint is disease control rate, which includes intracranial benefit defined as stable disease, partial response, and complete response at 6 months.

9.2 Sample Size and Accrual Rate

Based on prior studies we assume an 85% disease control rate in the lung for this regimen and will assume a similar rate in the brain.[22,24,43] A sample size of 45 patients achieves 90% power to detect a non-inferiority difference of -0.0500 using a one-sided Z-test with a continuity correction at 0.05 significance level.

For enrolled patients with RANO-BM-defined measurable disease: Response will be assessed by traditional RANO-BM criteria for measurable disease using gadolinium-enhanced MRI.

For enrolled patients with *nonmeasurable* disease (as noted in 3.1.2): Response will also be assessed via gadolinium-enhanced MRI, using the following definitions of response:

a. *Presence of 3 lesions that can be followed*:
   Response will be assessed as presence/absence of the identified lesions
b. *Presence of one lesion measuring ≥5mm PLUS a second lesion that can be followed*:
   Response will be assessed by:
   i. the presence/absence of the two identified lesions post-treatment
   ii. if either of the two lesions doubled in size from baseline
   iii. if either of the two identified lesions measure ≥5mm post-treatment

We expect to accrue 1-2 patients per month and thus, accrual is projected to be completed in 45 months.

9.3 Stratification Factors

None.

9.4 Interim Analysis

An initial set of 25 patients is proposed for internal funding atMCC. Interim analysis will be performed after 25 patients have been enrolled in the trial prior to proceeding to accrual of 45 patients. Specifically, Bayesian posterior probability will be calculated to assess if disease control rate is within the non-inferiority threshold of 80%. A futility rate $\leq$ 80% will be assumed and the probability for stopping for futility will be set at 80%. The beta distribution for the efficacy/success rate is utilized with a non-informative Jeffrey's prior equal to beta (0.5, 0.5). Bayesian posterior probability will be calculated after 25 patients are enrolled. The stopping bound for futility is shown in the table below (https://trialdesign.org). If at least 19 out of 25 patients exhibit disease control rate, we will proceed to accrue a total of 45 patients. We will then proceed with performing a hypothesis test of non-inferiority in disease control rate after

a total of 45 patients.

Futility Early Stopping Boundaries

Table SB1: Futility Early Stopping Boundaries

# Patients (inclusive)	# Responses (inclusive) are considered futile	Actions
25	0 - 18	Early stopping

9.5 Statistical Analysis Plan for Primary Endpoint

Disease control rate will be estimated along with 95% exact binomial confidence interval. After 45 patients have been enrolled, test for non-inferiority will be performed using the Z-test. The primary analysis will be an intent-to-treat analysis on all patients who received treatment. Evaluable patients will be defined as those receiving at least 1 cycle of treatment. Patients who are non-evaluable will not be replaced.

9.6 Statistical Analysis Plan for Secondary Endpoints

9.6.1 Overall Survival at 12-months post-enrollment

Kaplan-Meier estimates will be calculated for overall survival along with estimates of median survival time and proportion of surviving at specific time points (6 and 12 months).

9.6.2 Evaluate extracranial disease control (6-month PFS)

Kaplan-Meier estimates will be calculated for progression-free survival along with estimates of median survival time and proportion of surviving at specific time points (6 and 12 months).

9.6.3 Assess changes in Quality of Life (FACT-Cog, FACT-Brain, FACIT-Fatigue)

Quality of life (QOL) measures (FACT-Cog, FACT-Brain and FACIT-Fatigue) will be summarized at baseline and follow-up time points (every 3 months coinciding with routine clinic visits). Changes in scores will be analyzed using paired t-test as well as linear mixed models for multiple repeated measurements. Exploratory comparisons of these three QOL measures with disease control status will be performed using two-group comparison tests.

9.6.4 Evaluate changes in Neurocognitive Functioning (MoCA)

Neurocognitive functioning (MoCA) will be summarized at baseline and follow-up time points (3-, 6-, 9- and 12-months coinciding with routine clinic visits). Changes in scores will be analyzed using paired t-test as well as linear mixed models for multiple repeated measurements. Exploratory comparisons of the MoCA with disease control status will be performed using two-group comparison tests.

9.6.5 Assess changes/decrements in ECOG Performance Status and MoCA

ECOG Performance Status scores will be recorded at baseline and follow-up time points. Changes in scores will be analyzed using non-parametric test for paired data as well as linear mixed models for multiple repeated measurements. Correlations between ECOG PS scores and MoCA scores will be assessed using Pearson or Spearman's correlation. Exploratory comparisons of ECOG PS scores with disease control status will be performed using two-group comparison tests.

9.7 **Statistical Analysis Plan for Correlative Endpoint**

9.7.1 Evaluate immune-based biomarker activity (PD-1 and activation of cytotoxic T-cells)

PD-1 and several immune-based markers, such as cytotoxic T cells, will be measured and summarized descriptively. Correlations with PD-1 and between markers will be estimated using Pearson or Spearman's correlation coefficient. Exploratory association of these biological markers with DCR will be performed using two-group comparison tests. Adjustment for multiple testing due to several immune-based markers will be considered using Holm's p-value adjustment method.

9.8 **Reporting and Exclusions**

9.8.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with Pembrolizumab.

9.8.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Evaluable patients are defined as those who had at least 1 cycle of treatment. The primary analysis will be an intent-to-treat analysis on all patients who received treatment. Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. Non-evaluable patients will not be replaced.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting to Overall PI and DSMC via the OnCore **in addition** to routine reporting.

10.1 Expected Toxicities for Pembrolizumab

Per standard of care, we will follow well-established AE reporting for all chemotherapy-immunotherapy combinations. In this trial we will limit the Adverse Events reporting to include:

- Adverse Events that are clinically significant
- grade 4 and grade 5 AEs know to be associated with Pembrolizumab
- all neurologic/CNS Adverse Events

Rare but serious known potential toxicities of Pembrolizumab, <1%:

Adrenocortical insufficiency, anaphylaxis, chronic inflammatory demyelinating polyneuropathy, diabetic ketoacidosis, encephalitis, Guillain-Barré syndrome, hemolytic anemia, hypersensitivity reaction, hypophysitis, myasthenia gravis, myelitis, myocarditis, nephritis, organ transplant rejection (solid), pancreatitis, sarcoidosis, subacute cutaneous lupus erythematosus, type 1 diabetes mellitus, vasculitis

Less Common known potential toxicities of Pembrolizumab, 1% - 10%:

Cardiovascular: Facial edema (10%), pericarditis (4%), pericardial effusion (2%)
Immunologic: Antibody development (2%; neutralizing: <1%)
Nervous system: Peripheral neuropathy (2% to 10%), insomnia (7%), dizziness (5%), peripheral sensory neuropathy (1%)
Ophthalmic: Uveitis (≤1%)
Renal: Acute renal failure (2%)
Miscellaneous: Infusion related reaction (≤9%)

Common known potential toxicities of Pembrolizumab, >10%:

Cardiovascular: Peripheral edema (11% to 15%), cardiac arrhythmia (11%)
Genitourinary: Hematuria (12% to 19%), urinary tract infection (12% to 19%)
Hematologic & oncologic: Lymphocytopenia (24% to 54%; grades 3/4: 1% to 25%), anemia (17% to 54%; grades 3/4: 1% to 24%), leukopenia (35%; grades 3/4: 9%), neutropenia (7% to 30%; grades 3/4: 1% to 11%), thrombocytopenia (12% to 27%; grades 3/4: 4%), increased INR (19% to 21%), hemorrhage (19%; grades 3/4: 5%), prolonged partial thromboplastin time (14%)
Infection: Infection (16%)
Nervous system: Fatigue (23% to 43%), pain (22%), headache (11% to 14%)

Other potential toxicities/AEs of Pembrolizumab (frequency not defined):

Cardiovascular: Acute myocardial infarction, cardiac failure, cardiac tamponade, edema, pulmonary embolism, septic shock
Dermatologic: Cellulitis, dermatitis, erythematous rash, follicular rash, maculopapular rash
Genitourinary: Uterine hemorrhage
Hematologic & oncologic: Rectal hemorrhage

Infection: Candidiasis, *Clostridioides difficile* associated diarrhea, herpes zoster infection, sepsis
Nervous system: Confusion, polyneuropathy
Neuromuscular & skeletal: Osteomyelitis
Respiratory: Epistaxis, hemoptysis, pleural effusion, respiratory failure
Miscellaneous: Fistula, physical health deterioration

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All treatment areas should have access to a copy of the CTCAE version 5.0., downloaded from http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- For expedited reporting purposes only:
  - AEs for Pembrolizumab that are listed above in Section 10.1 should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section 10.3.3, under the heading, "Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions."

