A Randomized Trial of Consolidative Immunotherapy with vs without Thoracic Radiotherapy and / or Stereotactic Body Radiation Therapy (SBRT) after First-line Systemic Therapy for Metastatic NSCLC
Wake Forest Baptist Comprehensive [redacted] Center
WFBCCC # 62718

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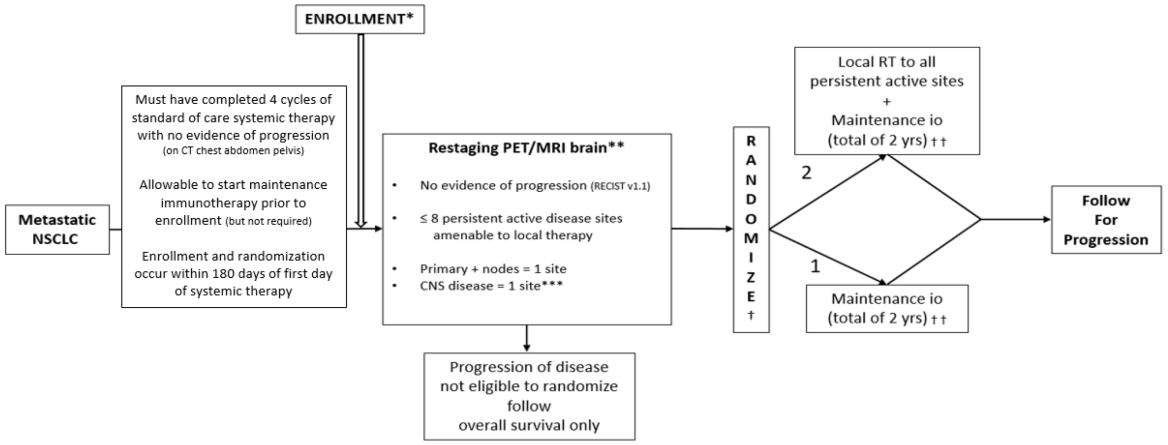

*Enrollment may occur after 4 cycles of standard of care systemic therapy (usually this will consist of combination chemo immunotherapy, but in some cases may be chemotherapy or immunotherapy alone). Neither enrollment nor randomization may occur more than 180 days from the first day of cycle 1 of systemic therapy. Protocol directed therapy should occur within 21 days of randomization (i.e-The start of RT or the resumption of maintenance io)

** If a PET has been performed within 30 days of enrollment with no evidence of progression per RECIST v1.1, then this scan may be used and does not have to be repeated prior to randomization
If an MRI brain has been performed within 90 days of enrollment with no evidence of progression per RECIST v1.1, then this scan may be used and does not have to be repeated prior to randomization

*** Treatment of CNS disease with stereotactic radiosurgery or resection as appropriate per CNS team may take place prior to completion of first line chemotherapy, for stratification purposes this will still count as 1 site of disease

† Randomization will be stratified by number of metastatic sites (1-3, 4-6, or 7-8)
† † Total maintenance immunotherapy includes any maintenance therapy given prior to randomization
Treatment of non-squamous histology may include concurrent pemetrexed with immunotherapy consolidation

1.0 Introduction and Background

In 2017, there were approximately 222,500 new cases of lung cancer diagnosed in the US, with an estimated 155,870 deaths[1]. Approximately 60% of newly diagnosed non-small cell lung cancers (NSCLC) present with metastatic disease on diagnosis[2]. Chemotherapy is generally accepted as the first-line treatment in most patients with metastatic disease. Outcomes with traditional platinum doublet-based chemotherapy alone in these patients remains poor with median overall survival of approximately 11 months[3]. However, for the subset of patients with limited disease burden who show any response to chemotherapy, it is becoming increasingly more common in modern practice to aggressively manage all known metastatic sites with local therapies.

1.1 Oligometastatic Radiation

The concept of oligometastatic disease was initially proposed by Hellman and Weichselbaum in 1995[4,5]. This proposal, that a diffusely metastatic state is preceded by an intermediate phase of truly limited metastatic disease in discrete “seed” sites, has become particularly attractive in the modern era. Enormous advancements have been made in both imaging, and therapy delivery, allowing for earlier detection, as well as more precise and well tolerated treatments than previously possible. Such improvements have also presented new challenges of determining exactly how many sites of disease represent “too many” to still be considered limited oligometastatic disease. This remains unclear which subgroups of metastatic patients will have the best outcomes; however, such uncertainties should not preclude investigation into the potential benefits of local therapy for these patients.

In the subgroup of metastatic patients who truly have a limited disease burden and a favorable response to first line systemic therapies, aggressive localized treatment of persistent disease could theoretically be curative. Clinical data from a variety of disease settings have empirically supported this hypothesis.

Numerous reports have shown that the original sites of gross metastatic disease are those most likely to first progress after initial chemotherapy[5,6]. In a retrospective review of 64 patients treated with first-line systemic therapy at the University of Colorado Cancer Center, first extra-cranial progression was limited to sites of initial disease present prior to the start of systemic therapy in 64% (i.e. local progression)[6]. In those patients who would have been eligible for local radiation therapy, the median time to first local progression was 3.0 months from the start of first-line systemic therapy. The median time to progression in previously uninvolved sites was 5.7 months. Six-month progression-free survival probability in patients with local-first progression was 17.4% compared to 45.5% in patients with distant or combined local and distant progression. This suggests that an effective local therapy, when judiciously applied in the metastatic setting, might improve time to progression in a substantial proportion of patients.

A retrospective review from the University of Rochester compares the outcomes of NSCLC patients treated with curative chemoradiotherapy for stage III disease compared with patients having limited (≤ 8) metastatic sites who received stereotactic body radiation therapy (SBRT) to all sites of disease[7]. Those with limited metastatic disease exhibited favorable survival outcomes compared to the stage III patients (5-year overall survival [OS] 14% v. 7%, respectively).

In 2012, De Ruysscher et al. reported long-term results from a prospective single arm trial of radical local therapy in oligometastatic NSCLC. Patients had less than five metastases at diagnosis and underwent a combination of local therapies to all sites of disease including surgery, conventional chemo-radiation, or SBRT at the physician's discretion. Median progression-free survival (PFS) was 12.1 months and median OS was 13.5 months. Of patients with recurrent disease, in-field failure was 5%. Treatment was overall well-tolerated[8].

There are a few key differences between the above paradigm and our proposed schema: surgery and fractionated radiotherapy were allowed, each brain metastasis counted as an individual site, chemotherapy was not standardized, and the use of immunotherapy was not reported. Despite these limitations, this study provides evidence for the overall safety and feasibility of radical therapy to all sites of oligometastatic NSCLC.

In another prospective, phase II trial from Belgium, 26 patients with oligometastatic NSCLC (≤ 5 metabolically active sites) were treated with SBRT to 50 gray (Gy) in 10 fractions to the primary and metastatic sites after induction chemotherapy[9]. Acute grade 3 toxicity occurred in 8% and there were no grade ≥ 4 toxicities. Median PFS was 11.2 months and median OS was 28.4 months. In-field failure occurred in 15%. After failure, further aggressive local salvage therapies were performed in 19 patients.

Petty (2018) recently reported results of a Wake Forest lead prospective multi-institutional phase II study. They analyzed outcomes in metastatic NSCLC patients who did not progress after 3-6 cycles of first line systemic therapy and had up to five total sites of disease including the untreated primary and or nodal disease. All residual sites were treated with SBRT without maintenance chemotherapy. Although the trial was closed early due to slow accrual, results were promising with a median PFS of 11 months (95% confidence interval [CI], 7.4-15.9) and a median OS of 22.2 months (95% CI, 13.3-45.8). The 5-year OS and PFS was 29%[10].

In 2016, Gomez et al., presented results of their multicenter phase II randomized study in which patients with stage IV NSCLC with three or fewer non-progressive metastatic lesions after first-line systemic therapy, were randomized to either local consolidation with SBRT or surgery to all metastatic sites with or without maintenance chemotherapy vs maintenance alone, which could include consolidative chemotherapy or observation. The study was stopped early due to clear benefit in the consolidative local therapy arm with median progression free survival of 11.9 months vs 3.9 months. HR 0.35 (90% CI, 0.18–0.66), log-rank p = 0.0054. Aggressive local therapy was well tolerated with no grade 4 or 5 toxicities. Of the 13 patients in the local consolidation arm, 10 failures were distant, 1 was locoregional, and 2 were both. Conversely, in the 17 patients on maintenance only, there were 6 distant failures, 4 locoregional, and 7 both local and distant failures[2].

This illustrated a shift from the typical pattern of first local progression at original sites of metastatic disease. Furthermore, this study showed that by aggressively treating all oligometastatic sites, the time to appearance of new lesions was increased. In the local consolidative therapy group, the time to the appearance of a new lesion was longer at 11.9 months (90% CI, 5.7-not evaluable) than in the maintenance arm at 5.7 months (3.1-7.0) p = 0.0497, which lends credence to the concept that ablation of all known sites of disease can prevent those sites from seeding further metastatic cascades.

Similarly, Iyengar et al. (2018) presented another randomized single institution experience from UT Southwestern showing favorable outcomes with local consolidation then maintenance chemotherapy as presented in Table 1 below[11].

Table 1. Prospective trials of radical therapy to all sites of oligometastatic NSCLC

	Number of Sites	Dose/Fractionation	Median PFS (mo)	Median OS (mo)	In-field Failure (%)
(De Ruysscher et al. 2012)	1-5	EQD2 ≥ 60 Gy Surgery allowed	12.1	13.5	5.1
(Collen et al. 2014)	1-5	50 Gy/10 fx	11.2	23.0	15
(Gomez et al. 2016)	1-3	Variable	11.9	NR	12*
(Petty et al. 2018)	1-5	Variable	11.0	22.2	12
(Iyengar et al. 2017)	1-6	21-27 Gy/1 fx 26.5-33 Gy/3 fx 30-37.5 Gy/5 fx 45 Gy/15 fx	9.7	NR	0

EQD2, equivalent dose in 2-Gy daily fractions; Fx, fraction(s); NR, not reached; OS, overall survival; PFS, progression-free survival
*Reported locoregional failure

1.2 Stereotactic Radiation for Brain Metastases

In patients with advanced NSCLC, the brain is a frequent site of metastases. Data from the University of Maryland suggest that, in patients with solitary brain metastases and aggressively treated primary disease, that durable progression-free and overall survival can be achieved in a proportion of patients[12]. This study included 42 patients with NSCLC who presented with stage I-III thoracic disease with a solitary, synchronous brain metastasis. All patients received gamma knife radiosurgery (median dose 18 Gy prescribed to 50% isodose line (IDL) with or without whole brain radiation therapy. Sixty-two percent also received definitive treatment to the primary site with chemoradiation or surgery. Overall, the 5-year survival was 21%, and was 35% specifically in patients receiving definitive treatment to the thoracic primary site.

1.3 Emerging Data for Immunotherapy

In the short time interval since publication of the studies above, an abundance of promising immunotherapy data has emerged and is starting to dramatically alter the systemic therapy landscape for numerous malignancies[13-15]. The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. The Programmed Death Receptor Ligand (PD-L1) pathway presents a particularly attractive immunotherapy target, as it is involved in both antigen and self-recognition, and is a major pathway hijacked by tumors to suppress immune control.

PD-1 and family members are type I transmembrane glycoproteins containing an immunoglobulin (Ig) Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail, which is responsible for the binding of signaling molecules. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. The cytoplasmic tail of PD-1 contains two tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD 1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins.

Tumor cells expressing PD-L1 can modulate the immune response to appear non-foreign and avoid destruction. Expression of PD-L1 and PD-L2 has been found in multiple solid tumor types including melanoma, NSCLC, and some lymphoid malignancies[16]. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. Several studies have shown that the cancer microenvironment manipulates the PD-L1/PD-1 pathway and that the induction of PD-L1 expression on tumor cells leads to the inhibition of immune responses against cancer, permitting cancer progression and metastasis[17]. In a combined analysis of the Checkmate 017 and 057 assessing PD-L1 expression levels in squamous cell and non-squamous cell NSCLC, the proportion of PD-L1 positivity at cutoff expression levels of 1%, 5%, 10% and 50% in primary tumors was roughly 28.1%, 27.4%, 22.6%, and 13.0% respectively. The overall concordance of primary and metastatic tumor PD-L1 expression was 75.2%[18]. These data suggest that PD-L1 should be considered as an attractive target for therapeutic intervention.

1.4 Immunotherapy alone

The evidence that PD-L1 is commonly up-regulated in NSCLC and that PD-1 is expressed on the majority of tumor infiltrating lymphocytes, represented the rationale for the development of monoclonal antibodies against PD-L1 or PD-1, and several agents are currently under investigation[19]. As covered in detail below, Pembrolizumab is approved in the frontline setting alone for patients with advanced NSCLC and PD-L1 tumor proportion score (TPS) of 50% or greater and in combination with pemetrexed and carboplatin for patients with non-squamous histology. It is also approved in the second line setting for patients with PD-L1 TPS > 1%.

The first anti-PD1 antibody approved for NSCLC was nivolumab. In the Checkmate 017 trial, 272 patients with advanced/metastatic squamous cell NSCLC whose disease progressed during or after first-line chemotherapy were randomized to nivolumab, 3 mg/kg every two weeks, or docetaxel, 75 mg/m^2 every three weeks. The median overall survival (OS) was 9.2 months with nivolumab versus six months with docetaxel. The response rate was 20% with nivolumab versus 9% with docetaxel. The median progression free survival (PFS) was 3.5 months with nivolumab versus 2.8 months with docetaxel. In this study, PD-L1 was neither prognostic nor predictive of benefit. Treatment-related adverse events of grade 3 or 4 were reported in 7% of the patients in the nivolumab group as compared with 55% of those in the docetaxel group. The most frequently reported (in ≥ 3% of patients) treatment-related select adverse events of any grade were hypothyroidism (4% with nivolumab vs. 0% with docetaxel), diarrhea (8% vs. 20%), pneumonitis (5% vs. 0%), increased blood creatinine level (3% vs. 2%), and rash (4% vs. 6%). Three treatment-related select AEs of grade 3 were reported in the nivolumab group, with one case each of tubulointerstitial nephritis, colitis, and pneumonitis; no grade 4 events were reported. No patients died in the immunotherapy arm versus three patients in the docetaxel arm[20].