- Definitions of **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 MCC Expedited Adverse Event Reporting Guidelines

Investigators within MCC will report SAEs directly to the MCC DSMC per the MCC DSMC SOP and the University of Kentucky IRB reporting policy, as specified in the tables below. Use the MCC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

For MCC Investigator-Initiated Trials (IITs), investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 90 days of the last dose of Pembrolizumab on the local institutional SAE form. This applies to the following categories:

- **Grade 3 (severe) *Medical* Events** – Only events that are both Unexpected and Possibly, Probably or Definitely Related / Associated with Pembrolizumab (the Intervention).
- **ALL Grade 4 (life threatening or disabling) *Medical* Events** – Unless expected AND specifically listed in protocol as not requiring reporting.
- **ALL Grade 5 (fatal) Events** regardless of study phase or attribution.

Note: If subject is in Long Term Follow-Up, death is reported at continuing review.
Note: Abnormal laboratory values are not considered medical events, unless determined to be causative of SAE by the investigator or grade 5.

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.3.1 Required Forms and Reporting Structure for Clinical Trials

The following table outlines the required forms and reporting structure for MCC clinical trials.

Study type	Expedited reporting to MCC	Expedited reporting to External Agency	Non-expedited AE	Form	IRB
IIT by MCC investigator of commercially available agent (non-IND)	• Grade 3 – Unexpected AE **PLUS** Possibly, Probably or Definitely Related • ALL Grade 4 AEs, *Unless* AE is expected <u>AND</u> listed in the protocol as not requiring expedited reporting. • ALL Grade 5 (fatal) Events	FDA: Suspected AE that is both serious <u>and</u> Unanticipated (not listed in IDB or in the consent)	OnCore and DSMC reporting only	Voluntary Medwatch 3500 for Serious and unanticipated OnCore for all AEs, including SAEs	Per IRB regulations

10.3.2 MCC Expedited Reporting Guidelines for MCC IITs

Table 10.3.2 -- MCC Reportable AEs (expedited)

Attribution	Gr. 3 AE Expected	Gr. 3 AE Unexpected	Gr. 4 AE Expected	Gr. 4 AE Unexpected	ALL Gr. 5 AEs
Unrelated Unlikely	Not required	Not required	5 calendar days #	5 calendar days	24 hours *
Possible Probable Definite	Not required	5 calendar days	5 calendar days #	5 calendar days	24 hours *

NOTES:
If listed in protocol as expected and not requiring expedited reporting (Section 10.3.3), event does not need to be reported.
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within <u>24 business hours</u> of learning of the event.

10.3.3 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting to the Overall PI or the MCC DSMC, however, these AEs still must be reported through the routine reporting mechanism (i.e., case report form) and to the UK IRB (as outlined in IRB SOP: C2.0350).

Adverse Event	Grade	Attribution
Alopecia	All	All causes
Laboratory abnormalities	1-2	Deemed not clinically significant by the treating MD
Rash	1-2	Deemed not clinically significant by the treating MD
Diarrhea	1-2	Deemed not clinically significant by the treating MD
All other AEs	1-2	Deemed not clinically significant by the treating MD

10.4 **Expedited Reporting to External Agencies**

Overall PI will comply with the policies of all external funding agencies, FDA and the UK IRB regarding expedited reporting, as per the UK IRB's Mandated Reporting to External Agencies SOP C4.0150.

10.5 **Expedited Reporting to Hospital Risk Management**

Participating investigators will report to the UK Office of Risk Management any participant safety reports or sentinel events that require reporting according to institutional policy.

10.6 **Routine Adverse Event Reporting**

All Adverse Events **must** be reported in routine study data submissions with the exception of those listed in Section 10.3.3. **AEs reported expeditiously to the Overall PI and DSMC via OnCore must also be reported in routine study data submissions.**

10.7 **Pregnancy**

Pregnancy is considered an unanticipated events and pregnancy as well as its outcome must be documented and reported to overall PI and DSMC and Office of Research Integrity, as well the FDA and sponsor in according to reporting requirements. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old.

10.8 **Secondary Malignancy**

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

All secondary malignancies that occur following treatment with an agent under an NCI IND/IDE must be reported to overall PI and DSMC and Office of Research Integrity, as well the FDA and sponsor in according to reporting requirements. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.9 **Second Malignancy**

A *second* malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

11. STUDY CALENDAR

	Pre-enrollment	Planned Treatment with Carboplatin + pemetrexed + pembrolizumab; or carboplatin + paclitaxel (or nab-paclitaxel) + pembrolizumab; *4 cycles of treatment Q3 weeks* or pembrolizumab alone. *2 cycles of treatment Q6 weeks**		Maintenance Phase with pemetrexed + pembrolizumab; *Treatment Q3 weeks* * *(if benefit, up to 13 additional cycles)* or pembrolizumab alone ***Treatment Q6 week****	Post-Treatment Follow-Up		Off - Treatment	Off - Study
Assessment:	**Screening**	**Cycle 1**	**Cycles 2 - 4**	**Cycles 5 & above** *(up to 13 cycles)*	**120-Day Follow-Up**	**1-year Follow-Up**		
Visit Windows	Day -30 to -1	**(± 3 days)**	**(± 3 days)**	***(± 7 days*)**	**(+14 days)**	**(+14 days)**		
Informed Consent	X							
Demographics, Medical History	≤ 28 days							
Interval History	-----	Day 1 of every cycle (C1 – C8)						
Physical Exam	≤ 14 days	X / Day 1 of every cycle			X	X		
Weight	≤ 28 days	X / Day 1 of every cycle			X	X		
Height		X						
ECOG PS	≤ 14 days	X / Day 1 of every cycle			X	X		
MOCA	≤ 28 days	X/ pre-treatment, and at 1-mos, 3-mos, 6-mos, 9-mos and 12-mos.						
QOL	≤ 28 days	X / FACT-Cog, FACT-Brain Cancer and FACIT-Fatigue quality of life (QOL) measures every 3-months (same window at MOCA) through 12-mos.						
Vital Signs	≤ 14 days	X	Day 1 of every cycle		X	X		
12-lead ECG	≤ 12 weeks	As clinically indicated						
CBC w/ diff, Platelets, CMP	≤ 14 days	X / Day 1 of every cycle			X	X		
Pregnancy test**	≤ 28 days	X						
TSH test	≤ 14 days	X	Q6 weeks at clinic visit					
Body Imaging: **CT/PET scan**	Within 4-8 weeks of treatment initiation	CT of the chest, abdomen and pelvis or CT of the chest with MRI of the abdomen and pelvis or SOC radiographs will be performed in all subjects at screening or within 28-56 days of starting therapy. Then every 6-12 weeks after initiation of treatment as per SOC. Tumor imaging will continue until either 12-months post-treatment initiation OR until radiographic disease progression per RECIST 1.1 as determined by the investigator. PR or CR per RECIST 1.1 at a given time point must be confirmed by repeat assessments ≥ 4 weeks after the criteria for response are first met.						
Brain Imaging: **MRI *****	Within 2 weeks of treatment initiation	Initial MRI within 2 weeks of starting therapy; and then following 2 cycles, can then be done every 6 to 12 weeks. Tumor imaging will continue until either 12-months post-treatment initiation OR until radiographic disease progression per RANO-BM (and UK MOD that has been modified) as determined by the investigator. PR or CR per RANO-BM (and UK MOD to RANO-BM criteria) at a given timepoint must be confirmed with repeat scan ≥ 4 weeks after the criteria for response are first met.						
Correlative Blood Draws (2x Whole Blood Tube w/ Anticoagulant, ACD Sol A 8.5 cc Yellow top—BD product #364606)	Within 1 week prior to treatment	X / 15 mL blood in Whole blood tube w/ Anticoagulant, BD Vacutainer™ CPT™ Tube with Sodium Citrate. 4 collection timepoints for each participant: Initial collection within one week prior to treatment (or on the day of treatment); and three additional collections every six weeks ±2 weeks after initiation of treatment (e.g., at 6-weeks, 12-weeks, and 18-weeks post treatment initiation).						

Tumor biopsy	X, *if available*							
Con Meds	X							
Adverse Events	≤ 28 days	X	X	X	X	X		
Pembrolizumab + chemotherapy (IV infusion) ****		X*	X*	* *Could continue*				
Tumor Assessment to determine PFS and OS		Imaging/scans will be assessed per RECIST and iRECIST and the results (PR, CR, etc.) will be noted in the eCRF to support interim analysis (initial 25 patients) and the final analysis if the trial is not stopped early for futility.						
Survival Status		Interim analysis will be conducted after the first 25 patients are enrolled and will be followed for an event (disease progression, death). Patients will be followed Until death or until 1-year post-treatment initiation. NOTE: PFS at 6-months is study objective 1.2.2.						
Note reason for early discontin-uation of treatment (or the reason for removal from study participation)							X	X
	Screening	**Cycle 1**	**Cycles 2 - 4**	***Cycles 5 & above (up to 13 cycles)***	**120-Day Post-TX Follow-Up**	**1-year Post-TX Follow-Up**	**Off - Treatment**	**Off - Study**

NOTES for the STUDY CALENDAR:
D= day; H&P= history and physical; ECOG PS= Performance Status; ECG= electrocardiogram; TSH= thyroid stimulating hormone test; CBC= complete blood count w/ differential, CMP=comprehensive metabolic panel; CT= Computerized Tomography, PET= Positron Emission Tomography, MRI= Magnetic Resonance Imaging; RANO-BM= response criteria for brain metastases, PR=Partial Response, CR=Complete Response; mL=milliliter; Con Meds= concurrent medications; IV= intravenous; PFS=progression-free survival, OS=overall survival.

* Pembrolizumab Q6week can be considered as per treating physician.

** Only in woman of reproductive potential. Women with amenorrhea for <2 years and who have not had a hysterectomy and oophorectomy will only be considered not to be of reproductive potential if they have a documented FSH value in the postmenopausal range.

*** All effort to be done to obtain MRI. However, if not possible due to baseline reasons (e.g. Claustrophobia, contrast intolerance), may obtain CT head with and without contrast.

**** Standard of care chemo-immunotherapy regimens.

12. MEASUREMENT OF EFFECT

Evaluable for Adverse Events. All patients will be evaluable for adverse event evaluation from the time of their first treatment.

Evaluable for Response. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of Cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

Patients with measurable disease will be assessed by iRECIST (for systemic) and RANO-BM criteria (for brain) that has been modified for our study: RANO-BM UK MOD.[44,45]
Patients with nonmeasurable disease by traditional RANO-BM enrolled on-study will be assessed by RANO-BM UK MOD. [44,45]

12.1 Antitumor Effect (CNS/brain): RANO-BM Criteria

Only those participants who have measurable CNS disease present at baseline (per the UK Modified RANO-BM criteria), have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable). Definitions of CNS treatment response and progression are based on RANO-BM criteria that has been modified (RANO-BM UK MOD) as specified below.

12.1.1 Disease Parameters for Intracranial Disease Response

Measurable disease
RANO-BM has measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with MRI. **However**, asymptomatic lesions identified on screening are often smaller in size. A lesion of ≥5 mm will be considered as our RANO-BM UK MOD for this trial. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
For multifocal intracranial disease, no more than 5 target measurable lesions (each >=5mm in diameter) should be selected for measurement. Target lesions should be selected on the basis of their size (lesions with longest diameter), be representative of other lesions and lend themselves to reproducible repeated measurements.

Non-measurable disease
Masses with margins not clearly defined, lesions with maximal diameter < 0.5cm, dural metastases, bony skull metastases, cystic-only lesions.

Target lesions
All measurable lesions up to a maximum of 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), and in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameter for all target lesions will be calculated and reported as the baseline sum diameters.

Non-target lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods of Evaluation of Disease

All measurements of the imaging-based evaluation should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Gadolinium-enhanced MRI is strongly encouraged as the default standard imaging technique, although CT with and without contrast could be considered in specific circumstances (e.g., severe claustrophobia, intolerance to contrast).

12.1.2 Response Criteria in Intracranial Disease

Complete Response (CR): Requires all of the following

- complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks
- no new lesions
- stable or decreasing corticosteroids (the steroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan)
- stable or improved clinically

Partial Response (PR): All of the following criteria must be met:

- Greater than or equal to 30% decrease in the sum longest diameter of CNS target lesions compared to baseline sum of target lesions sustained for at least 4 weeks. In the absence of a confirming scan 4 weeks later, this scan will be considered only stable disease.
- no progression of non-measurable disease.
- no new lesions
- stable or reduced corticosteroid dose (the steroid dose at the time of the scan
- evaluation should be no greater than the dose at time of baseline scan)
- stable or improved clinically

Progressive Disease (PD): At least one of the following must be true:

- At least 20% increase in the sum of longest diameter of target lesions using the same techniques as baseline, taking as reference the smallest sum on study (this includes baseline if that is the smallest sum), ***however*** if lesion initially at baseline is 5-9 mm in diameter, an increase by at least 5 mm in diameter is required.
- clear worsening of any non-measurable disease*
- appearance of any new enhancing lesion/site
- clear clinical worsening (unless clearly unrelated to this cancer, e.g. seizures, medication side effects, complications of therapy, cerebrovascular events, infection)
- failure to return for evaluation due to death or deteriorating condition

*Progression of non-measurable CNS lesions is defined as follows:

- a lesion initially at baseline </=5mm in diameter that increases to >/= 10mm in diameter

Stable Disease (SD): All of the following criteria must be met:

- Does not qualify for CR, PR or progression
- All measurable and non-measurable sites must be assessed using the same techniques as baseline
- Stable clinically

Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. If a response recorded at one scheduled MRI does not persist at the next regular scheduled MRI, the response will still be recorded based on the prior scan, but will be designated as a non-sustained response. If the response is sustained, i.e. still present on the subsequent MRI at least four weeks later, it will be recorded as a sustained response, lasting until the time of tumor progression.

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

12.2 **Antitumor Effect (systemic) – Immune-Related RECIST Criteria (iRECIST)**

12.2.1 Definitions

Response and progression will be evaluated in this study using the 'immune'-Revised International Criteria (iRECIST) which is based on RECIST version 1.1 proposed by the RECIST committee.[46] Investigators should note the different requirements for confirmatory scans as well as follow up for the iRECIST criteria.

12.2.2 iRECIST Response and Evaluation Endpoints

Measurable Disease. Measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm with chest X-ray and as ≥10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). Malignant lymph nodes must be ≥15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

Non-Measurable Disease. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

Target Lesions. When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

Non-Target Lesions. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent."

12.2.3 Response Criteria

All patients will have their best response from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): Disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures <10 mm (Note: continue to record the measurement even if <10 mm and considered CR). Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases before CR can be accepted. Confirmation of response is only required in non-randomized studies.