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab was later approved in the second-line setting based off the KEYNOTE-010 study. It was a randomized phase 2/3 trial which assessed pembrolizumab in patients with previously treated advanced non-squamous and squamous NSCLC who were PD-L1 positive (≥ 1%). There were three arms in this trial: pembrolizumab at 2 mg/kg, pembrolizumab at 10 mg/kg, and docetaxel at 75 mg/m² every three weeks. The median OS was 10.4 months for the lower dose of pembrolizumab, 12.7 months for the higher dose, and 8.5 months for docetaxel. OS was significantly longer for both doses of pembrolizumab when compared with docetaxel. When compared with docetaxel, there were fewer grade 3 to 5 treatment-related AEs at either dose of pembrolizumab (pembrolizumab 2 mg/kg: 13% [43/339] of patients, pembrolizumab 10 mg/kg: 16% [55/343], and docetaxel: 35% [109/309]). A total of six treatment-related deaths occurred in patients receiving pembrolizumab (three at each dose) and five treatment-related deaths occurred in the docetaxel arm[21].

Due to the good response of pembrolizumab in the second-line setting, it was studied as a potential first-line agent. The KEYNOTE-024 trial was an open-label, phase 3 trial, which randomized 305 patients with untreated advanced NSCLC with PD-L1 expression on at least 50% of tumor cells without the presence of a driver mutation to pembrolizumab 200 mg every three weeks versus platinum-based chemotherapy of the investigators choice. Crossover from the chemotherapy group was permitted at the time of progression. Primary end point of the study was PFS with OS, ORR, and safety being key secondary endpoints. At a median follow-up of 11.2 months, median PFS was significantly longer in the pembrolizumab arm 10.3 months versus 6.0 months. At a median follow-up of 25.2 months, OS was significantly longer with pembrolizumab versus chemotherapy at 30.0 months versus 14.2 months, despite significant crossover in the chemotherapy arm. The 12-month and 18-month OS data favored the immunotherapy arm, 70.3% vs 54.8% at 12 months; 51.5% vs 34.5% at 18 months. The response rate was higher in the immunotherapy arm 45.5% vs 29.8% in the chemotherapy arm. The median time to response was similar in both

arms, 2.1 and 2.2 months. Median duration of response was not reached in the pembrolizumab arm compared to 7.1 months in the chemotherapy arm. Of the 82 patients who crossed over to immunotherapy arm from the chemotherapy arm, the ORR was 20.7%. Treatment related AE's of any grade were less frequent when compared to the chemotherapy arm as were grade 3, 4, or 5 treatment-related AEs (26.6% vs 53.3%)[22].

1.5 Combination immunotherapy and chemotherapy

Chemotherapy is known to modulate immunologic effects; thus, it was hypothesized that combining chemotherapy with an anti-PD-1 inhibitor may have a synergistic effect[23]. Initially, the KEYNOTE-021 phase 2 study showed the safety and efficacy of combining chemotherapy and immunotherapy in the front line treatment of stage IV NSCLC. These findings were confirmed by two large, double-blind phase 3 registration trials (KEYNOTE-189 and KEYNOTE-407), one for each major subtype of NSCLC.

For non-squamous subtype, KEYNOTE-189 found that the addition of pembrolizumab to pemetrexed/platinum (either carboplatin or cisplatin) significantly improved overall survival (median OS not reached vs. 11.3 months, HR 0.49; survival at 12 months 69% vs. 49%). Toxicity was only moderately increased with the addition of immunotherapy, as AE's due to any cause led to treatment discontinuation in 14% (vs 8% control) and death in 7% (vs. 6% control). The treatment arm had higher rates of idiosyncratic autoimmune AE's (Table 3: 23% vs. 12%), diarrhea (31% vs. 21%), pyrexia (20% vs. 15%), peripheral edema (19% vs. 13%), and thrombocytopenia (18% vs. 15%). This study excluded patients with the targetable mutations EGFR or ALK[24].

For squamous subtype, KEYNOTE-407 found that the addition of pembrolizumab to carboplatin/taxane (either paclitaxel or nab-paclitaxel) significantly improved overall survival (15.9 mo vs. 11.3 mo, 0.64; 95% CI, 0.49 to 0.85). Similar to KEYNOTE-189, toxicity was only moderately increased with the addition of immunotherapy, as AE's due to any cause led to treatment discontinuation in 13% (vs. 6% control) and death in 8% (vs. 6% control). The treatment arm had higher rates of idiosyncratic autoimmune AE's (Table 3: 29% vs. 9%), alopecia (46% vs. 36%), neutropenia (38% vs. 33%), nausea/vomiting (36% vs. 32%; 16% vs. 12%), thrombocytopenia (31% vs. 23%), diarrhea (30% vs. 23%), arthralgia (21% vs. 14%), and peripheral neuropathy (21% vs. 16%)[25].

1.6 Immunotherapy as consolidation after radiation

Immunotherapy has been studied as consolidation therapy after concurrent chemotherapy and radiation. The PACIFIC investigators designed a phase III study which compared anti-PD-L1 antibody, durvalumab, with placebo in patients with stage III NSCLC who did not have disease progression after two or more cycles of platinum-based chemoradiotherapy. Patients were randomly assigned in a 2:1 ratio, to receive intravenous durvalumab 10mg/kg or placebo every two weeks for up to 12 months. The study drug was administered 1 to 42 days after the patients had received chemoradiotherapy. The co-primary end-points were PFS (as assessed by means of blinded independent central review) and OS. Of 713 patients who underwent randomization, 709 received consolidation therapy (473 received durvalumab and 236 received placebo). The median PFS from randomization was 16.8 months with durvalumab versus 5.6 months with placebo (stratified hazard ratio for disease progression or death, 0.52; 95% CI, 0.42 to 0.65; $P < 0.001$); the 12-month PFS was 55.9% versus 35.3%, and the 18-month PFS was 44.2% versus 27.0%. The response rate was higher with durvalumab than with placebo (28.4% vs. 16.0%; $P < 0.001$), and the median duration of response was longer (72.8% vs. 46.8% of the patients had an ongoing response at 18 months). The median time to death or distant metastasis was longer with durvalumab than with placebo (23.2 months vs. 14.6 months; $P < 0.001$). Grade 3 or 4 adverse events occurred in 29.9% of the patients who received durvalumab and 26.1% of those who received placebo; the most common adverse event of grade 3 or 4 was pneumonia (4.4% and 3.8%, respectively). A total of 15.4% of patients in the durvalumab group and 9.8% of those in the placebo group discontinued the study drug because of adverse events. Based off this study, the FDA approved durvalumab as consolidation therapy after concurrent chemoradiotherapy in stage III NSCLC[13].

1.7 Immunotherapy and SBRT

Data now suggest that radiation therapy (RT) can modulate a systemic immune response to the tumor. Radiation releases tumor-associated antigens and facilitates the release of tumor associated antigens by dendritic cells (DC) and cross complementation on major histocompatibility complex-1 (MHC-1)[26]. Radiation also appears to enhance DC activation and immune priming against tumor cells[27]. Preclinical evidence suggests that when radiotherapy and immunotherapy are administered concomitantly, a synergistic antitumor response is observed[28]. Thus, RT can act as an in-situ tumor vaccine and provide long-lived immunologic memory[29].

A retrospective subgroup analysis of 97 patients with progressive locally advanced, or metastatic NSCLC from Keynote 001, compared patients who received pembrolizumab and had any prior history of radiation vs those who had never received radiation. In those patients who had any prior history of radiation the median PFS and OS were significantly improved from 2.1 months to 4.4 months and from 5.3 months to 10.7 months respectively. In those who had only received extracranial RT, the improvements in median PFS and OS were more pronounced from 2 months to 6.3 months and 5.3 months to 11.6 months respectively[30].

Although limited and retrospective, this supports the hypothesis that radiation may sensitize immunotherapy or allow for better tumor cell antigen exposure after radiation induced cell death. There has been concern however that immune sensitization with radiation could potentially lead to over stimulation of the immune response and substantial toxicity. This is currently an area of intense research.

In a phase 1 dose-finding clinical trial performed by the University of Chicago, patients with progressively metastatic solid tumors (after initial standard-of-care therapies) with at least two tumors amenable to SBRT were treated to a range of doses prior to initiation of immunotherapy. Pembrolizumab (200 mg IV every 3 weeks) was given within seven days after the final fraction of SBRT. The primary outcome was optimal RT dose; secondary outcomes included adverse events ≥ grade 3, response rates, tumor control and survival. Seventy-three patients had 1-3 sites of metastatic disease treated with SBRT. No per-protocol reductions in radiotherapy dose were required. A total of six patients experienced grade 3 toxicity (pneumonitis, 3; colitis, 2; hepatotoxicity, 1) for an overall rate of dose-limiting treatment-related toxicity rate of 9.7%, providing evidence of safety and feasibility for stereotactic radiotherapy shortly followed by PDL1 blockade[31].

1.8 First Line Chemotherapy for Metastatic Lung Cancer

Patients with advanced stage IV NSCLC who are negative for sensitizing EGFR mutations, ALK rearrangements, ROS1 rearrangements, and with PD-L1 < 50% and who have a good performance status benefit from platinum-based chemotherapy. NCCN guidelines recommended chemotherapy regimens include platinum agents (cisplatin and carboplatin), taxanes (paclitaxel, docetaxel, albumin-bound paclitaxel), vinorelbine, etoposide, pemetrexed, and gemcitabine. Schiller and colleagues (2002) compared the rates of progression-free and overall survival using four widely accepted third-generation chemotherapy doublets as first-line treatment for advanced NSCLC: cisplatin and paclitaxel, cisplatin and gemcitabine, cisplatin and docetaxel or carboplatin and paclitaxel[32]. No differences in clinical outcome were detected, with median times to progression of 3.1-4.2 months and median overall survival of 7.4-8.1 months. The drug regimen with the highest likelihood of benefit with toxicity deemed acceptable to both the physician and patient should be given as initial treatment. The histology (non-squamous versus squamous) should be taken into account prior to selection of therapy. Scagliotti et al. (2008) published a phase III, randomized study comparing OS between treatment regimens in treatment naive, stage IIIB or IV NSCLC and PS 0-1. Overall survival was statistically superior for cisplatin/pemetrexed versus cisplatin/gemcitabine in patients with adenocarcinoma (n = 847; 12.6 v 10.9 months, respectively) and large-cell carcinoma histology (n = 153; 10.4 v 6.7 months) respectively. In contrast, for patients with squamous cell histology, there was a significant improvement in survival with cisplatin/gemcitabine versus cisplatin/pemetrexed (n = 473; 10.8 v 9.4 months, respectively). For cisplatin/pemetrexed, rates of grade 3 or 4 neutropenia, anemia, and thrombocytopenia (P = .001); febrile neutropenia (P =.002); and alopecia (P = .001) were significantly lower, whereas grade 3 or 4 nausea (P = .004) was more common. This was the first prospective phase III study in NSCLC to show survival differences based on histologic type[33].

The study is designed to ascertain if oligometastatic SBRT in combination with local radiation therapy followed by consolidative immunotherapy improves the outcomes for patients with stage IV NSCLC when compared to those patients receiving consolidative immunotherapy alone.

2.0 Objectives

2.1 Primary Objective(s)

2.1.1 We plan to compare progression-free survival of patients randomized to radiation and consolidative immunotherapy against those receiving consolidative immunotherapy alone.

2.2 Secondary Objective(s)

2.2.1 We plan to estimate overall survival in all patients and will compare overall survival of those randomized to radiation and consolidative immunotherapy against those receiving consolidative immunotherapy alone.

2.2.2 In patients who experience subsequent failures after initiating protocol directed therapy, we will assess whether these failures occurred at known or new sites of disease.

2.2.3 We plan to evaluate toxicity associated with the addition of consolidative radiation therapy to upfront chemoimmunotherapy followed by additional consolidative immunotherapy. This will include calculating rates of adverse events depending on treatment site. Potential toxicities reported would include pneumonitis, esophagitis, chest wall pain, dermatologic toxicity, renal dysfunction, gastrointestinal toxicity including nausea, vomiting, and diarrhea, hepatotoxicity, and abdominal pain. These toxicities would be assessed according to site of irradiation by the treating physician and graded as per CTCAE 5.

3.0 Patient Selection

ENROLLMENT

- Patients are eligible for enrollment if they have metastatic NSCLC and have undergone at least 4 cycles of upfront standard of care systemic therapy (usually this will consist of combination chemo immunotherapy, but in some cases may be chemotherapy or immunotherapy alone). Patients must have a CT chest abdomen pelvis (ideally with IV contrast) performed after the point of completion of 4 cycles of systemic therapy, but no later than 180 days from the first day of systemic therapy. This CT scan must be completed within 180 days of the first day of systemic therapy, and must demonstrate no evidence of disease progression per RECIST v1.1.

- Patients may start their standard of care maintenance immunotherapy at the discretion of their treating medical oncologist prior to enrollment. Patients must be enrolled AND randomized no later than 180 days from the first day of cycle 1 of systemic therapy. The first day of cycle 1 of combined systemic therapy is considered day # 1. At most, an additional 179 days may elapse from this point to remain eligible for inclusion on this study.

RANDOMIZATION

- Once enrolled, patients will have a restaging PET/MRI brain *(exceptions below)*
  If restaging scans demonstrate ≤ eight sites of non-progressive active residual disease, then patients are eligible for randomization. If restaging scans demonstrate progression of disease, then these patients will not be eligible for randomization, but will be followed by their primary medical oncologist or radiation oncologist every 3 months for overall survival only.

  ***** *If a PET has been performed within **30** days of enrollment with no evidence of progression per RECIST v1.1, then this scan may be used and does not have to be repeated prior to randomization*

  ***** *If an MRI brain has been performed within **90** days of enrollment with no evidence of progression per RECIST v1.1, then this scan may be used and does not have to be repeated prior to randomization*

- Randomization should occur within 21 days of enrollment.
- Once randomized, protocol directed therapy should occur within 21 days from randomization (ie. start of consolidative RT or resumption of maintenance immunotherapy)

If randomized to consolidative radiation therapy then maintenance immunotherapy:

Maintenance immunotherapy may NOT be delivered concurrently with consolidative radiation. Concurrently is defined as on the same day of any radiation treatment or on any day between the first and last treatment of radiation. Resumption of maintenance immunotherapy after completion of radiation therapy is at the discretion of the treating medical oncologist. They may resume maintenance immunotherapy as early as 24 hrs after the last radiation treatment, but resumption should be no later than 8 weeks from the last radiation treatment. If treatment related toxicities prohibit administration of maintenance immunotherapy, then restarting this therapy is at the discretion of the treating medical oncologist. In such cases, patients will remain on study until they experience progression or death. If they experience progression, patients will be followed for overall survival only per appendix L past the point of progression.

If randomized to continued maintenance immunotherapy alone:

Patients will begin or resume maintenance immunotherapy no later than 21 days following randomization.