Partial Response (PR): At least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is only required in non-randomized studies.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional

circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Integration of target, non-target, and new lesions into response assessment

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response For This Category Also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes <10 mm
CR	Non-CR/non-PD	No	PR	Normalization of tumor markers, tumor nodes <10 mm
CR	Not all evaluated	No	PR	
PR	Non-PD/not all evaluated	No	PR	
SD	Non-PD/not all evaluated	No	SD	Documented at least once ≥4 weeks from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumor markers, tumor nodes <10 mm
No Target	Non-CR/non-PD	No	Non-CR/ non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes*	PD	
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment. *Investigators should record all new lesions separately. If the new lesion is felt to be equivocal, treatment may be continued pending further assessments.				

12.2.4 iRECIST Response Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

Confirming progression: iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks, after iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumor burden (from iUPD) where definitions of progression had been met (from nadir) in target, non-target disease, or new lesions.
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum.
    - Continued unequivocal progression in non-target disease with an increase in tumor burden.
    - Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- iRECIST criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR, or iCR if those criteria are met compared to baseline). The prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

New lesions:

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis [or 15 mm in short axis for nodal lesions]), and recorded as New Lesions - Target (NLT) and New Lesion - Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Time-point (TP) iResponse

Target Lesions*	**Non-Target Lesions***	**New Lesions***	**Time Point Response**	
			No prior iUPD**	**Prior iUPD**, *****
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD.
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD).
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in SOM of at least 5 mm, otherwise remains iUPD.
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • previously identified T lesion iUPD SOM ≥5 mm and/or • NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • previously identified T lesion iUPD ≥5 mm and/or • previously identified NT lesion iUPD (need not be unequivocal) and/or

Time-point (TP) iResponse

Target Lesions*	**Non-Target Lesions***	**New Lesions***	**Time Point Response**	
			No prior iUPD**	**Prior iUPD**, *****
				• size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on increase in size or number of new lesions previously identified.
* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR, and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.				

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

iRECIST best overall response (iBOR)

TPR 1	TPR 2	TPR 3	TPR 4	TPR 5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

Table assumes a randomized study where confirmation of CR or PR is not required.

- NE = not evaluable that cycle.
- Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.
- For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

12.2.5 Response and Stable Disease Duration (iRECIST)

Response duration will be measured from the time measurement criteria for iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or PD is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

12.2.6 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (*e.g.*, 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (in this trial, this only applies to non-CNS metastases from lung cancer). For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter

for the "merged lesion."

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.*, for body scans). Other specialized imaging or other techniques may also be appropriate for individual case. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (*e.g.*, with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or SD and PD.

12.3 **Other Response Parameters – Quality of Life and Neurocognitive Functioning**

The trial will assess quality of life and cognition as an important secondary endpoint.

12.3.1 Quality of Life

Patient-reported outcomes will be assessed through use of the Functional Assessment of Cancer Therapy-Brain (FACT-Br) and the FACIT Fatigue Scale (FACIT-F) questionnaires. Assessments will be conducted every 3 months during interim visits.

The FACT-Br is a commonly used instrument measuring general quality of life (QOL) that reflects symptoms or problems associated with brain malignancies across 5 subscales.[47] The measure yields information about total QOL, as well as information about the dimensions of physical well-being, social/family well-being, emotional well-being, functional well-being, and disease-specific concerns. The FACT-Br is written at the 4th grade reading level, and subjects can complete it in 5-10 minutes. FACT-Br questionnaire is found in **Appendix E**.

The FACIT Fatigue Scale (FACIT-F) is a short, 13-item, easy to administer tool that measures an individual's level of fatigue during their usual daily activities over the past week.[48] The level of fatigue is measured on a four-point Likert scale (4 = not at all fatigued to 0 = very much fatigued). Subjects can complete the questionnaire in 2-3 minutes. FACIT-Fatigue scale is found in **Appendix F**.

12.3.2 Patient-Reported Cognitive Functioning

The Functional Assessment of Cancer Therapy-Cognitive (FACT-Cog) questionnaire was developed to assess perceived cognitive function and impact on quality of life (QOL) in cancer patients. FACT-Cog has been widely administered across clinical settings and validated across different cultures and languages. Subjects can complete it in 5 minutes. FACT-Cog questionnaire and scoring is found in **Appendix G**.

12.3.3 Screener for Mild Cognitive Impairment – MoCA

In an effort to screen for significant cognitive decline and potential differences in the study population, a screening test of cognitive functioning will be employed, the Montreal Cognitive Assessment (MoCA). The MoCA is a ten-minute cognitive test validated in >50 languages (including English, French, and Spanish). The MoCA will be administered to study participants every 3 months during routine clinic visits. The MoCA screener and instructions and scores are found in **Appendix H**.

The MoCA is comprised of 15 items assessing multiple cognitive domains:

DOMAIN	**Task**	**Possible total points per item**
Delayed Recall	Memory & 5-min recall	5 points
Visuospatial / Executive	Visuoconstructional - clock drawing	3 points
	Visuoconstructional - Cube copy task	1 point
	Alternative Trail making- part B	1 point
Naming	Phonemic fluency	3 points
Attention	Target detection – letter A	1 point
	Serial 7s (subtraction)	3 points
	Digits forward	1 point
	Digits backward	1 point
Language	Sentence repetition	2 points
	Semantic fluency – F words in one minute	1 point
Abstraction	Similarities	2 points
Orientation	Date, month, year, day, place & city	6 points

The MoCA is scored to obtain an item total, scores can range from 0 to 30. One point is added for individuals who have 12 years or less of formal education (the number of years of education must actually be counted starting after kindergarten such that kindergarten is not included in the count). The total possible score is a maximum of 30 points.

The MoCA has been found to be more sensitive than the Mini Mental State Examination (MMSE) in detecting mild cognitive impairment.[49] In a prospective study, the MoCA exhibited excellent sensitivity (96%) and specificity (95%) when a cutoff score of 23 or below was utilized to define cognitive impairment.[50] The MoCA has been prospectively evaluated in patients with brain metastases and found to be predictive of survival.[51,52] The MoCA has also been prospectively evaluated in patients with resected brain metastases and greater than 90% of patients did not find the MoCA a burden.[53]

12.4 **CORRELATIVE STUDIES**

Identify the immunologic response profile with clinical response
Fluorescence-activated cell sorting (FACS) sorting to assess activated PD-1 positive immune T-cell subsets prior and during therapy with pembrolizumab and combination of chemotherapy and pembrolizumab.

Goal
Identify the immunologic response profile with clinical response and mechanism of action of checkpoint blockade therapy in the CNS.

Burden to Subject
Minimal, extra 8.5 ml blood within seven days prior to treatment and every six weeks for three additional collection.

Overview
This exploratory study assesses the T-cell subsets and monitors PD-1 expression along with activation and will correlate with therapy. Multiplex immunofluorescence will be used to evaluate spatial relationships between immunologic factors in the tumor microenvironment. The study is based on peripheral blood to assess immune activation. The following steps for processing and cryopreservation of blood samples listed below are to be performed in Flow Cytometry and Immune Monitoring (FCIM) SRF. FCIM provides flow cytometric analysis and cell sorting as well as human immune monitoring services. These services include blood processing and cryopreservation of PBMC. All samples cryopreserved by FCIM are then banked and managed by Bio Specimen and Tissue Procurement (BSTP) SRF until all samples for a subject have been collected. Once all samples are collected, all stored samples for a subject will be thawed and analyzed simultaneously by FCIM to obtain correlative endpoints as described above. Data analysis will be performed by Dr. Cohen with members of his laboratory along with review and discussion of data with Drs. Subbarao Bondada, Val Adams, and John L. Villano.

Correlative endpoints
The correlative studies are based on peripheral blood to assess immune activation. The following steps for processing and cryopreservation of blood samples listed below are to be performed in Flow Cytometry and Immune Monitoring (FCIM) SRF. FCIM provides flow cytometric analysis and cell sorting as well as human immune monitoring services. These services include blood processing and cryopreservation of PBMC. All samples cryopreserved by FCIM are then banked and managed by Biospecimen and Tissue Procurement (BSTP) SRF until all samples for a subject have been collected. Once all samples are collected, all stored samples for a subject will be thawed and analyzed simultaneously by FCIM to obtain correlative endpoints as described below. Data analysis will be performed by Dr. Don Cohen with members of his FCIM laboratory along with review and discussion of data with Drs. Subbarao Bondada, Val Adams, and John L. Villano. Our investigation will have the following correlative endpoints.

Percentage of PD-1+ CD4+ T (helper) cells and PD-1+ CD8+ T (cytotoxic) cells prior to treatment versus with concurrent treatment: PD-1 can effectively inhibit functioning and proliferation of T-cells, reduce secretion of IL-2, IL-10 and IFN-γ cytokines that can enhance effector T-cell function. An increase in the percentage of both PD-1+ CD4+ T and PD-1+ CD8+ T-cells is found in many advanced disease states (e.g., sepsis).

Percentage of CD8+ T-cells that are gamma-interferon positive during treatment. A significant change, an increase of 50% or more, may demonstrate an improved anti-tumor response.

PD-L1+ CD4+ and PD-L1+ CD8+ T-cell expression differences during treatment. PD-L1+ T-cells have been correlated with response to anti-PD-1 therapy and evaluation of this during concurrent treatment may provide more robust data. CD 3+ cells will also be analyzed in an exploratory manner.

13. STUDY APPROVAL, OVERSIGHTAND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0 (Adverse Events: List and Reporting Requirements).

13.1 Protocol Review and Monitoring Committee and Institutional Review Board Review

Before implementing this study, the protocol must be reviewed by the Markey Cancer Center's Protocol Review and Monitoring Committee and the protocol, the proposed informed consent form and other information to subjects, must be reviewed by the University of Kentucky Institutional Review Board (IRB). A signed and dated UK IRB initial review approval memo must be maintained in the Markey Cancer Center Clinical Research Office (MCC CRO) regulatory binder. Any amendments to the protocol, other than administrative ones, must be reviewed and approved by the PRMC, study sponsor and the UK IRB.

13.2 Quality Assurance

The MCC places the highest priority on ensuring the safety of subjects participating in clinical trials and on the quality of data obtained from clinical and translation research. The MCC Quality Assurance (QA) Office oversees the maintenance of quality standards in clinical cancer research through clinical data monitoring of Investigator Initiated Trials (IITs) and routine audits.

13.2.1 Data Monitoring

The MCC QA Office will collaborate with the PI, Biostatisticians and Lead OnCore® Data Management Specialist in creating a Clinical Data Monitoring Plan (CDMP) using a risk based approach. The CDMP will describe the scope, communication plan, and frequency of monitoring visits. In addition, describe query submissions and resolutions, action items and monitoring reports.

The QA monitor assigned to the trial will perform the monitoring tasks in accordance with the protocol specified CDMP. The monitoring process will provide research staff and PI with the opportunity to evaluate the progress of the study, verify the accuracy and completeness of the case report forms, assure that all protocol requirements, including applicable regulations and investigator's obligations are being fulfilled, and prompt resolution of any inconsistencies in the study records.

13.2.2 Audit

To ensure compliance with Good Clinical Practices and all applicable regulatory requirements, the MCC Audit Committee will conduct a quality assurance audit. A minimum of 10% of patients enrolled in the study may be selected for review. The purpose of a MCC audit is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements.

13.3 **Data and Safety Monitoring Committee**

The MCC Data and Safety Monitoring Committee (DSMC) will oversee the conduct of this trial. The MCC DSMC performs routine real-time data monitoring and safety review of all trials, with a special focus upon investigator-initiated trials (IITs). The MCC DSMC will conduct review of the trial on a schedule determined the MCC Protocol Review & Monitoring Committee (PRMC). The MCC DSMC will monitor the following elements of the trial: adverse event analysis, serious adverse events, protocol deviations/violations, and accrual. In addition, when applicable will review QA audits and monitoring reports, previous reviews by the DSMC, suggested actions by other committees, such as the IRB, UK Risk Management Committee, and other parameters and outcomes as determined by the DSMC. If appropriate, the DSMC will designate and monitor corrective action(s) based on review outcome. The MCC DSMC has the authority to amend, temporarily suspend, or terminate the trial based upon patient safety or compliance matters.

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0 (Adverse Events: List and Reporting Requirements).

13.4 **Data Reporting**

13.4.1 Method

This study will require data submission and reporting via the OnCore Enterprise Research Clinical Trials Management System, which is the official database of the Markey Cancer Center. Instructions for submitting data is listed in study-specific guidance documents authored by a member of the MCC Data Management Team. These guidance documents may include any of the following, as appropriate for the scope of the study: eCRF Completion Guidelines, Data Management Specifications, Subject Console Guide, and Query Resolution Guide. These guidance documents will be approved and housed within OnCore to ensure access to approved versions to facilitate data submission.

13.4.2 Responsibility for Data Submission

This trial will be monitored by the MCC Data and Safety Monitoring Committee (DSMC) on a schedule determined by the Protocol Review and Monitoring Committee at the initial PRMC review. Study staff are responsible for submitting study data and/or data forms to OnCore as per the Markey Cancer Center SOPs. Study staff are responsible for compiling and submitting data for all participants and for providing the data to the Principal Investigator for review.

13.5 **Data Management**

Data management will be performed by cross-team members at MCC. These team members will include representatives from the Data Management Team, Biostatistics and Bioinformatics SRF, and the Quality Assurance Office. They will work closely with study staff to ensure timely and accurate data submission. A protocol specific Data Management Plan (DMP) will be authored by a senior data manager in collaboration with the biostatistician and Principal Investigator with each expected to review and approve the finalization of the DMP. In order to maintain best clinical practices in data management, the DMP may include, but not be limited to CRF/eCRF design, database build and design, database training, edit check/validation specifications, study database testing/release, data and paper workflow, report, metrics, query/discrepancy management, management of external (including lab) data, medical coding, SAE handling/reconciliation, data transfers and database lock. The protocol specific DMP will additionally define the schedule at which data will be accessed by data management and study statistician to perform statistical programming for conduct of data quality, data control, data management, generation of interim reports and statistical analysis. Cross-team members will collaborate to establish procedures and timelines for quality control, audits, query resolution, annual reports, interim analysis and final data analysis.

13.6 **Compliance with Laws and Regulations**

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, any applicable local health authority, and Institutional Review Board (IRB) requirements. The PI or designee will be responsible for obtaining continuing and not less than annual IRB re-approval throughout the duration of the study. Copies of the Investigator's annual report to the IRB and copies of the IRB continuance of approval must maintained by the MCC CRO. The PI or designee is also responsible for notifying the Data and Safety Monitoring Committee of the MCCC and the UK IRB of any significant adverse events that are serious and/or unexpected, as per SOP's of those entities. DSMC will review all adverse events of this IIT as per its SOP.

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APPENDIX A. PERFORMANCE STATUS CRITERIA

ECOG/WHO Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B. FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

Formulas to estimate renal function using serum creatinine.

Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg\ /\ dL)} \{\times 0.85\ for\ female\ patients\}$$

Followed by conversion to a value normalized to 1.73 m^2 with the patient's body surface area (BSA).

Cockcroft, D.W. and M.H. Gault. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*. 16:31-41.

APPENDIX C. CONTRACEPTION GUIDANCE AND PREGNANCY TESTING

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP:

- *Premenarchal*
- *Premenopausal female with 1 of the following:*
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- *Postmenopausal female*
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method as described in Table below when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
  - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use one of the contraception methods described in Table below consistently and correctly during the protocol-defined time frame.

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test. Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Acceptable Contraceptive Methods *Failure rate of >1% per year when used consistently and correctly.*
● Male or female condom with or without spermicide ● Cervical cap, diaphragm or sponge with spermicide
Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progestogen- containing) hormonal contraception [b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progestogen- only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomized partner** A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e. when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 30 days [corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment . c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

APPENDIX D. LAB MANUAL FOR PROCESSING CORRELATIVES

Isolation of Mononuclear Cells from Peripheral Blood

a. The FCIM group will perform the following steps to process for cryopreservation.
   - CPT blood tubes will be centrifuged at 400 x g for 30 minutes at room temperature
   - Aspirate buffy coat at interface, resuspend in sterile saline and wash by centrifugation. Repeat wash procedure twice.
   - Resuspend pellet containing PBMCs in ice cold 100% fetal calf serum (FCS)
   - Determine cell concentration and viability
   - Store on ice for cryopreservation by FCIM

NOTE: PBMCs from all blood collections from each patient will be cryopreserved by FCIM and banked by BSTP SRF until all blood collections are completed. Flow cytometric analysis by FCIM will be performed in bulk on all collected samples per patient.