3.1 Inclusion Criteria for Enrollment

3.1.1 Patients who are 18 years or older

3.1.2 Performance Status 0-2 (ECOG)
at time of consult with radiation oncology

3.1.3 Pathologically proven NSCLC with evidence of metastatic disease.

3.1.4 Must have received 4 cycles of standard of care systemic therapy (usually this will consist of combination chemo immunotherapy), with a CT chest abdomen pelvis that was performed after completion of these 4 cycles and demonstrates no evidence of progression per RECIST v1.1

3.1.5 To be eligible for enrollment and randomization, patients must be within 180 days from their first dose of standard of care systemic therapy. Cycle 1 day 1 is defined as day 1. If enrolled on day 180, the patient would need to be randomized the same day.

3.1.6 Persistent active disease must be amenable to radiation treatment per the treating radiation oncologist, and patients must have at least one residual site of disease which can be identified by CT or PET/CT and targeted with radiation.

3.1.7 Patients who previously had earlier stage NSCLC treated definitively and have now developed new distant disease, are eligible for inclusion if they have undergone at least 4 cycles of standard of care systemic therapy for their metastatic recurrence, and they meet all criteria above.

3.1.8 There are no strict size or tumor number limitations in a given organ (lung, liver, abdomen pelvis, or spine). This is at the discretion of the treating radiation oncologist.

3.2 Exclusion Criteria from Enrollment

3.2.1 More than 180 days has elapsed since day 1 of cycle 1 of standard of care systemic therapy.

3.2.2 Pregnant or lactating women

3.2.3 The patient has received treatment for other carcinomas within the last three years (Except for cured non-melanoma skin cancer, low-risk prostate cancer, T1/T2 glottic cancer, stage 0 or stage I breast cancer, non-invasive bladder cancer, or treated in-situ cervical cancer). Prior lung cancer diagnosis now with oligometastatic recurrence is not an exclusion criteria.

3.2.4 Patients with major activating mutations in EGFR (del19, L858R, and T790M) or ROS 1 or ALK gene rearrangements are excluded

3.3 Eligibility for Randomization

Once enrolled on study, patients will have a PET/MRI brain for restaging. Patients with no evidence of progression and 8 or fewer sites of active persistent disease per the treating physician are eligible for randomization.

If a PET has been performed within 30 days of enrollment with no evidence of progression per RECIST v1.1, then this scan may be used and does not have to be repeated prior to randomization

If an MRI brain has been performed within 90 days of enrollment with no evidence of progression per RECIST v1.1, then this scan may be used and does not have to be repeated prior to randomization

3.4 Inclusion of Women and Minorities

Men and women of all races and ethnicities who meet the above-described eligibility criteria are eligible to participate in this study. The study consent form will also be provided in Spanish for Spanish-speaking participants.

Based on WFBCCC population estimates, we may expect approximately 44% of participants to be women. We may enroll approximately 10-13% Black or African American. Based on our catchment area and hospital demographics we do not expect accruals of individuals of Hispanic/ Latino, American Indian/Alaska Native or Asian ancestry; however, no individual will be excluded from the study if they satisfy the above inclusion/exclusion criteria. Should we not meet or exceed these estimates, the PI will engage the Office of the Center of Health Equity to discuss strategies to enhance recruitment in these target populations.

4.0 Registration Procedures

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be linked to the study in EPIC within 48 hours of Informed Consent. Randomization and protocol designated treatment must take place within 8 weeks of the last dose of first line systemic therapy.
You must perform the following steps to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix A)
2. Complete the Protocol Registration Form (Appendix B)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist, Protocol Registration Form to the registrar These forms may be sent by either by fax or e-mail.
4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Contact Information:
Protocol Registrar PHONE [redacted]
Protocol Registrar FAX [redacted]
Protocol Registrar E-MAIL [redacted]
*Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.
Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.
To complete the registration process, the Registrar will:
Assign a patient study number, register the patient on the study,
Randomize through Wake Forest OnCore

Institutions outside of Winston Campus Wake Forest Baptist University Medical Center will contact the protocol registrar and randomization will be assigned through the Wake Forest OnCore program. Randomization will then be communicated to the

outside institution by the Wake Forest protocol registrar. If technically feasible at the time that this study begins, we will allow outside institutions remote access to our Wake Forest OnCore program for direct data entry and randomization.

5.0 Outcomes

5.1 Primary Outcome

5.1.1 Progression-free survival from the date of starting first line standard of care systemic therapy.

5.2 Secondary Outcome

5.2.1 Overall survival over 5 years from the date of starting first line standard of care systemic therapy.

5.2.2 In patients who experience subsequent failures after initiating protocol directed therapy, we will assess whether these failures occurred at known or new sites of disease.

5.2.3 Frequency of adverse events per CTCAE v5.0

6.0 Pembrolizumab

In order to maintain dose-intensity and cumulative dose-delivery, reasonable efforts should be made to minimize dose reductions and treatment delays. Any subject whose treatment is delayed should be evaluated on a weekly basis until adequate hematologic and non-hematologic parameters have been met. Patients may elect to delay doses of maintenance treatment for up to 3 weeks due to personal preference and this will not constitute a protocol deviation.

Toxicities may require the dose reduction of one or more of the study required medications. The investigator will carefully assess all treatment associated toxicities and, whenever possible, determine if the toxicities can reasonably be attributed to a single agent or a causal relationship with one of the agents can reasonably be ruled out. If appropriate, dose reductions should not affect the dose of other products.

CTC-AE measures will occur at each cycle of consolidation immunotherapy. Dose modifications and treatments for adverse events will be managed at the discretion of the treating physicians per their standard practice. Guidance statements regarding dose modifications and ae management are provided as suggestions for treating physicians but are not mandatory. Reasons for dose delays, dose modifications, or addition of steroid treatments must be documented by the treating physician.

- Toxicity grades are defined using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0
- Dose escalations are not allowed

6.1 Pembrolizumab dose and timing of administration

Patients randomized to immunotherapy will begin treatment within 8 weeks of the last dose of their upfront systemic therapy. Patients randomized to radiation followed by immunotherapy will begin treatment within 8 weeks of the last treatment of radiation. Immunotherapy consolidation treatment of non-squamous histology may include concurrent pemetrexed with pembrolizumab consolidation,

per standard institutional practice. The initial dose of pembrolizumab will be utilized during consolidative immunotherapy either alone or in combination with pemetrexed.

REGIMEN DESCRIPTION

Agent	Dose	Route	Schedule	Cycle Length
Pembrolizumab	200 mg	30 minute intravenous infusion	Day 1	3 weeks

In patients randomized to consolidative immunotherapy after radiation may begin as early as 24 hours after the last treatment of radiation therapy at the discretion of the treating medical oncologist; however it must be administered no later than 8 weeks from the last treatment of radiotherapy.

In patients who are randomized to receive consolidative immunotherapy alone, they must resume maintenance immunotherapy within 8 weeks of their last dose of chemo immunotherapy or maintenance immunotherapy.

6.2 Pembrolizumab dose modifications (for immune-related adverse events)

Pembrolizumab dose delays and treatment of pembrolizumb related adverse events will be at the investigators discretion. For general management of immune-related adverse events due to pembrolizumab consider:

1) Patient evaluation to identify any alternative etiology.
2) In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related.
3) Symptomatic and topical therapy should be considered for low-grade events.
4) Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
5) More potent immunosuppressives should be considered for events not responding to systemic steroids.

While treatment delays and treatment of adverse events will occur at the investigator's discretion, the tables below are provided for general guidance and management of pembrolizumab immune-related adverse effects.

Immune-related AE	Severity	Dose Modifications	Toxicity Management
Pneumonitis/ ILD	Any Grade		Monitor subjects for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Subjects should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
	Grade 1	No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	For Grade 1 (Radiographic Changes Only) - Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated - Consider pulmonary and infectious disease consult
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date	For Grade 2 (Mild to Moderate New Symptoms) Monitor symptoms daily and consider hospitalization Discuss with study physician and consider systemic steroids (eg, prednisone 1-2mg/kg/day or IV equivalent Reimaging as clinically indicated If no improvement within 3 to 5 days, additional workup and treatment with IV methylprednisolone 2-4mg/kg/day should be considered If no improvement within 3 to 5 days, further immunosuppressive therapy (eg, infliximab) should be considered. Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics Consider pulmonary and infectious disease consult
Immune-related AE	**Severity**	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4	Permanently discontinue study drug/study regimen	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening Discuss with study physician pulmonary and infectious disease consult Hospitalize the patient Supportive Care (oxygen, etc.) Initiate empiric IV corticosteroids (eg, methylprednisolone or equivalent) at 1 to 4 mg/kg/day If no improvement within 3 to 5 days, additional workup and treatment with additional immunosuppressive therapy (eg, infliximab) should be considered Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics
Diarrhea/ Enterocolitis	Any Grade		Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits) Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, infections, etc.) Steroids should be considered if an alternative etiology is not determined, even for low grade events, in order to prevent potential progression to higher grade event Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1	No dose modification	For Grade 1: - Close monitoring for worsening symptoms - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide
Immune-related AE	**Severity**	**Dose Modifications**	**Toxicity Management**
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date	For Grade 2: Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide If event is persistent (> 3 to 5 days) or worsens, consider prednisone 0.5 to 1 mg/kg/day or IV equivalent If not responsive within 3 to 5 days, consider IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 2 mg/kg/day If event is not responsive within 3 to 5 days or worsens, additional workup and treatment with IV methylprednisolone 2-4mg/kg/day should be considered If no improvement within 3 to 5 days, further immunosuppressives (eg, infliximab) should be considered Consult study physician if no resolution to Grade ≤1 in 3 to 4 days Once improving, gradually taper steroids over ≥4 weeks
	Grade 3 or 4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: Discuss with study physician Monitor stool frequency and volume and maintain hydration Urgent GI consult and imaging as appropriate Initiate empiric IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 4 mg/kg/day If no improvement within 3 to 5 days, consider further immunosuppressives (eg, infliximab). Caution: Ensure GI consult to rule out bowel perforation and refer to label before using infliximab. Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics
Hepatitis (Elevated LFTs)	Any Grade		Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications)
	Grade 1	No dose modification. If it worsens, treat as Grade 2 event	Continue LFT monitoring per protocol

Immune-related AE	Severity	Dose Modifications	Toxicity Management
	Grade 2	Hold Study drug/study regimen dose until grade 2 resolution to Grade ≤1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If improves to baseline then treat at next scheduled treatment date	Discuss with study physician if no resolution to Grade ≤1 in 1-2 days Recheck LFT's in 1 to 2 days. If event is persistent (> 3 to 5 days) or worsens, consider prednisone 0.5 to 1 mg/kg/day or IV equivalent. If no improvement within 3 to 5 days, consider additional workup and treatment with IV methylprednisolone 2-4mg/kg/day If no improvement within 3 to 5 days, consider further immunosuppressives (eg, mycophenolate mofetil) Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics
	Grade 3	For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN - Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline - Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade Grade ≤1 or baseline within 14 days Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue Study drug/study regimen Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria	For Grade 3 or 4: Discuss with the study physician Initiate empiric IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 4 mg/kg/day If no improvement within 3 to 5 days, consider further immunosuppressive therapy (eg, mycophenolate mofetil) If still no further improvement within 3 to 5 days consider other immunosuppressive therapy per local guidelines Hepatology consult, abdominal workup, and imaging as appropriate. Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics
	Grade 4	Permanently discontinue study drug/study regimen	
Rash (excluding Bullous skin formations)	Any Grade		Monitor for signs and symptoms of dermatitis (rash and pruritus) **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED**
	Grade 1		For Grade 1: Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream)

Immune-related AE	Severity	Dose Modifications	Toxicity Management
	Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves then resume administration at next scheduled dose	For Grade 2 : - Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream) - Consider moderate-strength topical steroid - If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening, discuss with study physician and consider systemic steroids prednisone 0.5 to 1 mg/kg/day or IV equivalent - Consider dermatology consult - Consider skin biopsy if persistent for >1-2 weeks or recurs
	Grade 3	Hold study drug/study regimen until resolution to Grade ≤1 or baseline If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue Study drug/study regimen	For Grade 3 or 4: - Discuss with study physician - Consider hospitalization - Monitor extent of rash [Rule of Nines] - Consult dermatology - Consider skin biopsy (preferably more than 1) as clinically feasible. - Initiate empiric IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 4 mg/kg/day - Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics
	Grade 4	Permanently discontinue study drug/study regimen	
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)	Any Grade		Monitor subjects for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, infections, etc.) Monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs depending on suspected endocrinopathy. If a subject experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing

Immune-related AE	Severity	Dose Modifications	Toxicity Management
	Grade 1	No dose modification	For Grade 1: (including those with asymptomatic TSH elevation) Monitor patient with appropriate endocrine function tests If TSH <0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1 • If worsens then treat as Grade 3 or Grade 4 t • If toxicity improves to baseline then treat at next scheduled treatment date	For Grade 2: (including those with symptomatic endocrinopathy) Discuss with study physician Initiate hormone replacement as needed for management Evaluate endocrine function, and as clinically indicated, consider pituitary scan For subjects with abnormal endocrine work up, consider short-term, high-dose corticosteroids (eg, methylprednisolone or IV equivalent) with relevant hormone replacement (eg, levothyroxine, hydrocortisone, or sex hormones) For subjects with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.
	Grade 3	Hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled Resume study drug/study regimen administration if controlled at the next scheduled dose	For Grade 3 or 4: Discuss with study physician Initiate empiric IV corticosteroids (eg, methylprednisolone IV or equivalent) at 1 to 2 mg/kg/day Administer hormone replacement therapy as necessary
	Grade 4	Permanently discontinue study drug/study regimen	For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity Consult endocrinologist Once improving, gradually taper immunosuppressive steroids over ≥4 weeks
Immune mediated Neurotoxicity (except Myasthenia Gravis and Guillain-Barre)	Any Grade		- Subjects should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes and medications, etc.) - Monitor subject for general symptoms (headache, nausea, vertigo, behavior change, or weakness) - Consider appropriate diagnostic testing (eg electromyogram and nerve conduction investigations) - Symptomatic treatment with neurological consult as appropriate

Immune-related AE	Severity	Dose Modifications	Toxicity Management
	Grade 1	No modifications	
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1 For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. If toxicity worsens then treat as Grade 3 or Grade 4 If toxicity improves to baseline then treat at next scheduled treatment date	Discuss with the study physician Consider Neurology Consult Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine, etc.) Consider systemic steroids prednisone 1-2mg/kg/day or IV equivalent at 0.5 to 1 mg/kg/day If no improvement within 3 to 5 days, consider additional workup and treatment with additional immunosuppressive therapy (eg IVIgG)
	Grade 3	• Hold Study drug/study regimen dose until resolution to Grade ≤1 • Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days.	Discuss with study physician Consult Neurology Consult Consider hospitalization Consider empiric IV corticosteroids (eg, methylprednisolone or IV equivalent) at 1 to 2 mg/kg/day
	Grade 4	Permanently discontinue study drug/study regimen	If no improvement within 3 to 5 days, consider additional workup and treatment with additional immunosuppressants (eg IVIgG) Once stable, gradually taper steroids over ≥4 weeks