   - Following determination of cell number and viability, PBMCs in FCS will be adjusted to a concentration of 2 x 10^6 viable cells/ml.
   - 2 x 10^6 viable cells will be added to cryopreservation vials containing DMSO to obtain a final concentration of 10% DMSO.
   - Vials will be transferred to cryopreservation containers for slow freezing in a -80°C freezer.
   - Following overnight freezing, vials will be transferred to liquid nitrogen freezers maintained by BSTP for banking until all patient blood samples are collected.

b. Activation of Peripheral Blood Mononuclear Cell (PBMC) for Intracellular IFNγ detection (performed by FCIM SRF).
   - Culture 2 x 10^6 freshly thawed PBMC will be incubated for 5 hours in 37°C incubator in complete RPMI medium containing PMA (50ng/ml) and Ionomycin (1ug/mL), plus Brefeldin A to activate cells
   - Cells will then be washed by centrifugation and then stained as follows for flow cytometry analysis:
     - Suspend cells in FACS buffer (PBS, 1% BSA, sodium azide [0.01%]) at a concentration of 10^7 cells per ml
     - Add Fc Block to all tubes and incubate for 10 minutes on ice
     - Add all of the indicated fluorochome-labelled antibodies for surface membrane staining
       - CD4 FITC/CD8 PE/CD3 PerCP
       - PE-Cy7 Mouse anti-Human CD279 (PD-1)
     - Incubate on ice in the dark for 30 minutes
     - Wash cells twice with PBS+Azide to remove excess antibody
     - Fix and permeabilize cells (paraformaldehyde/saponin)
     - Stain cells for intracellular IFNγ with fluorochrome-labeled anti-human IFNγ antibody
     - Wash cells by centrifugation and resuspend in FACS buffer for flow cytometry analysis

c. Flow cytometric analysis (performed by FCIM SRF).
- Set the flow cytometer on the following gates
  - Live cell gate
  - Lymphocyte gate
- Set the following fluorescent gates on the live lymphocyte population
  - CD3+, CD4+ to identify helper T-cells
  - CD3+, CD8+ to identify cytotoxic T-cells
- Analyze both the helper T-cell and cytotoxic T-cell subpopulations for the following
  - Surface expression levels of PD-1
  - Intracellular expression levels of IFNγ

d. Analysis and storage of flow cytometric data (performed by FCIM SRF).
- flow cytometric data will be analyzed using FlowJo analytical software to determine the percentage of T cell subsets ($CD4^+$ and $CD8^+$) which express PD-1 and/or IFNγ
- Calculated results for each patient and blood collection will be recorded in an Excel spreadsheet. Note: patients will be identified only with the unique code assigned for each patient.
- Spreadsheet containing all results will be stored in a private folder on Dr. Cohen's UK server site, which UK backs up daily.
- Raw flow cytometry data and spreadsheet containing calculated results will also be submitted to the OnCore Database, the official database of the MCC CRO, as required.
- Only the following individuals will have access to the results in the private folder of Dr. Cohen: Dr. Villano, Dr. Bondada, biostatistician assigned to the study.

APPENDIX E. BRAIN CANCER (FACT-BR) QUESTIONNAIRE

Questionnaire, instructions and scoring are found on the following pages.

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.* ☐					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quitea bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
Br1	I am able to concentrate	0	1	2	3	4
Br2	I have had seizures (convulsions)	0	1	2	3	4
Br3	I can remember new things	0	1	2	3	4
Br4	I get frustrated that I cannot do things I used to	0	1	2	3	4
Br5	I am afraid of having a seizure (convulsion)	0	1	2	3	4
Br6	I have trouble with my eyesight	0	1	2	3	4
Br7	I feel independent	0	1	2	3	4
NTX6	I have trouble hearing	0	1	2	3	4
Br8	I am able to find the right word(s) to say what I mean	0	1	2	3	4
Br9	I have difficulty expressing my thoughts	0	1	2	3	4
Br10	I am bothered by a change in my personality	0	1	2	3	4
Br11	I am able to make decisions and take responsibility	0	1	2	3	4
Br12	I am bothered by the drop in my contribution to the family	0	1	2	3	4
Br13	I am able to put my thoughts together	0	1	2	3	4
Br14	I need help in caring for myself (bathing, dressing, eating, etc.)	0	1	2	3	4
Br15	I am able to put my thoughts into action	0	1	2	3	4
Br16	I am able to read like I used to	0	1	2	3	4
Br17	I am able to write like I used to	0	1	2	3	4
Br18	I am able to drive a vehicle (my car, truck, etc.)	0	1	2	3	4
Br19	I have trouble feeling sensations in my arms, hands, or legs	0	1	2	3	4
Br20	I have weakness in my arms or legs	0	1	2	3	4
Br21	I have trouble with coordination	0	1	2	3	4
An10	I get headaches	0	1	2	3	4

FACT-Br Scoring Guidelines (Version 4) – Page 1

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (TOI, FACT-G & FACT-Br).
5. **The higher the score, the better the QOL.**

Subscale	**Item Code**	**Reverse item?**	**Item response**		**Item Score**
PHYSICAL	GP1	4	-	_____	=_____
WELL-BEING	GP2	4	-	_____	=_____
(PWB)	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**PWB subscale score**

SOCIAL/FAMILY	GS1	0	+	_____	=_____
WELL-BEING	GS2	0	+	_____	=_____
(SWB)	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**SWB subscale score**

EMOTIONAL	GE1	4	-	_____	=_____
WELL-BEING	GE2	0	+	_____	=_____
(EWB)	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 6: _____
Divide by number of items answered: _____=**EWB subscale score**

FUNCTIONAL WELL-BEING (FWB)	GF1	0	+	_____	=_____
	GF2	0	+	_____	=_____
	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**FWB subscale score**

FACT-Br Scoring Guidelines (Version 4) – Page 2

Subscale	**Item Code**	**Reverse item?**	**Item response**	**Item Score**		
BRAIN	Br1		0	+	_____	
=_____						
CANCER	Br2	4	-	_____		=_____
SUBSCALE	Br3	0	+	_____		=_____
(BrCS)	Br4		4	-	_____	
=_____						
	Br5	4	-	_____		=_____
Score range: 0-92	Br6	4	-	_____		=_____
	Br7	0	+	_____		=_____
	Ntx6	4	-	_____		=_____
	Br8	0	+	_____		=_____
	Br9	4	-	_____		=_____
	Br10	4	-	_____		=_____
	Br11	0	+	_____		=_____
	Br12	4	-	_____		=_____
	Br13	0	+	_____		=_____
	Br14	4	-	_____		=_____
	Br15	0	+	_____		=_____
	Br16	0	+	_____		=_____
	Br17	0	+	_____		=_____
	Br18	0	+	_____		=_____
	Br19		4	-	_____	
=_____						
	Br20		4	-	_____	
=_____						
	Br21		4	-	_____	
=_____						
	An10	4	-	_____		=_____

Sum individual item scores:_____
Multiply by 23 : _____
Divide by number of items answered: _____=**BrC Subscale score**

To derive a FACT-Br Trial Outcome Index (TOI):
Score range: 0-148

_____ + _____ + _____ =_____=**FACT-Br TOI**
(**PWB** score) (**FWB** score) (**BrCS** score)

To Derive a FACT-G total score:
Score range: 0-108

_____ + _____ + _____ + _____=_____=**FACT-G Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To Derive a FACT-Br total score:
Score range: 0-200

_____ + _____ + _____ + _____ + _____ =_____=**FACT-Br Total score**
(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**BrCS** score)

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org

APPENDIX F. FATIGUE (FACIT-FATIGUE, V4) QUESTIONNAIRE

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some -what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

FACIT-Fatigue Subscale Scoring Guidelines (Version 4) – Page 1

Instructions: * 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. **The higher the score, the better the QOL.**

Subscale	**Item Code**	**Reverse item?**	**Item response**	**Item Score**	
FATIGUE	HI7	4	-	_____	=_____
SUBSCALE	HI12	4	-	_____	=_____
	An1	4	-	_____	=_____
	An2	4	-	_____	=_____
Score range: 0-52	An3	4	-	_____	=_____
	An4	4	-	_____	=_____
	An5	0	+	_____	=_____
	An7	0	+	_____	=_____
	An8	4	-	_____	=_____
	An12	4	-	_____	=_____
	An14	4	-	_____	=_____
	An15	4	-	_____	=_____
	An16	4	-	_____	=_____

Sum individual item scores: _____
Multiply by 13: _____
Divide by number of items answered: _____=**Fatigue Subscale score**

*For guidelines on handling missing data and scoring options, please refer to the Administration and Scoring Guidelines in the manual or on-line at www.facit.org.

APPENDIX G. COGNITIVE FUNCTIONING (FACT-COG) PATIENT QUESTIONNAIRE

Below is a list of statements that other people with your condition have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PERCEIVED COGNITIVE IMPAIRMENTS	**Never**	**About once a week**	**Two to three times a week**	**Nearly every day**	**Several times a day**
CogA1	I have had trouble forming thoughts	0	1	2	3	4
CogA3	My thinking has been slow	0	1	2	3	4
CogC7	I have had trouble concentrating	0	1	2	3	4
CogM9	I have had trouble finding my way to a familiar place	0	1	2	3	4
CogM10	I have had trouble remembering where I put things, like my keys or my wallet	0	1	2	3	4
CogM12	I have had trouble remembering new information, like phone numbers or simple instructions	0	1	2	3	4
CogV13	I have had trouble recalling the name of an object while talking to someone	0	1	2	3	4
CogV15	I have had trouble finding the right word(s) to express myself	0	1	2	3	4
CogV16	I have used the wrong word when I referred to an object	0	1	2	3	4
CogV17b	I have had trouble saying what I mean in conversations with others	0	1	2	3	4
CogF19	I have walked into a room and forgotten what I meant to get or do there	0	1	2	3	4
CogF23	I have had to work really hard to pay attention or I would make a mistake	0	1	2	3	4
CogF24	I have forgotten names of people soon after being introduced	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogF25	My reactions in everyday situations have been slow	0	1	2	3	4
CogC31	I have had to work harder than usual to keep track of what I was doing	0	1	2	3	4
CogC32	My thinking has been slower than usual	0	1	2	3	4
CogC33a	I have had to work harder than usual to express myself clearly	0	1	2	3	4
CogC33c	I have had to use written lists more often than usual so I would not forget things	0	1	2	3	4
CogMT1	I have trouble keeping track of what I am doing if I am interrupted	0	1	2	3	4
CogMT2	I have trouble shifting back and forth between different activities that require thinking	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>COMMENTS FROM OTHERS</u>	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogO1	Other people have told me I seemed to have trouble <u>remembering information</u>	0	1	2	3	4
CogO2	Other people have told me I seemed to have trouble <u>speaking clearly</u>	0	1	2	3	4
CogO3	Other people have told me I seemed to have trouble <u>thinking clearly</u>	0	1	2	3	4
CogO4	Other people have told me I seemed <u>confused</u>	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

		Not at all	A little bit	Some -what	Quite a bit	Very much
	<u>PERCEIVED COGNITIVE ABILITIES</u>					
Cog PC1	I have been able to concentrate	0	1	2	3	4
Cog PV1	I have been able to bring to mind words that I wanted to use while talking to someone	0	1	2	3	4
Cog PM1	I have been able to remember things, like where I left my keys or wallet	0	1	2	3	4
Cog PM2	I have been able to remember to do things, like take medicine or buy something I needed	0	1	2	3	4
Cog PF1	I am able to pay attention and keep track of what I am doing without extra effort	0	1	2	3	4
Cog PC H1	My mind is as sharp as it has always been	0	1	2	3	4
Cog PC H2	My memory is as good as it has always	0	1	2	3	4
Cog PM T1	I am able to shift back and forth between two activities that require	0	1	2	3	4
Cog PM T2	I am able to keep track of what I am doing, even if I am	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	<u>IMPACT ON QUALITY OF LIFE</u>	Not at all	A little bit	Some-what	Quite a bit	Very much
CogQ35	I have been upset about these problems	0	1	2	3	4
CogQ37	These problems have interfered with my ability to work	0	1	2	3	4
CogQ38	These problems have interfered with my ability to do things I enjoy	0	1	2	3	4
CogQ41	These problems have interfered with the quality of my life	0	1	2	3	4

FACT-Cog Scoring Guidelines (Version 3) – Page 1

Instructions:* 1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores (Not applicable to the FACT-Cog*).
5. **The higher the score, the better the QOL.**

Subscale	Item Code	Reverse item?	Item response		Item Score	
PERCEIVED COGNITIVE IMPAIRMENTS (CogPCI) *Score range:* 0-72	CogA1 4	-	_____		=_____	
	CogA3 4	-	_____		=_____	
	CogC7 4	-	_____		=_____	
	CogM9 4	-	_____		=_____	
	CogM10 4	-	_____		=_____	
	CogM12 4	-	_____		=_____	
	CogV13 4	-	_____		=_____	
	CogV15 4	-	_____		=_____	
	CogV16 4	-	_____		=_____	
	CogV17b	4	-	_____		=_____
	CogF19 4	-	_____		=_____	
	CogF23 4	-	_____		=_____	
	CogF24 4	-	_____		=_____	
	CogF25 4	-	_____		=_____	
	CogC31 4	-	_____		=_____	
	CogC32 4	-	_____		=_____	
	CogC33a	4	-	_____		=_____
	CogC33c	4	-	_____		=_____
	CogMT1		NOT CURRENTLY SCORED			
	CogMT2		NOT CURRENTLY SCORED			

Sum individual item scores: _____
Multiply by 18: _____
Divide by number of items answered: _____=**CogPCI subscale score**

Subscale	Item Code	Reverse item?	Item response	Item Score
IMPACT OF PERCEIVED COGNITIVE IMPAIRMENTS ON QUALITY OF LIFE (CogQOL) *Score range:* 0-16	CogQ35 4	-	_____	=_____
	CogQ37 4	-	_____	=_____
	CogQ38 4	-	_____	=_____
	CogQ41 4	-	_____	=_____

Sum individual item scores: _____
Multiply by 4: _____
Divide by number of items answered: _____=**CogQOL subscale score**

Subscale	Item Code	Reverse item?	Item response	Item Score
COMMENTS FROM OTHERS (CogOth) *Score range:* 0-16	CogO1 4	-	_____	=_____
	CogO2 4	-	_____	=_____
	CogO3 4	-	_____	=_____
	CogO4 4	-	_____	=_____

Sum individual item scores: _____
Multiply by 4: _____
Divide by number of items answered: _____=**CogOth subscale score**

PERCEIVED COGNITIVE ABILITIES (CogPCA) *Score range:* 0-28	CogPC1 0	+	_____		=_____	
	CogPV1 0	+	_____		=_____	
	CogPM1	0	+	_____		=_____
	CogPM2	0	+	_____		=_____
	CogPF1 0	+	_____		=_____	
	CogPCh1	0	+	_____		=_____
	CogPCh2	0	+	_____		=_____
		CogPMT1	NOT CURRENTLY SCORED			
		CogPMT2	NOT CURRENTLY SCORED			

Sum individual item scores: _____
Multiply by 7: _____
Divide by number of items answered: _____=**CogPCA subscale score**

*FACIT recommends that either cognitive impairments or cognitive abilities be selected as a 'primary' score (we currently recommend cognitive impairments be used).