Immune-related AE	Severity	Dose Modifications	Toxicity Management
Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis	Any Grade		The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain subjects may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability Subjects should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in subjects with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be considered for plasmapheresis (or IVIgG, as an alternative)
	Grade 1	No dose modification	Discuss with the study physician Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above Consider a neurology consult unless the symptoms are very minor and stable

Immune-related AE	Severity	Dose Modifications	Toxicity Management
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1 Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	Grade 2 : Moderate Discuss with the study physician Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above Obtain a Neurology Consult Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine, etc.) MYASTHENIA GRAVIS Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIgG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. GUILLAIN-BARRE: Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be considered for plasmapharesis (or IVIgG, as an alternative).
	Grade 3	Hold study drug/study regimen dose until resolution to Grade ≤1 Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	For severe or life threatening (Grade 3 or 4) events: Discuss with study physician Recommend hospitalization Monitor symptoms and obtain neurological consult MYASTHENIA GRAVIS
Immune-related AE	**Severity**	**Dose Modifications**	**Toxicity Management**
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1 Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	Grade 2 : Moderate Discuss with the study physician Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above Obtain a Neurology Consult Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine, etc.) MYASTHENIA GRAVIS Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIgG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. GUILLAIN-BARRE: Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be considered for plasmapharesis (or IVIgG, as an alternative).
	Grade 3	Hold study drug/study regimen dose until resolution to Grade ≤1 Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	For severe or life threatening (Grade 3 or 4) events: Discuss with study physician Recommend hospitalization Monitor symptoms and obtain neurological consult MYASTHENIA GRAVIS
Immune-related AE	**Severity**	**Dose Modifications**	**Toxicity Management**
	Grade 4	Permanently discontinue study drug/study regimen	Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. Subjects unable to tolerate steroids may be candidates for treatment with plasmapharesis or IVIgG. If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. GUILLAIN-BARRE: Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be considered for plasmapharesis (or IVIgG, as an alternative).

AChE acetylcholine esterase; AE Adverse event; ALP Alkaline phosphatase; ALT Alanine transaminase; AST Aspartate transaminase; CT Computed Tomography; GI Gastrointestinal; ILD Interstitial Lung Disease; IM Intramuscular; irAE immune-related adverse event; IV Intravenous; IVIgG Intravenous immunoglobulin G; LFT Liver function test; LLN Lower limit of normal; MRI Magnetic resonance imaging; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid stimulating hormone; ULN Upper limit of normal

6.3 Treatment associated nausea and vomiting

Nausea and vomiting may be acute (onset 1–4 hours after infusion) or delayed (begins or persists ≥ 24 hours after infusion). To combat chemotherapy-induced nausea and vomiting, the following algorithm should be used:

a) Nonsteroidal anti-emetics, such as a 5-HT3 antagonist (e.g., ondansetron), should be utilized for first-line management of symptoms
b) If dexamethasone on Day 1 followed by nonsteroidal antiemetics on subsequent days does not sufficiently manage symptoms, dexamethasone 8 mg orally may be administered on Day 2 and/or Day 3.

7.0 Radiation Therapy Details

7.1 Timing of Radiation

If randomized to the consolidative radiation arm, then radiation therapy will begin within 21 days of randomization.

7.2 Radiotherapy Dose and treatment methods

The total dose will be flexible based on the judgment of the treating radiation oncologist to respect normal tissue tolerances. Guidelines for suggested normal tissue constraints are listed below in section 7.6. Meeting these constraints are recommended, but not required for inclusion on the protocol. **Ultimately, dose selection is at the discretion of the treating radiation oncologist.** In general, for lung, liver, axial skeleton, and adrenal tumors, a dose of either 54 Gy in 3 fractions (fxs) or 5000 cGy in 5 fx using SBRT techniques will be appropriate if the GTV measures less than 5 cm. For tumors in these organs that are larger than 5 cm, or where normal tissue constraints are grossly exceeded, a dose of 3000-6000 cGy in 10 – 15 fractions may be more appropriate instead. In the case of an untreated primary with involved mediastinal lymph nodes, fractionated radiotherapy over the course of 30 – 33 treatments with or without concurrent chemotherapy may be necessary at the discretion of the treating physician and this is allowed.

Primary Site (Primary Lung Lesion, Mediastinal/Hilar/Supraclavicular Disease)
Radiation to the primary site can be delivered with 3D conformal therapy, Intensity Modulated Radiation Therapy (IMRT), or proton beam therapy (PBT) at the discretion of the treating radiation oncologist. The radiation dose to the primary site will be determined by the treating physician and based on normal tissue tolerance and institutional standards. Concurrent chemotherapy is permitted.

In addition, it is acceptable to utilize a simultaneous integrated or sequential boost to further increase dose to the CTV or GTV, at the physician's discretion.

Metastatic Sites
Radiation to the metastatic sites can be delivered with 2D/conventional techniques, 3D conformal therapy, IMRT, SRS, or PBT, at the discretion of the treating radiation oncologist. The radiation dose to metastatic sites will be determined by the treating physician and based on normal tissue tolerance and institutional standards.

7.3 Radiation Simulation "Planning" Details

Patients will be simulated on a CT scanner (for fractionated radiotherapy or SRS when MRI contraindicated) or using volumetric MRI (for SRS) and immobilized based on the site of disease. Immobilization devices will be at the discretion of the treating radiation oncologist. Typical immobilization devices include a head and neck mask for metastatic sites in this region, an upper body cradle for disease in the thorax with the arms elevated if possible, and a lower body cradle for disease in the abdomen, pelvis, or lower extremities. A stereotactic head frame or aquaplast mask will be used for SRS. Four-dimensional CT scanning will be utilized at the treating radiation oncologist's discretion, to assess for internal motion. The use of IV contrast will be at the discretion of the treating radiation oncologist. In order to ascertain the extent of tumor motion within the patient (primarily due to respiratory motion), commercially available 4-dimensional (4D) respiratory timed images should be obtained and utilized when possible at the discretion of the treating physician. Breath hold techniques that are reproducible at the time of simulation and treatment will be allowed in lieu of 4D imaging at the discretion of the treating physician.

7.4 Technical Factors

7.4.1 Photon energies of 6 or 10MV will be allowed.
7.4.2 Co-planar or non-coplanar beams will be used.
7.4.3 Correction for the heterogeneity of tissue must be used.

7.5 Definition of Target Volumes

Target volumes will be approved by the treating radiation oncologist, using the information obtained through clinical examination, radiologic images, the simulation planning study, and histologic specimens. When feasible and necessary, the patient's diagnostic images (CT scan, MRI study, or PET/CT imaging) will be fused with the simulation scan to delineate the suggested target volumes below. Gross Tumor Volume (GTV) – All known disease detected by the above methods, including nodal disease. Internal Gross Tumor Volume (IGTV or ITV) – GTV plus internal motion, if 4D scanning is obtained at the time of simulation.Clinical Target Volume (iCTV) – iGTV plus the region at risk for microscopic spread. This target volume will be added at the physician's discretion, given that all patients in this study will have metastatic disease and thus the utility of accounting for microscopic spread is limited. Planning Target Volume (PTV) – iGTV or iCTV plus a margin to account for patient movement and daily setup error. Organ at Risk Volumes (OAR) – Delineation of the pertinent organs at risk, to include the lung, heart, esophagus, spinal cord, kidney, and liver.

7.6 Dosimetric Guidelines/Critical Structure Constraints

Guidelines for suggested normal tissue constraints are listed below for various fractionation regimens. Meeting these constraints are strongly recommended, but not required for inclusion on the protocol. Ultimately, dose selection is at the discretion of the treating radiation oncologist.

In the setting of SBRT treatments (typically defined as 3 – 10 treatments) the external border of the PTV will be covered by a lower isodose surface than typically used in conventional radiotherapy planning, however this may range from 60-100%. This may be decided upon at the discretion of the treating radiation oncologist and per their institutional policies. The prescription dose will be delivered to the margin of the PTV and the maximal dose to any single metastatic lesion or the "hotspot", must exist within the PTV for that lesion.

THREE FRACTIONS

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
Spinal Cord	<0.5 cc	18 Gy (6 Gy/fx)	22 Gy (7.33 Gy/fx)	myelitis
Cauda Equina	<5 cc	21.9 Gy (7.3 Gy/fx)	24 Gy (8 Gy/fx)	neuritis
Sacral Plexus	<3 cc	22.5 Gy (7.5 Gy/fx)	24 Gy (8 Gy/fx)	neuropathy
Esophagus	<5 cc	21 Gy (7 Gy/fx)	27 Gy (9 Gy/fx)	stenosis/fistula
Ipsilateral Brachial Plexus	<3 cc	22.5 Gy (7.5 Gy/fx)	24 Gy (8 Gy/fx)	neuropathy
Heart/Pericardium	<15 cc	24 Gy (8 Gy/fx)	30 Gy (10 Gy/fx)	pericarditis
Great vessels	<10 cc	39 Gy (13 Gy/fx)	45 Gy (15 Gy/fx)	aneurysm
Trachea and Ipsilateral Bronchus	<4 cc	15 Gy (5 Gy/fx)	30 Gy (10 Gy/fx)	stenosis/fistula
Skin	<10 cc	22.5 Gy (7.5 Gy/fx)	24 Gy (8 Gy/fx)	ulceration
Stomach	<10 cc	21 Gy (7 Gy/fx)	24 Gy (8 Gy/fx)	ulceration/fistula
Duodenum	<5 cc	15 Gy (5 Gy/fx)	24 Gy (8 Gy/fx)	ulceration
Jejunum/Ileum	<5 cc	16.2 Gy (5.4 Gy/fx)	27 Gy (9 cGy/fx)	enteritis/obstruction
Colon	<20cc	20.4 Gy (6.8 Gy/fx)	30 Gy (10 Gy/fx)	colitis/fistula
Rectum*	<20cc	20.4 Gy (6.8 Gy/fx)	30 Gy (10 Gy/fx)	proctitis/fistula
Bladder wall	<20 cc	15 Gy (5 Gy/fx)	30 Gy (10 Gy/fx)	cystitis/fistula
Femoral Heads (Right & Left)	<10 cc	21.9 Gy (7.3 Gy/fx)		necrosis
Renal hilum/vascular trunk	<2/3 volume	18.6 Gy (6.2 Gy/fx)		malignant hypertension

FIVE FRACTIONS

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
Spinal Cord	<0.5 cc	22.5 Gy (4.5 Gy/fx)	30 Gy (6 Gy/fx)	myelitis
Cauda Equina	<5 cc	30 Gy (6 Gy/fx)	34 Gy (6.4 Gy/fx)	neuritis
Sacral Plexus	<3 cc	30 Gy (6 Gy/fx)	32 Gy (6.4 Gy/fx)	neuropathy
Esophagus	<5 cc	27.5 Gy (5.5 Gy/fx)	35 Gy (7 Gy/fx)	stenosis/fistula
Ipsilateral Brachial Plexus	<3 cc	30 Gy (6 Gy/fx)	32 Gy (6.4 Gy/fx)	neuropathy
Heart/Pericardium	<15 cc	32 Gy (6.4 Gy/fx)	38 Gy (7.6 Gy/fx)	pericarditis
Great vessels	<10 cc	47 Gy (9.4 Gy/fx)	53 Gy (10.6 Gy/fx)	aneurysm
Trachea and Ipsilateral Bronchus	<4 cc	18 Gy (3.6 Gy/fx)	38 Gy (7.6 Gy/fx)	stenosis/fistula
Skin	<10 cc	30 Gy (6 Gy/fx)	32 Gy (6.4 Gy/fx)	ulceration
Stomach	<10 cc	28 Gy (5.6 Gy/fx)	32 Gy (6.4 Gy/fx)	ulceration/fistula
Duodenum	<5 cc	18 Gy (3.6 Gy/fx)	32 Gy (6.4 Gy/fx)	ulceration
Jejunum/Ileum	<5 cc	19.5 Gy (3.9 Gy/fx)	35 Gy (7 Gy/fx)	enteritis/obstruction
Colon	<20cc	25 Gy (5 Gy/fx)	38 Gy (7.6 Gy/fx)	colitis/fistula
Rectum	<20cc	25 Gy (5 Gy/fx)	38 Gy (7.6 Gy/fx)	proctitis/fistula
Bladder wall	<20 cc	18.3 Gy (3.65Gy/fx)	38 Gy (7.6 Gy/fx)	cystitis/fistula
Femoral Heads (Right & Left)	<10 cc	30 Gy (6 Gy/fx)		necrosis
Renal hilum/vascular trunk	<2/3 volume	23 Gy (4.6 Gy/fx)		malignant hypertension

TEN FRACTIONS

Serial Tissue	Volume	Volume Max (Gy)	Max Point Dose (Gy)	Endpoint (≥Grade 3)
Spinal Cord	<0.5 cc	32 Gy (3.2 Gy/fx)	36 Gy (3.6 Gy/fx)	myelitis
Cauda Equina	<5 cc	36 Gy (3.6 Gy/fx)	40 Gy (4.0 Gy/fx)	neuritis
Sacral Plexus	<3 cc	37 Gy (3.7 Gy/fx)	44 Gy (4.4 Gy/fx)	neuropathy
Esophagus	<5 cc	40 Gy (4 Gy/fx)	50 Gy (5.0 Gy/fx)	stenosis/fistula
Ipsilateral Brachial Plexus	<3 cc	37 Gy (3.7 Gy/fx)	44 Gy (4.4 Gy/fx)	neuropathy
Heart/Pericardium	<15 cc	39 Gy (3.9 Gy/fx)	45 Gy (4.5 Gy/fx)	pericarditis
Great vessels	<10 cc	58 Gy (5.8 Gy/fx)	64 Gy (6.4 Gy/fx)	aneurysm
Trachea and Ipsilateral Bronchus	<4 cc	32 Gy (3.2 Gy/fx)	50 Gy (5.0 Gy/fx)	stenosis/fistula
Skin	<10 cc	38 Gy (3.8 Gy/fx)	45 Gy (4.5 Gy/fx)	ulceration
Stomach	<10 cc	35 Gy (3.5Gy/fx)	45 Gy (4.5 Gy/fx)	ulceration/fistula
Duodenum	<5 cc	32 Gy (3.2 Gy/fx)	45 Gy (4.5 Gy/fx)	ulceration
Jejunum/Ileum	<5 cc	32 Gy (3.2 Gy/fx)	45 Gy (4.5 Gy/fx)	enteritis/obstruction
Colon	<20cc	36 Gy (3.6 Gy/fx)	50 Gy (5.0 Gy/fx)	colitis/fistula
Rectum	<20cc	38 Gy (3.8 Gy/fx)	52 Gy (5.2 Gy/fx)	proctitis/fistula
Bladder wall	<20 cc	32 Gy (3.2 Gy/fx)	54 Gy (5.4 Gy/fx)	cystitis/fistula
Femoral Heads (Right & Left)	<10 cc	38 Gy (3.8 Gy/fx)		necrosis
Renal hilum/vascular trunk	<2/3 volume	35 Gy (3.5 Gy/fx)		malignant hypertension

Spine Radiosurgery (Special Cases)

3 Fraction (prior RT <50 Gy)

OARs	Dose Constraint	Margin	Rank
Cord	13.5Gy	10%	1
Esophagus	15Gy max pt	0 mm	1

Single Fraction

OARs	Dose Constraint	Margin	Rank
Cord	10 Gy	10%	1
Esophagus	15Gy 2cc	0 mm	1
Esophagus	20 Gy 2cc	3 mm	2

Recommended dose constraints for fractionated radiation < 3 Gy per fraction:		
Lung	V20Gy (Rt + Lt lung minus **PTV**)	< 37%
	Mean (Rt + Lt lung minus **GTV**)	< 20 Gy
Esophagus	Mean	< 34 Gy
Heart	V60 Gy	< 33%
	V45 Gy	< 66%
	V 40 Gy	< 100%
Brachial Plexus	Max dose	< 66 Gy
Spinal Cord	Max dose	< 48 Gy

8.0 Study Activities and Patient Assessment

8.1 Study Calendar

Study	Details	Enrollment[1]	Prior to Randomization	1 mo F/U[7]	Every 3 mo For 3 years	Every 6 mo For 2 years
History, Physical		All		PE PS	PE PS	PE PS
PFT's (Spirometry, Lung volume & DLCO)			X[3]			
RT-related Toxicities and Immunotherapy related toxicities	Graded per NCI CTCAE, v. 5.0	X[4]		X	X	X
MRI of Brain **FDG PET/CT** Base of skull to mid-thigh			X[5]			
CT of Chest Abdomen and Pelvis	To include lungs, liver, and adrenal glands	X[2]		X[6]	X[6]	X[6]
Serum or urine pregnancy test	Within 1 week prior to RT (if childbearing potential)	X				
Blood sample collection[8]			X	X		
Response Assessment	Determined by a radiologist utilizing RECIST criteria	X		X	X	X
Appendix H		X				
Appendix C,D			X			
Appendix E				X		
Appendix F				X		
Appendix G, J, L[9]				X	X	X

1. Enrollment and randomization must occur after completion of 4 cycles of standard of care systemic therapy, but no later than 180 days from the first day of cycle 1 of standard of care systemic therapy. Randomization will occur no later than 21 days from time of enrollment.
2. CT Chest Abdomen pelvis demonstrating no evidence of progression per RECIST v1.1, must be performed after completion of 4 cycles of standard of care systemic therapy prior to enrollment Ideal if CT prior to enrollment has IV contrast but not required.
3. PFTs within at least **6 months** of enrollment
4. Baseline evaluation should document any residual toxicity from previous therapies.
5. PET and MRI brain must be completed prior to randomization,
   a. If PET has been performed within 30 days of enrollment, scan does not need to be repeated.
   b. If MRI brain has been performed within 90 days of enrollment, scan does not need to be repeated.
6. Followup CT Chest abdomen pelvis to be performed with IV contrast unless medically contraindicated by renal function or contrast allergy.
   a. For patients randomized to the radiation arm – the first CT will be performed 1 month after the last treatment of radiation per standard of care
   b. For patients randomized to the immunotherapy arm – the first CT will be performed 1 month after the completion of the 2nd cycle of immunotherapy per standard of care
   c. The schedule above is standard of care for imaging followup. Should a patient be enrolled after starting maintenance immunotherapy and after their first 3 month followup scan, then they may be allowed to switch to 6 months interval imaging at 3yrs from the end of chemo-immunotherapy, rather than a full 3 yrs from the date of randomization in accordance with standard of care. At discretion of treating oncologist.
7. Definition of 1 mo. or 30 day followup
   a. For patients randomized to RT, this time point is considered 30 days +/- 14 days from end of all radiation therapy treatments
   b. For patients randomized to immunotherapy alone, this time point is considered 30 days +/- 14 days from the end of the 2nd cycle of on protocol maintenance immunotherapy
8. Two tubes of whole blood may be collected at time of registration or any time prior to initiating any protocol directed therapy and at the 1 month follow up +/- 2 weeks.
9. If patients progress and are not eligible for randomization, or if they progress at any point on the study, they are only followed w appendix L for survival after the point of progression

FOLLOWUP VISITS AND CT SCANS HAVE A FLEXIBILITY WINDOW OF +/- 8 WEEKS AROUND THE TIME POINT LISTED ON THE STUDY CALENDAR

8.2 Study Activities – Required Evaluations

8.2.1 A medical history, physical examination, weight, NCI comorbidities, and assessment of ECOG performance status within 12 weeks of enrollment. ECOG status will be documented at time of the radiation oncology consult in the electronic medical record.

8.2.2 A CT chest abdomen pelvis demonstrating no evidence of progression per RECIST v1.1 that has been performed after completion of 4 cycles of chemo-immunotherapy but no later than 180 days from the first day of chemo-immunotherapy.

8.2.3 A PET/CT and MRI brain will be performed, either prior to randomization or a PET that is within 30 days of enrollment, or MRI brain within 90 days of enrollment may be used for purposes of randomization.

8.2.4 Biopsy or cytology demonstrating a diagnosis of non-small cell lung carcinoma.

8.2.5 Two tubes of whole blood will be collected via routine blood draw and saved for future exploratory biomarker studies as listed on the study calendar, at time of registration and at the 1 month follow up +/- 2 weeks. For radiation patients this is 1 month after the last treatment of radiation. For immunotherapy only patients, this is 1 month after the second dose of maintenance immunotherapy on study.

8.2.6 Serum or urine pregnancy test within 1 week of RT in women of child bearing potential.

8.3 Data Management Procedures

Data should be submitted to Sharon Averill by fax or email:
Fax #: (336) 713-37748
Email: saverill@wakehealth.edu

8.4 During Follow Up

8.4.1 The dates of follow up and protocol related assessments are defined as below. Follow up and protocol directed assessments must be performed +/- 8 weeks from each specified FU time point.

For patients randomized to radiation:
Patients will undergo CT imaging of chest/abdomen/pelvis at 1 month after the last treatment of radiation is completed. Subsequently, they will undergo CT imaging of chest/abdomen/pelvis every 3 months for 3 years, then every 6 months for 2 years per standard of care.

For patients randomized to continue maintenance immunotherapy:
alone, they will undergo CT imaging of chest/abdomen/pelvis at 1 month after the 2nd cycle of protocol directed maintenance immunotherapy has been delivered. Subsequently, they will undergo CT imaging of chest/abdomen/pelvis every 3 months for 3 years, then every 6 months for 2 years per standard of care.

Should a patient be enrolled after starting maintenance immunotherapy and after their first 3 month followup scan, then they may be allowed to

switch to 6 months interval imaging at 3yrs from the end of chemo-immunotherapy, rather than a full 3 yrs from the date of randomization in accordance with standard of care. At discretion of treating oncologist.

If a patient, has suspicion of progression but requires closer interval followup than 3 months or additional imaging, this is allowable at the discretion of the treating physician. If ultimately, they are deemed to not have progressive disease, they would then resume the schedule listed in the study calendar above.

8.4.2 Patients who progress on or after protocol directed therapy will be followed for survival only as per Appendix L without further protocol follow up requirements. This includes progression of the protocol treated tumors, non-protocol treated tumors and the development of new metastatic disease. Tumor progression will be determined by RECIST criteria.

8.5 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for 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, or
- General or specific changes in the patient's condition render the patient Unacceptable for further treatment in the judgment of the investigator.

If a patient is unable to complete a total of 2 years of maintenance Immunotherapy due to toxicity, declining therapy, or intercurrent illness, or any other reason, they will continued to be followed on study until a progression event, death, or withdrawal from study.

8.6 Duration of Follow Up

All patients should be followed for study endpoints for a minimum of six months. Afterwards patients without progression will be followed as listed in the study calendar.

8.7 Response determination:

The use of international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee is required for response assessment. During follow up, PET imaging can be used to assist in adjudicating decisions regarding local failure as the SBRT process can in itself result in increases in the imaging abnormality on either a temporary or permanent but stable basis due to radiotherapy treatment effects such as tissue fibrosis.

8.8 Regional failure:

New nodal disease ≥ 1cm in size within the lung, hilum, or mediastinum. Equivocal nodes should be assessed with FDG PET or biopsy

8.9 Distant disease:

Appearance of distant cancer deposits consistent with metastatic spread. PET-CT or biopsy encouraged but not required.

8.10 Survival Definitions

Progression-Free Survival
Progression-Free Survival is defined as the duration from the start of first line standard of care systemic therapy to the time of progression, death, or date of last contact; those lost to follow-up will be censored.

Overall Survival
Overall Survival is defined as the duration from the start of first line standard of care systemic therapy to the date of death or date of last contact; those lost to follow-up will be censored.

9.0 Adverse Events List and Reporting Requirements

9.1 Adverse Event List for Radiotherapy

<table>
<tr><td colspan="2">Risks and side effects related to the SBRT</td></tr>
<tr><td>More common (>10% of patients):
• Damage to surrounding normal lung and/or collapse of a portion of treated lung
• Cough
• Increased phlegm production
• Changes in the lungs as the tumor shrinks; these changes will be recognized by your radiation doctor on your x-rays or scans as expected "scarring" that is developing. In most patients, no noticeable symptoms will result from this lung damage.
• Fatigue
• Redness of irritation of the skin in the treatment area
• Hair loss in the treatment area
• Some soreness of the ribs with an increased risk of rib fracture.</td><td>Less common (<10% of patients):
• Difficulty breathing, increased shortness of breath
• Fever
• Fracture or compression of the treated bones of the spine, which can result in pain and may need surgical treatment</td></tr>
<tr><td colspan="2">Rare (<1% of patients)
Some patients can have the following symptoms associated with lung scarring:
• Shortness of breath, cough, fever, and/or pain in the chest wall.
• These patients may require oxygen for a short time or permanently.
• Lung damage can be life threatening.
• Pericarditis
• Damage to the heart muscle, which can cause heart attack, heart failure, or death
• Damage to the spinal cord, which can cause numbness, weakness, tingling, and/or inability to use the arms and/or legs
• Damage to the esophagus, which can cause problems with swallowing
• Damage to the stomach or bowel which can lead to ulceration or perforation with a risk of infection and death.
• Damage to the large blood vessels surrounding the heart, which could cause coughing up of blood and possibly death
• Severe pain or skin damage leading to an open wound.
• The following are likely with SBRT to the bones of the spine in the neck:
• Inflammation of the lining of the mouth and esophagus
• Inflammation of the vocal cords, leading to hoarseness or loss of voice</td></tr>
<tr><td colspan="2">Risks and side effects related to non-SBRT or more “fractionated” radiation to the chest:</td></tr>
<tr><td>More common (>10% of patients):
• Temporary, difficulty, pain, or a burning sensation when swallowing
• Temporary fatigue
• Tanning, redness of the skin, and hair loss within the treatment area,
• Skin in the treatment area may remain permanently dry chest hair may not grow back
• Decrease in blood counts while undergoing treatment causing bleeding, and bruising
• Cough and some difficulty in breathing due to lung damage</td><td>Less common (<10% of patients):
• Narrowing of the esophagus causing difficulty swallowing (rarely requiring internal dilation or a feeding tube)</td></tr>
<tr><td colspan="2">Rare but serious (late) (<1% of patients)
• Pericarditis – irritation of the heart sac causing a rapid heart rate, or chest pain.
• Myocarditis – irritation of the heart muscle causing shortness of breath, chest pain, or permanent heart muscle damage
• Transverse myelitis – irritation of the spinal cord causing weakness or paralysis
• Bleeding from the airway
• Narrowing of the airway causing shortness of breath</td></tr>
</table>

9.2 Adverse Event List for Pembrolizumab

<table>
<tr><td colspan="2">In general, immunotherapy has a risk (>10%) of developing autoimmune complication(s), such as inflammation of the thyroid (hypothyroidism or hyperthyroidism), colon (colitis), lungs (pneumonitis), liver (hepatitis), or pituitary gland (hypophysitis), which can lead to the symptoms noted below. Autoimmune complications can potentially be life-threatening or permanent. In some cases they may be reversible with urgent administration of steroids and/or other immunosuppressant(s).</td></tr>
<tr><td>More common (>10% of patients):
• constipation
• depressed mood
• diarrhea
• dry skin and hair
• feeling cold
• flushing
• hair loss
• hoarseness or husky voice</td><td>Less common (<10% of patients):
• general feeling of discomfort or illness
• fever
• nervousness
• pain symptoms
• sensitivity to heat or cold
• slowed heartbeat
• stomach cramps
• sweating</td></tr>
</table>

• joint or muscle pain • muscle cramps or stiffness • skin rash or itching • unusual tiredness or weakness • stuffy or runny nose	• swelling of the face, feet, or lower legs • tenderness • cough or thickening of bronchial secretions • trouble breathing, chest pain, or chest tightness • trouble sleeping • upper right abdominal or stomach pain • watery or bloody diarrhea • weight change • yellow eyes and skin
Rare (<1% of patients) • bloating • dark, bloody, or cloudy urine • blurred vision or other change in vision • darkening of the skin • dizziness • drowsiness • eye pain • fainting • fast heartbeat • indigestion • loss of appetite • mental depression • nausea or vomiting • pains in the stomach, side, or abdomen, possibly radiating to the back • redness or irritation of the eye • sensitivity of the eye to light • skin blistering, peeling, loosening, or tearing	

9.3 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 appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

'Expectedness': AEs can be 'Unexpected' or 'Expected' (see Appendix D) for expedited reporting purposes only.

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.

9.4 DSMC SAE Reporting Requirements

The Data and Safety Monitoring Committee (DSMC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix D. DSMC currently requires that all unexpected 4 and all grade 5 SAEs on these trials be reported to them for review. All WFBCCC Clinical Protocol and Data Management (CPDM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for DSMC reporting are responsible for informing a clinical member of the DSMC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

9.5 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other

interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The principal investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The principal investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

9.6 Study Management

9.6.1 Personnel from the Comprehensive Cancer Center at the Wake Forest University Health Sciences will monitor the trial. All case report forms and source documentation must be sent to Wake Forest University Health Sciences for review by the Clinical Research Associates to assure proper conduct of the trial and proper collection of the data. Queries will be issued to the site by WFUHS which should be addressed in a timely manner.

9.6.2 Required Documentation

9.6.2.1 Before the study can be initiated at any site, the following documentation must be provided to the Clinical Research Management Office of Wake Forest University Health Sciences.

9.6.2.2 A copy of the official IRB approval letter for the protocol and informed consent

9.6.2.3 CVs and medical licensure for the principal investigator and any associate investigators who will be involved in the study

9.6.2.4 A copy of the IRB-approved consent form

9.6.2.5 CLIA Laboratory certification and institution lab normal values

9.6.3 Amendments to the Protocol

9.6.3.1 Should amendments to the protocol be required, the amendments will be originated and documented by the principal investigator at WFUHS. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

9.6.4 Study Monitoring / Auditing Procedure

9.6.4.1 Personnel from CCCWFU will monitor periodically to assure proper conduct of the trial and proper collection of the data. The investigator at the site will allow the monitor to review all source documents used in the preparation of the case reports. The Protocol office at CCCWFU can be reached at 336- 713-6513. The Affiliate site will be audited via scanning all protocol related documents (charts, regulatory, drug logs etc.) and emailing them to the study team at the designated time which will be determined by the principal investigator and communicated to the site by letter. The study team will consist of the principal investigator, study staff and other designated individuals as needed. The site will be given at least 4 weeks' notice. The affiliate site must have persons(s) available via phone during the audit process if questions arise.

9.6.4.2 The overall study principal investigator will review with the affiliate principal investigator the scoring of patient response or progression on a periodic basis once accrual has commenced at that site either through site visit or electronic means.

9.6.5 Record Retention

9.6.5.1 Study documentation includes all case report forms, data correction forms or queries, source documents, correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

9.6.5.2 Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinic research study.

9.6.5.3 Regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. Study documents should be kept on file until six years after the completion and final study report.

9.6.6 Obligations

9.6.6.1 The principal investigator is responsible for the conduct of the clinical trial at the site in accordance with title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The principal investigator is responsible for personally overseeing the treatment of all study patients. The principal investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol all regulations and guideline regarding clinical trials both during and after study completion.

9.6.6.2 The principal investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report forms. Periodically, monitoring contacts will be made and the principal investigator will provide access to his/her records for verification of proper data entry. At the completion of

the study, all case reports forms will be reviewed by the principal investigator.

10.0 Data Management

If technically feasible at the time that this study begins, we will allow outside institutions remote access to our Wake Forest OnCore program for direct data entry and randomization. Otherwise, all institutions will provide registration information to the Wake Forest protocol registrar and will be assigned randomization through the Wake Forest OnCore program. All other data collected as per the appendices below will be provided directly to Sharon Averill by fax or email: [redacted]

Informed consent document	EPIC
Protocol registration form	WISER/OnCore
Adverse Events Log	WISER/OnCore
30-day Treatment Follow-up	WISER/OnCore
Off-Study Form	WISER/OnCore
Treatment Response Evaluation Form	WISER/OnCore
Evaluation of Best Overall Response	WISER/OnCore
NCI Comorbidity Index	WISER/OnCore
Radiotherapy Technical Parameters	WISER/OnCore
Patient Baseline Characteristics	WISER/OnCore
Pulmonary Function Testing	WISER/OnCore
Protocol Deviation Form	WISER/OnCore
Follow-up Collection Form	WISER/OnCore
Study Incomplete/Withdrawal Form	WISER/OnCore
Withdrawal of Consent	WISER/OnCore
Survival Form	WISER/OnCore
Off-Treatment Form	WISER/OnCore

11.0 Pharmaceutical Information

11.1 Pharmaceutical Accountability

Pembrolizumab is commercially available

11.2 Pembrolizumab FDA pharmaceutical information (Keytruda)

Product description:
Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

KEYTRUDA for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-use vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5.

KEYTRUDA injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine

(1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

Solution preparation:
Reconstitution of KEYTRUDA for Injection (Lyophilized Powder) • 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 prior to administration. The solution is clear to slightly opalescent, colorless to slightly yellow. Discard the vial if visible particles are observed.

Dilute KEYTRUDA injection (solution) or reconstituted lyophilized powder prior to intravenous administration.

Withdraw the required volume from the vial(s) of KEYTRUDA and transfer into an intravenous (IV) bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Mix diluted solution by gentle inversion. The final concentration of the diluted solution should be between 1 mg/mL to 10 mg/mL.

Discard any unused portion left in the vial

Storage requirements:

Do not freeze. The product does not contain a preservative. Store the reconstituted and diluted solution from the KEYTRUDA 50 mg 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 infusion solution in the IV bag, 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 KEYTRUDA 100 mg/4 mL vial either:
• At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the infusion solution in the IV bag, 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**.**

Stability:
Include the stability of the original dosage form, reconstituted solution, and final diluted product, as applicable

Route of administration:
Administer infusion solution intravenously over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, 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.

Disposal:
Dispose of per the Wake Forest waste stream

12.0 Laboratory Correlative Studies

12.1 Future exploratory blood biomarker studies

Wake Forest (the sponsor) will conduct future biomedical research on blood and tumor tissue samples collected during this clinical trial. This research may include genetic analysis to be used for exploratory biomarker testing or analysis of circulating tumor cell DNA.

Samples will be stored in the Wake Forest biorepository

Common side effects of a biopsy or blood draw are a small amount of bleeding at the time of the procedure, pain at the biopsy site, which can be treated with regular pain medications, and bruising. Rarely, an infection can occur. In the event of recurrence, an additional biopsy to confirm the pathology of disease is strongly recommended. In the event that a biopsy is performed, as part of standard of care, a portion of the tumor sample will be sent to the Wake Forest Tumor Bank.

Submission of blood and tissue samples for future biomedical research is a required component of this protocol.

Two tubes of whole blood will be collected via routine blood draw and saved for future exploratory biomarker studies, These may be collected at time of registration or any time prior to initiating any protocol directed therapy and at the 1 month follow up +/- 2 weeks. Patients would routinely have standard bloodwork performed at these time points off protocol and this will not require extra visits.

13.0 Statistical Considerations

13.1 Power and Sample size

Based on previously published research and clinical experience, the predicted median progression-free survival (PFS) of patients treated with consolidation immunotherapy without SBRT is roughly 8 months[24] measured from date of first chemo-immunotherapy treatment. We estimate that, considering this 8 month median survival in the “control” arm, with our projected sample size of 112 patients (randomized 2:1 to SBRT + immunotherapy vs immunotherapy alone), and considering a two-sided alpha of 0.05 and power of 0.80, that we will be able to detect a median survival of approximately 15 months from start of chemo-immunotherapy in the SBRT + immunotherapy arm. This calculation assumes a 54 month accrual period and a 5 year total follow-up period. This difference in median survivals (8 months vs 15 months) corresponds to a hazard ratio of 0.53. Randomization will be stratified by number of metastatic sites (1-3, 4-6, or 7-8.)

Given the design of this trial, not all enrolled patients will be eligible for subsequent randomization. We estimate that ~10% may have evidence of progression of disease on restaging with PET/MRI. Such patients would remain on study, but will only be followed for survival. Given this potential for a 10% decrease in randomizable patients, the final number needed to enroll is 125 , in order to randomize 112.

13.2 Estimated Accrual Rate

We estimate that we will accrue roughly 1 - 4 patients per month.

13.3 Estimated Study Length

We estimate approximately 4- 5 years for total enrollment. Data will be collected until patient death or for a period of 5 years whichever occurs first.

13.4 Interim Analysis Plan

We have no planned formal interim analyses; however when we reach 50% of our planned accrual if 25% or greater have reached G3 or higher pneumonitis we will halt the study.

14.0 Data Analysis

14.1 Analysis of Primary Objective

Actuarial progression-free survival will be determined using the product-limit method of Kaplan and Meier. We will compare unadjusted median PFS between the 2 arms using a log-rank test. We will also use a proportional hazards model to compare progression-free survival between the two groups, adjusting for key covariates such as age, performance (ECOG) status, response to initial systemic therapy vs stable disease, the presence or absence of brain metastases, PD-L1 expression (< 1% vs > 50%), tumor histology (adenocarcinoma vs non-adenocarcinoma), number of disease sites treated (1-3 sites vs 4-6 sites vs 7-8 sites) and length of time between date of first chemotherapy-immunotherapy treatment and randomization date..

14.2 Analysis of Secondary Objective

The proportions with local control (LC) of SBRT-treated lesions, and overall survival (OS) parameter estimates, both secondary outcomes, will be first examined in simple univariate and bivariate analyses (e.g., means, medians, 85% confidence intervals around key parameter estimates.). LC will be assessed only in patients with at least 4-months of radiographic follow -up. The reason for specifying a minimum of 4 months follow-up to score LC was to avoid uncertainty associated with early transient radiographic changes within the high dose region; patients who died without a minimum of 4 months post-SBRT imaging study follow-up are not considered evaluable for LC but are evaluable for PFS and OS.[34-37]

Data will be collected for planned subset analysis of in-field local control of irradiated sites, progression-free and overall survival according to (1) tumor histology (adenocarcinoma vs other histology) and (2) response to initial chemotherapy (response vs stable disease).

In all randomized patients, time to progression at known sites of disease, as well as time to development of new disease sites, and number of new disease sites will be collected.

Overall survival comparison between the two randomized groups will be assessed with methods analogous to PFS described above in 13.1. Additionally, we will also examine OS in the group of patients who were enrolled but not randomized; however, we will not conduct statistical comparisons of this group with either randomized group.

All safety measures, including acute and late toxicity, will be reported using descriptive statistics (mean, median, SD, proportions, and 95% confidence intervals). This will include calculating frequency/risk of adverse events by treatment site. Potential toxicities reported would include pneumonitis, esophagitis, chest wall pain, dermatologic toxicity, renal dysfunction, gastrointestinal toxicity including nausea, vomiting, and diarrhea, hepatotoxicity, and abdominal pain. These toxicities would be assessed according to site of irradiation by the treating physician and graded as per CTCAE 5.

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Appendix A: Enrollment Eligibility Checklist

IRB Protocol No.		**WFBCCC Protocol No.**	62718
Study Title: A Randomized Trial of Consolidative Immunotherapy with vs without Thoracic Radiotherapy and / or Stereotactic Body Radiation Therapy (SBRT) after First-line Systemic Therapy for Metastatic NSCLC			
Principal Investigator: Michael Farris, M.D.			

ENROLLMENT

- Patients are eligible for enrollment if they have metastatic NSCLC and have undergone at least 4 cycles of upfront standard of care systemic therapy. Patients must have a CT chest abdomen pelvis (ideally with IV contrast) performed after the point of completion of 4 cycles of standard of care systemic therapy, but no later than 180 days from the first day of systemic therapy. This CT scan must be completed within 180 days of the first day of systemic therapy, and must demonstrate no evidence of disease progression per RECIST v1.1.

- Patients may start their standard of care maintenance immunotherapy at the discretion of their treating medical oncologist prior to enrollment. Patients must be enrolled AND randomized no later than 180 days from the first day of cycle 1 of standard of care systemic therapy. The first day of cycle 1 of systemic therapy is considered day # 1. At most, an additional 179 days may elapse from this point to remain eligible for inclusion on this study.

RANDOMIZATION

- Once enrolled, patients will have a restaging PET/MRI brain *(exceptions below)*
  If restaging scans demonstrate ≤ eight sites of non-progressive active residual disease, then patients are eligible for randomization. If restaging scans demonstrate progression of disease, then these patients will not be eligible for randomization, but will be followed by their primary medical oncologist or radiation oncologist every 3 months for overall survival only.

  ***** *If a PET has been performed within **30** days of enrollment with no evidence of progression per RECIST v1.1, then this scan may be used and does not have to be repeated prior to randomization*

  ***** *If an MRI brain has been performed within **90** days of enrollment with no evidence of progression per RECIST v1.1, then this scan may be used and does not have to be repeated prior to randomization*

- Randomization should occur within 21 days of enrollment.
- Once randomized, protocol directed therapy should occur within 21 days from randomization (ie. start of consolidative RT or resumption of maintenance immunotherapy)

If randomized to consolidative radiation therapy then maintenance immunotherapy:
Maintenance immunotherapy may NOT be delivered concurrently with consolidative radiation. Concurrently is defined as on the same day of any radiation treatment or on any day between the first and last treatment of radiation. Resumption of maintenance immunotherapy after completion of radiation therapy is at the discretion of the treating medical oncologist. They may resume maintenance immunotherapy as early as 24 hrs after the last radiation treatment, but resumption should be no later than 8 weeks from the last radiation treatment. If treatment related toxicities prohibit administration of maintenance immunotherapy, then restarting this therapy is at the discretion of the treating medical oncologist. In such cases, patients will remain on study until they experience progression or death. If they experience progression, patients will be followed for overall survival only per appendix L past the point of progression.

If randomized to continued maintenance immunotherapy alone:
Patients will begin or resume maintenance immunotherapy no later than 21 days following randomization.

Inclusion Criteria (as outlined in study protocol section 3.0) Must answer yes to all questions below, otherwise patient is not eligible	**Criterion is met**	**Criterion is NOT met**	**Source Used to Confirm * Document dates and lab results**
18 years or older	☐	☐	
Performance Status 0-2 (ECOG) at time of consult with radiation oncology	☐	☐	
Pathologically proven NSCLC with evidence of metastatic disease	☐	☐	
Must have received 4 cycles of standard of care systemic therapy, with a CT chest abdomen pelvis that was performed after completion of these 4 cycles and demonstrates no evidence of progression per RECIST v1.1	☐	☐	
To be eligible for enrollment and randomization, patients must be within 180 days from their first dose of systemic therapy. Cycle 1 day 1 is defined as day 1. If enrolled on day 180, the patient would need to be randomized the same day.	☐	☐	
Persistent active disease must be amenable to radiation treatment per the treating radiation oncologist, and patients must have at least one residual site of disease which can be identified by CT or PET/CT and targeted with radiation.	☐	☐	
Patients who previously had earlier stage NSCLC treated definitively and have now developed new distant disease, are eligible for inclusion if they have undergone at least 4 cycles of chemo-immunotherapy for their metastatic recurrence, and they meet all criteria above.	☐	☐	
There are no strict size or tumor number limitations in a given organ (lung, liver, abdomen pelvis, or spine). This is at the discretion of the treating radiation oncologist.	☐	☐	
Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm ***
More than 180 days has elapsed since day 1 of cycle 1 of systemic therapy.	□	□	
Pregnant or lactating women	□	□	
The patient has received treatment for other carcinomas within the last three years (Except for cured non-melanoma skin cancer, low-risk prostate cancer, T1/T2 glottic cancer, stage 0 or stage I breast cancer, non-invasive bladder cancer, or treated in-situ cervical cancer). Prior lung cancer diagnosis now with oligometastatic recurrence is not an exclusion criteria.	□	□	
Patients with major activating mutations in EGFR (del19, L858R, and T790M) or ROS 1 or ALK gene rearrangements are excluded	□	□	
Patient eligibility for immunotherapy is at the discretion of the treating medical oncologist. Immunologic conditions including Lupus, rheumatoid arthritis, psoriasis or other conditions requiring immune suppression are **NOT** strict exclusions			

This subject is ☐ eligible / ☐ ineligible for enrollment in this study.

OnCore Assigned PID: ___ ___ ___ ___ ___ ___ ___ ___
Signature of research professional confirming eligibility: _____
Date: ___ ___ / ___ ___ / ___ ___ (MM/DD/YYYY)

Signature of Treating Physician: _____
Date: ___ ___ / ___ ___ / ___ ___ (MM/DD/YYYY)

Signature of Principal Investigator**: _____
Date: ___ ___ / ___ ___ / ___ ___ (MM/DD/YYYY)

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: "Pathology report, 01/01/14" or "Clinic note, 01/01/14" **Principal Investigator signature can be obtained following registration if needed

Appendix B: Protocol Registration

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB __ __/__ __/__ __ (MM/DD/YYYY)

ZIPCODE: ___ ___ ___ ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic ☐ Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐ BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2

Primary Diagnosis: _____

Date of Diagnosis: __ __/__ __/__ __ (MM/DD/YYYY)

Performance Status: ___ ECOG

PROTOCOL INFORMATION

Date of Registration: __ __/__ __/__ __ (MM/DD/YYYY)

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by OnCore): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday. Compete the eligibility checklist in WISER and then give the completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-713-6772 or registra@wakehealth.edu, respectively.

Appendix C: Eligibility for Randomization

Randomize within 21 days of enrollment

OnCore Assigned PID: ___ ___ ___ ___ ___ ___ ___ ___

This subject is ☐ eligible / ☐ ineligible for randomization in this study.

Signature of research professional confirming eligibility for randomization : _____
Date: __ __/__ __/__ __ (MM/DD/YYYY)

Signature of Treating Physician: _____
Date: __ __/__ __/__ __ (MM/DD/YYYY)
Signature of Principal Investigator**: _____
Date: __ __/__ __/__ __ (MM/DD/YYYY)

Appendix D: Numbering Sites of Disease

Completed prior to randomization by the treating radiation oncologist

How many total active sites of persistent disease are present after PET/MRI restaging _____

Location and number of extracranial disease sites to be treated
_____

CNS lesions (Y/N)_____ managed w resection/SRS _____ (Y/N)
Signature _____ Date_____

Appendix E: Radiotherapy Technical Parameters

Radiotherapy Technical Parameters/Data Collection Form completed by the treating radiation oncologist
The following information will be collected for **EACH** extra cranial tumor treated with radiation

Tumor Location (side/lobe if applicable):		
Dose Prescribed (Gy):		
Total number of fractions:		
Treatment volumes (cm^3):	**GTV:**	**PTV:**
% PTV receiving prescribed dose:		
Volume of isodose for 50% prescription dose:		
Volume of isodose for 100% prescription dose:		
Was the plan 3D, VMAT, or IMRT?		

Appendix F: 30-day Treatment Follow-up Form

Definition of 1 mo. or 30 day followup

1. For patients randomized to RT, this time point is considered 30 days +/- 14 days from end of all radiation therapy treatments
2. For patients randomized to immunotherapy alone, this time point is considered 30 days +/- 14 days from the end of the 2nd cycle of on protocol maintenance immunotherapy

Study Number: __ __ __ __ __ PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Michael Farris M.D. Date: __ __/__ __/__ __ (MM/DD/YYYY)

Instructions: Complete this form to follow-up with patients for adverse events.

Name of Person Competing form_____

Did the subject have any adverse events in the last 30 days? Yes ☐ No ☐
If yes, please report on AE log in WISER
(Note*: If an SAE occurs in this period, report the event as required in Appendix S):

Was the subject removed from the study? Yes ☐ No ☐
If yes, complete the Off-Study Form

Did the subject withdraw from the study? Yes ☐ No ☐
If Yes, complete the Withdrawal of Consent Form

Appendix G: Treatment Response Evaluation

Study Number: __ __ __ __ __ PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Michael Farris, M.D. ___ __/__ __/__ __ (MM/DD/YYYY)

Study Visit:

☐ After first-line systemic therapy
☐ Follow-Up: __ __/__ __/__ __ (MM/DD/YYYY)
☐ Other visit: (please specify) _____

Date of Scan: __ __/__ __/__ __ (MM/DD/YYYY)

Imaging Modality: ☐ CT ☐ PET/CT ☐ MRI ☐ Other_____

Evaluation of Target Lesions

☐ Complete Response (CR)

☐ Partial Response (PR)

☐ Progressive Disease (PD):

☐ Stable Disease (SD)

☐ NE

Evaluation of Non-Target Lesions

☐ Complete Response (CR)

☐ Non-CR/Non-PD

☐ Progressive Disease (PD):

☐ NE

Overall Response this Visit

☐ Complete Response (CR)

☐ Partial Response (PR)

☐ Progressive Disease (PD): Date of progression ___ ___ /___ ___ /___ ___

☐ Stable Disease

☐ NE

Treating Physician Signature: _____ Date: ___ ___ /___ ___ /___ ___

PI Signature: _____ Date: ___ ___ /___ ___ /___ ___

Appendix H: NCI Comorbidity

Instructions: Fill this form out to record comorbidities.

1. Medical Comorbidities
   - ☐ Acute Myocardial Infarction (1)
   - ☐ History of Myocardial Infarction (1)
   - ☐ Congestive Heart Failure (1)
   - ☐ Peripheral Vascular Disease (1)
   - ☐ Cerebrovascular Disease (1)
   - ☐ Chronic Obstructive Pulmonary Disease (COPD) (1)
   - ☐ Dementia (1)
   - ☐ Paralysis (Hemiplegia or Paraplegia) (2)
   - ☐ Diabetes (1)
   - ☐ Diabetes with Complications (2)
   - ☐ Renal Disease (2)
   - ☐ Mild Liver Disease (1)
   - ☐ Moderate/Severe Liver Disease (3)
   - ☐ Peptic Ulcer Disease (1)
   - ☐ Rheumatologic Disease (1)
   - ☐ AIDS (6)

   (Additional):_____

Appendix I: Pulmonary Function Testing

PID Number _____	DOB _____
1. Date of Test	/ /
5. Forced Vital Capacity (FVC): _____Liters	
6. Observed Forced Expiratory Volume in first second (FEV_1): _____Liters	
7. Predicted FEV_1: _____Liters	
8. % Predicted FEV_1: _____%	
9. DLCO/VA: _____%	

Appendix J: Follow-up Collection Form

PID Number _____ DOB _____

1. Date of follow-up __ __/__ __/__ __ (MM/DD/YYYY)

2. Visit Interval

Interval from date of day 1 of cycle 1 of chemo immunotherapy: _____days

3. Were there any delayed patient complications related to the radiotherapy procedure since the last visit? Y*/N

If yes, complete AE form

4. Since the last visit have there been any additional chemotherapy? Y*/N

If yes, specify agents used:

5. ECOG Performance Status _____

6. Weight (lbs) _____

7. Height (inches) _____

NEW THERAPIES

8. Is the patient receiving any new therapies for lung cancer? Y*/N

If yes, what therapies specifically _____

Appendix K: Progression of Disease

Has there been progression of disease _____ (Y/N)

Date of progression: __ __/__ __/__ __ (MM/DD/YYYY)

For patients randomized to the radiation arm:
Is progression inside or outside prior RT field (defined by 50% Isodose line) _____
Organ site of progression? _____
For patients randomized to the immunotherapy alone arm:
Is progression at a site of disease that was present prior to first line chemo-immunotherapy _____

Appendix L: Survival Form

Instructions: Fill this form out at protocol indicated survival assessments

1. Last known Survival Status:
   ☐ Alive
   ☐ Dead
   ☐ Lost to Follow-up: Date of last contact __ __/__ __/__ __ (MM/DD/YYYY)

2. Expired Date __ __/__ __/__ __ (MM/DD/YYYY)
   Is this an approximate date? ☐ Yes ☐ No

3. Last known Alive Date __ __/__ __/__ __ (MM/DD/YYYY)

4. Survival Status source: _____
   Instructions: Source can be EMR, obituary, family member etc. Phone call with patient
   Add to comments in WISER follow-up section

5. Comment:_____

Appendix M: Study Withdrawal

PID Number _____ DOB _____

1. Date Study Treatment Stopped or Withdrawal __ __/__ __/__ __ (MM/DD/YYYY)

2. Please check **ONE** of the following:

   ☐ Patient did not complete radiation therapy

   ☐ Patient withdrew or discontinued early

3. If withdrawn or discontinued early, indicate **ONE** primary below:

   ☐ Patient registered but not treated: Specify reason: _____

   ☐ Radiotherapy attempted, but not completed

   ☐ Progression during treatment

   ☐ Unanticipated Adverse Event/Serious Adverse Event

   ☐ Patient Died: Date of Death __ __/__ __/__ __ (MM/DD/YYYY) ☐ Unknown date

   Specify Cause of Death: _____ ☐ Unknown cause

   ☐ Lost to follow-up: Date of Last Contact __ __/__ __/__ __ (MM/DD/YYYY)

   ☐ Unknown : Date Last Known to be Alive __ __/__ __/__ __ (MM/DD/YYYY)

   ☐ Patient no longer willing to participate in study

Appendix N: Withdrawal of Consent

Withdrawal of consent for the intervention and medical record use

I withdraw consent for further study intervention/treatment.
☐Yes ☐No Initials: _____

I withdraw from further research activities (surveys, questionnaires, research assessments and other non-invasive research activities).
☐Yes ☐No Initials: _____

I withdraw my consent to allow the further collection of research-related information from my medical record to be used in this research.
☐Yes ☐No Initials: _____

Specimen collection/use withdrawal (no research specimen collection, skip section)
I withdraw my consent for any use of my specimen for this current research.
☐Yes ☐ No Initials: _____

I withdraw my consent for any use of my specimen for future research.
☐Yes ☐No Initials: _____

I acknowledge that any data or deidentified materials that have already been created from my specimen may still be used for research.

Initials: _____

Patient signature: _____ Date __ __/__ __/__ __ (MM/DD/YYYY)

Investigator signature: _____ Date __ __/__ __/__ __ (MM/DD/YYYY)

Appendix O: Off-Study Form

Study Number: __ __ __ __ __ PID: ___ ___ ___ ___ ___ ___ ___ ___

Investigator: Michael Farris M.D. Date __ __/__ __/__ __ (MM/DD/YYYY)

Instructions: Complete this form if the patient has completed or is removed from the study.

Name of Person Competing form_____

Off study date __ __/__ __/__ __ (MM/DD/YYYY)
Reason:
☐Adverse Event/Side Effects/Complications;
☐Death; (if death fill out Survival Form)
☐Enrolling Physician Decision;
☐Other;
☐Patient lost to follow-up; Date of last contact __ __/__ __/__ __ (MM/DD/YYYY)
☐Patient refused follow-up;
☐Protocol-defined follow-up completed

Explain_____
___

Did the patient withdraw consent to participate in the study? Yes ☐ No ☐
(If Yes, have the patient fill out the Withdrawal of Consent form)

Appendix P: Protocol Deviation Form

PID Number _____ DOB _____
Deviation Date: __ __/__ __/__ __ (MM/DD/YYYY)

Interval from date of day 1 of cycle 1 of chemo immunotherapy: _____days

Deviation
☐ Patient does not meet inclusion/exclusion criteria: **Specify reason for deviation.**
_____

☐ Patient did not sign informed consent prior to procedure: **Specify reason for deviation.**
_____

☐ Missed visit: **Specify reason for deviation.**
_____

☐ Visit not completed per protocol: **Specify reason for deviation.**
_____

☐ Visit out of window: **Specify reason for deviation.**
_____

☐ Missed test, exam: **Specify reason for deviation**
_____

☐ Other, **Specify**
_____

Appendix Q: Off Treatment

Instructions: Fill out this form when a patient goes off treatment.

Off Treatment:

1. Off Treatment Date __ __/__ __/__ __ (MM/DD/YYYY)
2. Off Treatment Reason:
   - ☐ Adverse Event/Side Effects/Complications
   - ☐ Alternative Therapy
   - ☐ Cytogenetic resistance
   - ☐ Death on Study (if death fill out the Survival Form)
   - ☐ Disease progression before active treatment
   - ☐ Disease progression, relapse before active treatment
   - ☐ Enrolling Physician Decision
   - ☐ Lost to follow-up: Date of last contact __ __/__ __/__ __ (MM/DD/YYYY)
   - ☐ No treatment, per protocol criteria
   - ☐ Patient off treatment for other complicating disease
   - ☐ Patient withdrawal or refusal after beginning protocol therapy
   - ☐ Patient withdrawal or refusal prior to beginning protocol therapy
   - ☐ Treatment completed per protocol criteria
   - ☐ Other

   Explain:_____
3. Is the patient evaluable for response?
   - ☐ Yes
   - ☐ No
   - ☐ Not assessed

   If No or Not assessed, please explain:_____

Appendix R: Mandatory DSMC SAE Reporting Guidelines

Data and Safety Monitoring Committee (DSMC) Serious Adverse Event (SAE) Notification SOP	**Date: 02/11/2021**

Mandatory DSMC SAE Reporting Requirements in WISER

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Data and Safety Monitoring Committee (DSMC).** A trial is considered a **WFBCCC Investigator Initiated interventional trial** if the following criteria are met:

1) The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
2) WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
3) The trial is designated as "Interventional" using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation. (https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

1) Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites.** These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2) Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites.
   There are three types of trials that are included in this category:
   a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the DSMC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either 1) **unexpected grade 4,** 2) **unplanned inpatient hospitalization > 24 hours (regardless of grade),** or **grade 5 (death)** must be reported to the DSMC using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the DSMC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the DSMC clinical member to obtain all details of the SAE, as well as all associated

toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire DSMC will be generated.

THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of attribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the DSMC.

What is considered during protocol intervention?
During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

What is considered as an Unexpected Grade 4 event?
Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to DSMC.

DSMC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:

1. Make a phone call (or speak in person) to the appropriate clinical member of the DSMC according to the schedule as listed below (page if necessary).
2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console in WISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the DSMC members will not be notified until a date is entered into the DSMC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., PI, study team members and DSMC members) will be notified; remember to file a copy of the confirmation.
3. Document that the appropriate person(s) on the DSMC has been contacted. Indicate the name of the DSMC clinician that was contacted and the date and time contacted in the Event Narrative field in the SAE console of the particular subject.
4. Document whether or not the protocol should be suspended based on the discussion with the DSMC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.
5. Follow up/update the clinical member(s) of DSMC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the DSMC clinician who was notified and Date/Time notified. In addition, state attribution by DSMC clinician as either "Unrelated", "Unlikely", "Possibly", "Probably", or "Definitely". Always include the following here:
    i. DSMC clinician name, date/time contacted and comments
    ii. Date of last dose before the event

iii. Is suspension of the protocol needed? Y/N

7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with DSMC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N
12. SAE Classification ***This is required in order for the email notification to be sent***
13. Adverse Event Details – Enter all details for each AE associated with the SAE.
    a. Course start date
    b. Category
    c. AE Detail
    d. Comments
    e. Grade/Severity
    f. Unexpected Y/N
    g. DLT Y/N
    h. Attributions
    i. Action
    j. Therapy
    k. Click ADD to attach the AE Detail to the SAE.
14. Enter Date Notified DSMC -- ***This is required for the email notification to be sent***
15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do not receive an email within 5 minutes, check that you have entered the "Date Notified DSMC" and the "SAE Classification". If these have been entered and the email still has not been received, take a screen shot of the SAE in WISER and immediately email it out to all of the STRC members listed in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the DSMC members immediately so that their assessment can be obtained within the 24 hour period requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

The Clinical Members of DSMC to Notify by Phone or Page:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser
Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes
Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman
Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed
Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu
Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within 30 minutes, then initiate contact with the next DSMC clinician listed in the table above on the particular day the SAE is being reported. Allow up to 30 minutes for the new DSMC clinician to respond to a phone call or page before contacting the next member in

the table. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the DSMC notification form. It is important to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of DSMC.

DSMC CLINICAN RESPONSIBILITY:

It is the responsibility of the DSMC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of DSMC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. DSMC reserves the right to disagree with the Investigator's assessment. If DSMC does not agree with the Investigator, DSMC reserves the right to suspend the trial pending further investigation. If there is any immediate danger or harm that could be present for a future patient based on the information provided in the DSMC report then an immediate suspension of enrollment shouldbe considered.

AMENDMENTS TO PREVIOUS REPORTS

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the DSMC and using that email "reply to all". Entitle this new email "**Amendment** for (list date of event and patient ID)" this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click Update. This will allow additionalinformation to be added.

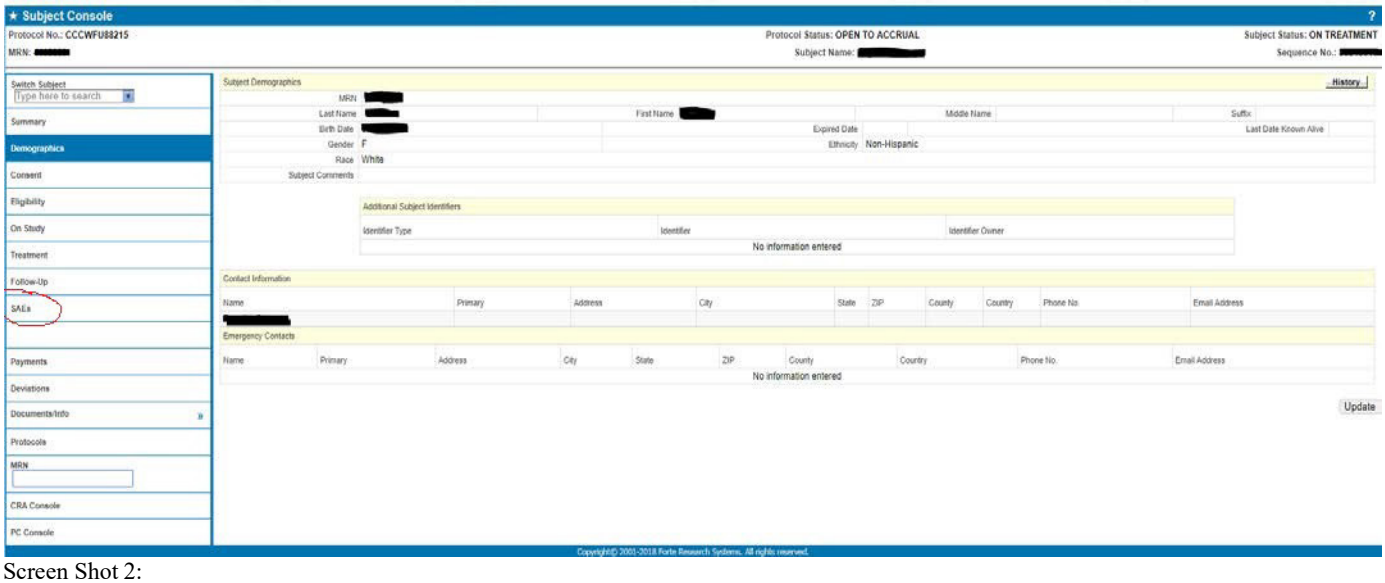
Acronyms

AE – Adverse Event
DSMC-Data and Safety Monitoring Committee
SAE-Serious Adverse Event
WFBCCC – Wake Forest Baptist Comprehensive Cancer Center
NCI-National Cancer Institute
WISER –Wake Integrated Solution for Enterprise Research

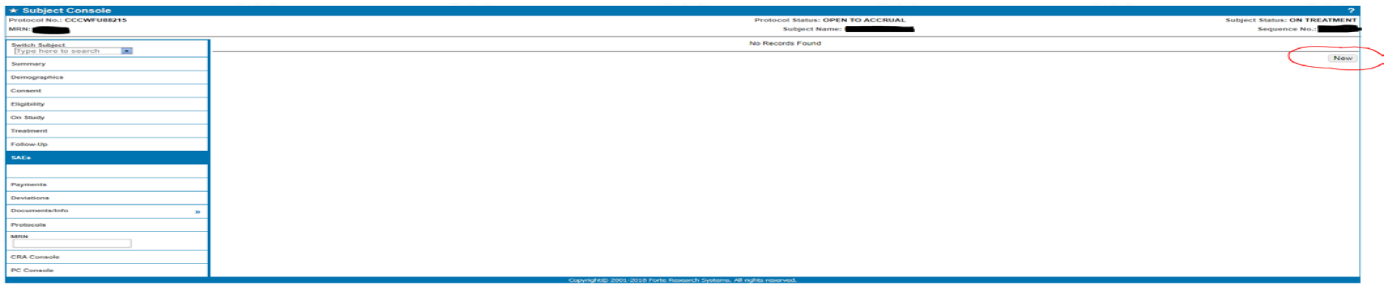
Screen Shots:

The following screen shots come from the SAE Console within the Subject Console in WISER.

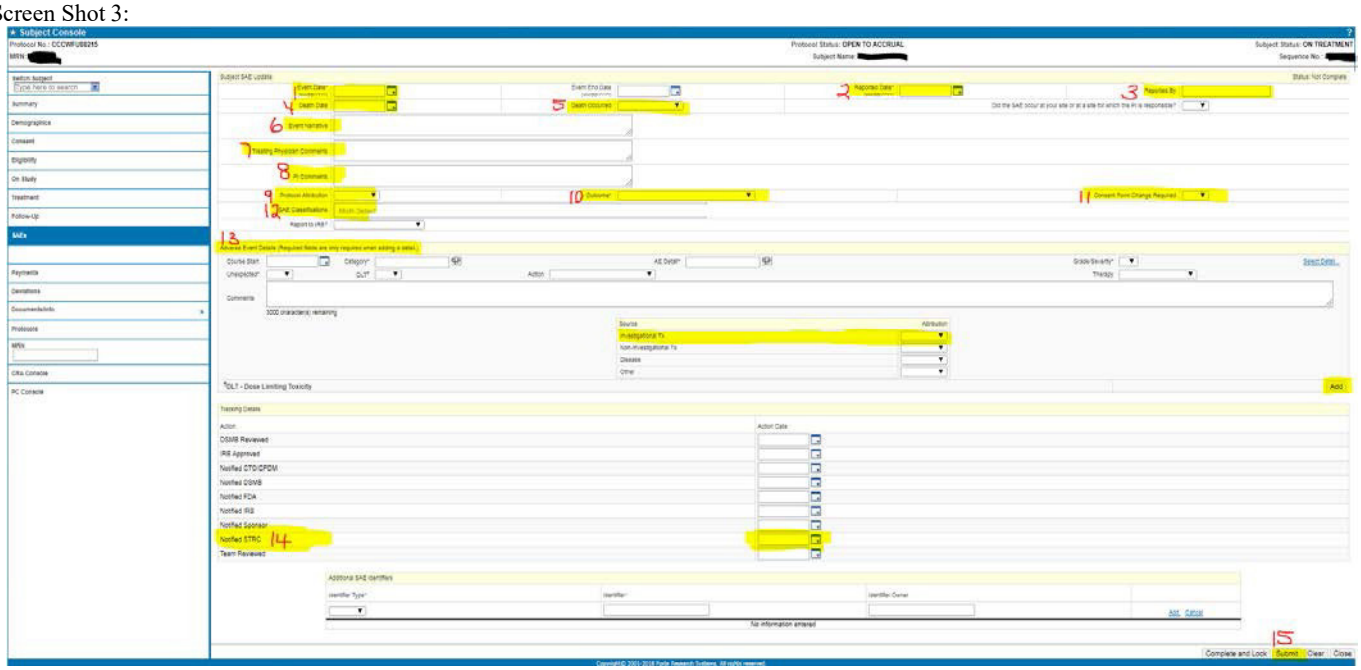
Screen Shot 1:



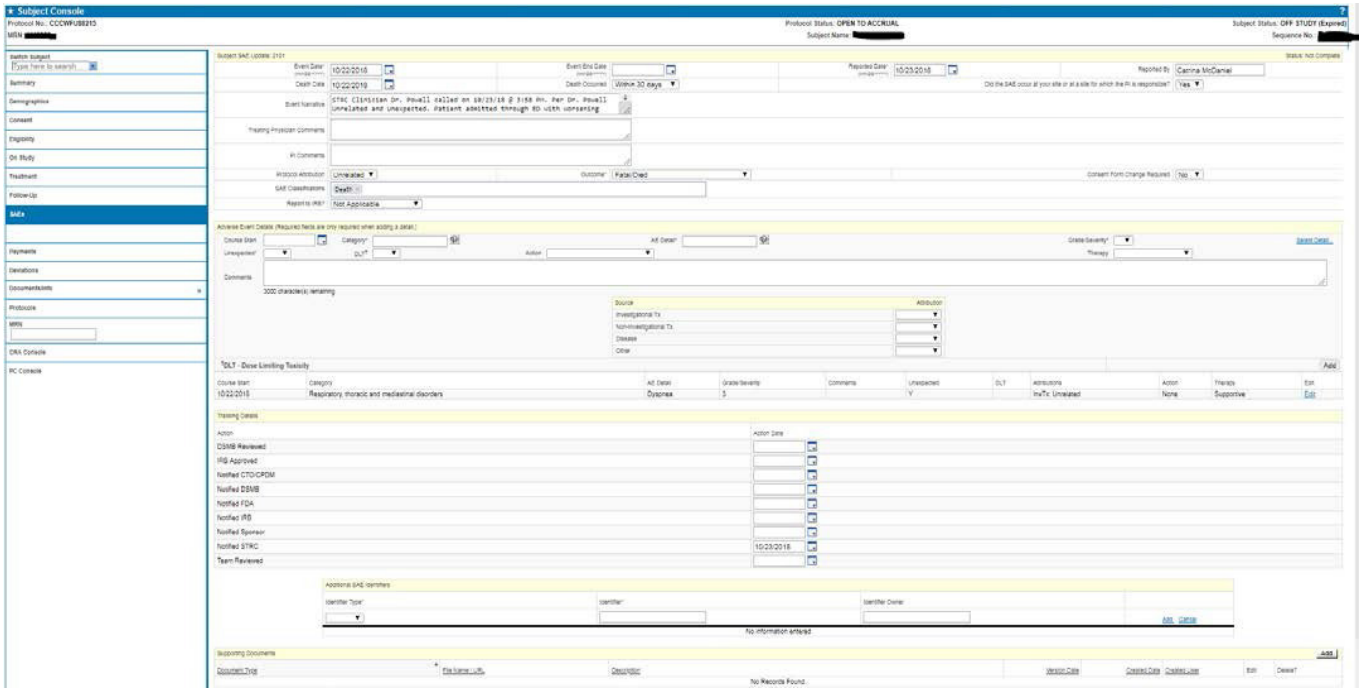
Screen Shot 2:



Screen Shot 3:



Screen Shot 4:



Appendix S: Adverse Event Log

WFBCCC Adverse Event (AE) Log

PI: _____ Subject PID: _____ **MRN: _____**

Cycle #: _____ Cycle Start Date: _____ Cycle Start Time: _____ Cycle End Date: _____ Cycle End Time: _____

Adverse Event CTC Term	**Lab Value**	**Grade** (1-5) per CTC	**Start Date**	**End Date**	**Attribution** DEF= Definite PROB= Probable POSS= Possible UNLK= Unlikely UNRL= Unrelated	**Expected** N=No Y=Yes	**Serious Adverse Event Detail** NO=No LT=Life Threatening DTH= Death DIS=Disability HOS=Hospitalized CA=Caused congenital anomaly RI=Required intervention to prevent impairment	**Dose Limiting Toxicity (DLT)** N=No Y=Yes	**Action Taken** NO=None DR= Dose Reduced RI=Regimen Interrupted TD=Therapy discontinued INTR=Interrupted then reduced	**Therapy Given** NO=None SYM=Symptomatic SUP= Supportive VSUP=Vigorous supportive	**Reportable?** IRB-IRB DSMC-DSMC FDA-FDA SPON-Sponsor (all that apply)	**Adverse Event Report (AER) Filed** N=No Y=Yes	**Outcome** R= Recovered TX=Still under treatment/ observation A=Alive with sequalae D=Died	**Treating MD Initials/ Date**

Serious Adverse Event: Hospitalization; Disability; Birth Defect; Life-threatening; Death.

CTCAE Version 5 - https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

DSMC- Safety and Toxicity Review Committee — Version 1/10/18