There are two options regarding the scoring of items CogMT1, MT2, PMT1 and PMT2: (1) include the 4 items in scoring and conduct some additional analyses to confirm the items fit with the scale (range 0-80, 0-36); or (2) score the scale without the additional 4 items (range 0-72, 0-28).

While CogMT1, MT2, PMT1 and PMT2 are not currently scored, they may be included in the total score if a measure of internal consistency (e.g., Cronbach's alpha) and individual item-total score correlation coefficients indicate that the items fit with the scale. These extra steps would be needed because the items were added later and not included in the initial validation analyses.

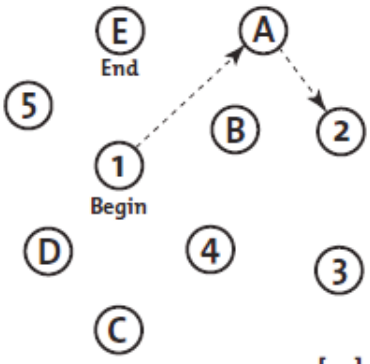
APPENDIX H. MONTREAL COGNITIVE ASSESSMENT (MOCA) – STAFF-ADMINISTERED

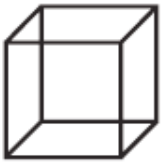
See next page.

MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS

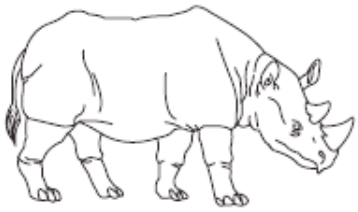


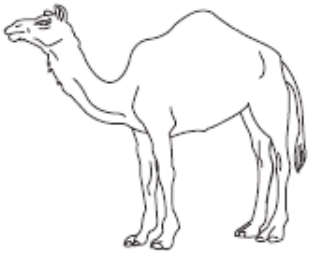


Copy cube [ ] [ ]

Draw CLOCK (Ten past eleven) (3 points) [ ] Contour [ ] Numbers [ ] Hands ___/5

NAMING





[ ] [ ] [ ] ___/3

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION

Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 ___/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B ___/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** ___/3

LANGUAGE

Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] ___/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) ___/1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler ___/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only
		[ ]	[ ]	[ ]	[ ]	[ ]	
Optional	Category cue						
	Multiple choice cue						

___/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City ___/6

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Normal ≥ 26 / 30

TOTAL ___/30
Add 1 point if ≤ 12 yr edu

Montreal Cognitive Assessment (MoCA) Administration and Scoring Instructions

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation.
Time to administer the MoCA is approximately 10 minutes.
The total possible score is 30 points; a score of 26 or above is considered normal.

Alternating Trail Making:
Administration: The examiner instructs the subject: *"Please draw a line, going from a number to a letter in ascending order. Begin here* [point to (1)] *and draw a line from 1 then to A then to 2 and so on. End here* [point to (E)]."
Scoring: Allocate one point if the subject successfully draws the following pattern:
1 A- 2- B- 3- C- 4- D- 5- E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

Visuoconstructional Skills (Cube):
Administration: The examiner gives the following instructions, pointing to the cube: *"Copy this drawing as accurately as you can, in the space below".*
Scoring: One point is allocated for a correctly executed drawing.
Drawing must be three-dimensional
All lines are drawn
No line is added
Lines are relatively parallel and their length is similar (rectangular prisms are accepted)
A point is not assigned if any of the above-criteria are not met.

Visuoconstructional Skills (Clock):
Administration: Indicate the right third of the space and give the following instructions:
"Draw a clock. Put in all the numbers and set the time to 10 after 11".
Scoring: One point is allocated for each of the following three criteria:
Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);
Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;
Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centred within the clock face with their junction close to the clock centre.
A point is not assigned for a given element if any of the above-criteria are not met.

Naming: _____

Administration: Beginning on the left, point to each figure and say: *"Tell me the name of this animal".*

Scoring: One point each is given for the following responses: (1) camel or dromedary, (2) lion, (3) rhinoceros or rhino.

Memory:

Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions: *"This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn't matter in what order you say them".* Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: "*I am going to read the same list for a second time. Try to remember and tell me as many words as you can, including words you said the first time."* Put a check in the allocated space for each word the subject recalls after the second trial.
At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying, "*I will ask you to recall those words again at the end of the test."*

Scoring: No points are given for Trials One and Two.

Attention:
Forward Digit Span: Administration: Give the following instruction: "*I am going to say some numbers and when I am through, repeat them to me exactly as I said them".* Read the five number sequence at a rate of one digit per second.
Backward Digit Span: Administration: Give the following instruction: "*Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order."* Read the three number sequence at a rate of one digit per second.

Scoring: Allocate one point for each sequence correctly repeated, (*N.B.:* the correct response for the backwards trial is 2-4-7).

Vigilance: Administration: The examiner reads the list of letters at a rate of one per second, after giving the following instruction: "*I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand".*

Scoring: Give one point if there is zero to one errors (an error is a tap on a wrong letter or a failure to tap on letter A).

Serial 7s: Administration: The examiner gives the following instruction: "*Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop."* Give this instruction twice if necessary.
Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond "92 – 85 – 78 – 71 – 64" where the "92" is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

Sentence repetition:
Administration: The examiner gives the following instructions: "*I am going to read you a sentence. Repeat it after me, exactly as I say it* [pause]*: I only know that John is the one to help today.*" Following the response, say: "*Now I am going to read you another sentence. Repeat it after me, exactly as I say it* [pause]*: The cat always hid under the couch when dogs were in the room."*
Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "only", "always") and substitutions/additions (e.g., "John is the one who helped today;" substituting "hides" for "hid", altering plurals, etc.).

Verbal fluency:
Administration: The examiner gives the following instruction: "*Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready?* [Pause] *Now, tell me as many words as you can think of that begin with the letter F.* [time for 60 sec]. *Stop."*
Scoring: Allocate one point if the subject generates 11 words or more in 60 sec. Record the subject's response in the bottom or side margins.

Abstraction:
Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: "*Tell me how an orange and a banana are alike"*. If the subject answers in a concrete manner, then say only one additional time: "*Tell me another way in which those items are alike"*. If the subject does not give the appropriate response (*fruit*), say, "*Yes, and they are also both fruit.*" Do not give any additional instructions or clarification.
After the practice trial, say: *"Now, tell me how a train and a bicycle are alike".* Following the response, administer the second trial, saying: "*Now tell me how a ruler and a watch are alike".* Do not give any additional instructions or prompts.
Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:
Train-bicycle = means of transportation, means of travelling, you take trips in both; Ruler-watch = measuring instruments, used to measure.
The following responses are not acceptable: Train-bicycle = they have wheels; Ruler-watch = they have numbers.

Delayed recall:
Administration: The examiner gives the following instruction: "*I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember.* Make a check mark (✓) for each of the words correctly recalled spontaneously without any cues, in the allocated space.
Scoring: Allocate 1 point for each word recalled freely without any cues.

Optional:
Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (✓) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled

words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, "*Which of the following words do you think it was, NOSE, FACE, or HAND?"*
Use the following category and/or multiple-choice cues for each word, when appropriate:

FACE:	category cue: part of the body	multiple choice: nose, face, hand VELVET:
	category cue: type of fabric	multiple choice: denim, cotton, velvet CHURCH:
	category cue: type of building	multiple choice: church, school, hospital DAISY:
	category cue: type of flower	multiple choice: rose, daisy, tulip
RED:	category cue: a color	multiple choice: red, blue, green

Scoring: **No points are allocated for words recalled with a cue.** A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

Orientation:
Administration: The examiner gives the following instructions: "*Tell me the date today"*. If the subject does not give a complete answer, then prompt accordingly by saying: *"Tell me the [year, month, exact date, and day of the week]."* Then say: *"Now, tell me the name of this place, and which city it is in."*
Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.

TOTAL SCORE, MoCA:
Sum all subscores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal.