A Single-Arm Phase II Study with a Safety Lead-in of Magnetic Resonance-Guided Hypofractionated Adaptive Radiation Therapy with Concurrent Chemotherapy and Consolidation Durvalumab for Inoperable Stage IIB, IIIA, and Select IIIB and IIIC Non-small Cell Lung Cancer

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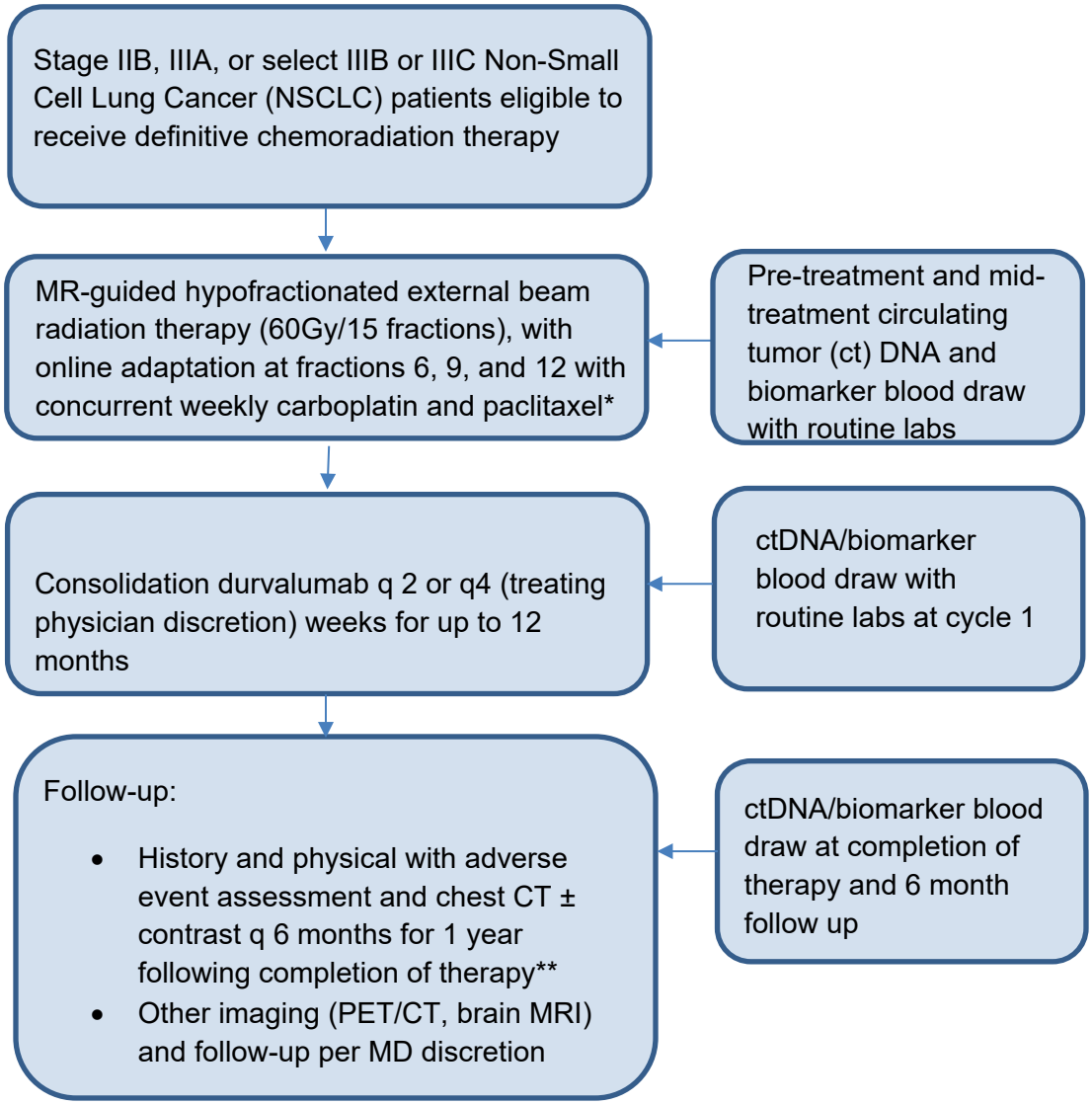
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A Single-Arm Phase II Study with a Safety Lead-in of Magnetic Resonance-Guided Hypofractionated Adaptive Radiation Therapy with Concurrent Chemotherapy and Consolidation Durvalumab for Inoperable Stage IIB, IIIA, and Select IIIB and IIIC Non-small Cell Lung Cancer

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STUDY SCHEMA



*After first 6 patients accrued, trial will be suspended for evaluation of serious adverse events
**Assuming a full 12 months of consolidation immunotherapy. If <12 months of durvalumab due to discontinuation for toxicity, follow up will be for 2 years after completion of chemoradiation. Total follow-up for patients is 2 years after start of chemoradiation.

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1.0 INTRODUCTION

1.1 Local Control and Survival after Definitive Chemoradiation for Locally-Advanced NSCLC

In the United States, lung cancer remains the leading cause of cancer-related mortality in both men and women, comprising approximately 25% of all cancer deaths. (1) For 2018, there will be an estimated 234,000 new cases, of which 85% will be non-small cell lung cancer (NSCLC). (1) Of this proportion, approximately one-third of patients are diagnosed with loco-regional disease. As the majority of patients with locally advanced NSCLC are not surgical candidates, radiation therapy is a critical component of definitive therapy and the stand of care is concurrent chemoradiation. This combined treatment results in superior outcomes over sequential chemoradiation or radiation alone (2). However, outcomes even with concurrent therapy remain poor with median survivals historically around 16-17 months (3). Outcomes are significantly improved with the addition of consolidation immunotherapy with durvalumab as recently demonstrated in the PACIFIC trial (4). Specifically, an approximately 11-month improvement in median progression-free survival (PFS) and almost 9-month improvement in median time to death or distant metastasis were seen in the durvalumab group, and the addition of consolidation durvalumab in now standard of care after current chemoradiation. However, prolonged disease control (both loco-regional and distant) and survival remain the exception rather than the rule. With regard to loco-regional therapy with radiation, the past decade has seen advancements in technology including image guidance radiation therapy (IGRT), intensity modulated radiation therapy (IMRT), and tumor-motion management resulting in reduced toxicity. Unfortunately, the rates of local tumor failure remain high. (5-7) A pooled analysis of seven Radiation Therapy Oncology Group (RTOG) trials for locally advanced NSCLC reported a 5-year loco-regional control (LRC) rate of 32% with concurrent chemoradiation. (2) While distant disease progression is also a major contributor to mortality for this population, the RTOG pooled analysis did demonstrate a significant association between LRC and overall survival (OS), with a hazard ratio for local failure of 1.42 (95% CI 1.26-1.60, $p<0.0001$). (5)

1.2 History of Dose Escalation in Locally Advanced Lung Cancer

Previous work demonstrated that dose-escalation of radiation therapy with conventional fractionation (from the standard dose of 60Gy/30 fractions) with concurrent chemotherapy may be one method to improve LRC and OS. On a phase I/II trial of dose-escalation with concurrent chemotherapy for inoperable local or loco-regional NSCLC (RTOG 0117), 74Gy/37 fractions (using 3D conformal radiation therapy, or 3D-CRT) was determined to be the maximum tolerated dose with concurrent paclitaxel and carboplatin therapy and demonstrated low rates of acute and late lung toxicities. (8) In a pooled analysis of RTOG locally advanced chemoradiation therapy trials, increasing biologically effective dose (BED) was independently associated with improved LRC and OS. (9) As the BED is a function of radiation dose, number of fractions, and fraction size as well as inherent biological factors (equation below), the two possibilities for increasing BED include increasing the prescription dose, or increasing the dose per fraction.

$$\boldsymbol{BED = nd(1+(d/[\alpha/\beta]))}$$

n = number of fractions
d = dose/fraction
α/β = ratio of radiosensitivity of the tissue to fraction size and dose (for lung, $\alpha/\beta = 10Gy$)

In the largest effort to test dose escalation to date, RTOG 0617, a prospective phase III trial of over 500 patients, compared standard dose radiation therapy (60Gy/30 fractions) to high dose radiation therapy (74Gy/37 fractions) with concurrent chemotherapy. The results of this trial found that median overall survival was actually higher for the standard dose patients than the dose escalated patients (28.7 months versus 20.3 months, respectively, $p=0.004$). (10) Both of these rates did

compare favorably to historically reported median OS for locally advanced NSCLC treated with concurrent chemoradiation (approximately 17 months), but the difference observed on this trial did raise concern for toxicity with dose-escalation that was not detected on the initial Phase I/II trials. On survival analysis, increasing heart V5 (volume of the heart receiving at least 5Gy) and esophagitis ≥ grade 3 were both associated with an increased mortality hazard. A secondary analysis of RTOG 0617 sought to evaluate the impact of intensity modulated radiation therapy (IMRT) versus 3D-CRT planning on outcomes and found no difference in loco-regional failure (LRF), progression-free survival (PFS), distant-metastasis free survival or 2-year OS, despite a higher proportion of IMRT patients having larger tumors and Stage IIIB (versus Stage IIIA) disease. (11) In this analysis, IMRT plans had significantly improved Planning Target Volume (PTV) coverage, decreased heart dose, and decreased rates of severe (≥ grade 3) pneumonitis, suggesting the role for more conformal radiation therapy to mitigate toxicities and improve tumor coverage.

With modern treatment planning techniques such as 3D-CRT and IMRT, dose to organs at risk (OAR) can be reduced compared to 2-dimensional planning, with resultant decreases in toxicity for conventionally fractionated plans. (11, 12) However, because the majority of Stage IIIA NSCLCs involve mediastinal lymph nodes, have a central location, and/or large tumor size, significant dose may still be given to critical OARs including the heart, great vessels, lungs, and esophagus. As previously described, OS in RTOG 0617 was negatively influenced by heart dose and esophageal toxicity, both of which were significantly higher in the dose-escalated arm. (10) In a retrospective review of over 400 locally advanced NSCLC patients treated at Washington University, heart V50 (volume of the heart receiving >50 Gy) and lung V5 (percent of the lung receiving 5Gy) were each independently associated with worse OS. (13) When comparing patients with a heart V50 <25% versus ≥25%, one-year OS rates were 70.2% versus 47%, respectively. Furthermore, median heart V50 was significantly higher in patients with a cardiac toxicity of Common Terminology Criteria for Adverse Events (CTCAE) cardiac toxicity of ≥1 (20.8% versus 13.9% respectively).

1.3 Hypofractionation as a Method to Improve Local Tumor Control

Another strategy to improve local control for locally advanced NSCLC draws upon the experience of stereotactic body radiation therapy (SBRT) for early stage disease, which delivers a higher dose per fraction to the tumor volume, in fewer total treatments (hypofractionation). SBRT has now been widely practiced in the lung and other disease sites for over a decade, and was made possible by developments in image-guidance, motion control, and treatment delivery techniques to allow very high doses of radiation to be directed to a specific set of coordinates within the body, with multiple convergent co-planar and non-coplanar beams to ensure steep dose fall-off to the surrounding tissue. Because of these critical developments, SBRT has been able to increase the relative BED traditionally seen in conventionally fractionated plans. BED delivered with a typical lung SBRT treatment (54 Gy / 3 fractions or 50 Gy / 5 fractions) is often in excess of 100 Gy_{10}, while the comparative BED for a standard 60 Gy / 30 fraction schema is 72 Gy_{10}. The ability of SBRT to deliver ablative doses to the tumor substantially improved overall survival for inoperable Stage I NSCLC patients, from a historic rate of 3-year OS of 20% with conventionally fractionated RT to 56% with SBRT. (14) Additionally, 3-year local control with SBRT is approximately 90% or greater with low rates of toxicity. (14-16)

Aside from an increased BED, there are additional advantages to hypofractionated therapy. In prolonged courses of conventionally fractionated therapy, decreases in local control rates have been documented, likely due to tumor repopulation before the entire prescription dose has been delivered. (17) This is of particular concern for lung cancer, where rapid tumor repopulation has been demonstrated. (18) In an analysis of overall treatment time on outcomes after concurrent chemoradiation for locally advanced NSCLC from 3 prospective RTOG trials, a 2% increase in the risk of death for each day of treatment prolongation was seen on multivariable analysis. (19) Because there are fewer treatments, hypofractionation reduces the likelihood of treatment breaks/interruptions. Reductions in the number of treatments are also more convenient for patients,

as noted in similar trials of hypofractionated radiation for breast cancer and prostate cancer. (20, 21)

1.4 Toxicity as a Limiting Factor to Dose Escalation and Hypofractionation

While hypofractionation may lead to improvements in local tumor control, it can also increase rates of acute and late toxicity to the surrounding tissues. Increasing radiation dose to the esophagus and lung are highly correlated with increased rates of acute esophagitis and late pneumonitis. (22, 23) These toxicities in hypofractionated lung regimens are particularly a concern for central lung tumors. Early in the Stage I NSCLC SBRT experience, an increased rate of severe toxicity was seen for central lung tumors (tumors within 2cm of the trachea, carina, or proximal bronchial trees) as compared to peripheral lesions (2-year freedom from severe toxicity 54% versus 83%, respectively). (24). Largely due to the observed toxicity in these early studies with central lung tumors, alternative doses and fractionation studies were evaluated to determine the optimum balance between obtaining an appropriate BED_{10} and acceptable toxicity profile. In a phase I trial at Washington University to determine the maximum tolerated dose of SBRT in patients with early stage centrally located NSCLC, 5 fraction SBRT was performed from a range of 45, 50, 55, and 60 Gy.(25) At this entire range of doses, no ≥ grade 2 toxicities were reported, and a primary tumor control rate of 95.5% was reported. In RTOG 0813 (Trial of SBRT for Centrally Located NSCLC), rates of both early and late ≥ grade 3 toxicity were also substantially lower when SBRT was delivered with either 57.5 Gy/5 fractions or 60Gy/5 fractions. (26)

1.5 Role of Hypofractionated Radiotherapy and Chemotherapy for Locally Advanced NSCLC

Compared to hypofractionated radiation for early stage, peripheral lung tumors, hypofractionated therapy for locally advanced NSCLC must take into account tumor size and location, involvement of mediastinal lymph nodes, and the fact that the patient will be receiving concurrent chemotherapy, as each of these factors would contribute to additional toxicity risk. Table 1 details the studies to date that have evaluated hypofractionation for locally advanced NSCLC. The University of Wisconsin experience does underscore the rationale for methods to decrease toxicity in the hypofractionated setting for locally advanced NSCLC. (27) In that phase I trial for locally-advanced NSCLC patients, dose-escalated hypofractionation was tested with doses ranging from 57Gy to 85.5Gy over 25 fractions with helical tomotherapy (with neoadjuvant or adjuvant, but not concurrent chemotherapy due to toxicity concerns). In long term follow-up, 12/79 patients experienced grade 2 pneumonitis, 1 had a grade 4 tracheoesophageal fistula, and 5 had grade 5 toxicities (death). On univariable analysis, prescription dose ≥ 75 Gy and dose to the bronchial tree were predictive of grade 4-5 toxicity. From this analysis, they established the maximum-tolerated dose (MTD, or dose with ≤20% risk of severe toxicity) as 63.24Gy in a 25 fraction regimen. However, this trial was without concurrent chemotherapy, which is the standard of care for non-operative locally-advanced NSCLC. (28)

In another series, Ren and colleagues performed a phase I study to determine the maximum tolerated dose (MTD) of hypofractionated 3D-conformal radiotherapy (3D-CRT) with concurrent chemotherapy for unresectable Stage III NSCLC. (29) Doses investigated included 66Gy/22 fractions, 69Gy/23 fractions, and 72Gy/24 fractions (all delivering 3Gy/fraction) with concurrent vinorelbine and carboplatin. In this trial of 13 patients, four patients experienced dose limiting toxicity, including Grade 3 esophagitis, Grade 3 pneumonitis, and Grade 4 neutropenia, all of which occurred in the 72Gy dose group. Based on these findings, the MTD was determined to be 69Gy. However, on a phase II trial for hypofractionated concurrent chemoradiation therapy of 69Gy/23 fractions by Ren and colleagues, the trial was terminated after 12 patients had been enrolled due to 5 cases of acute grade 3 esophagitis.(30) For patients where the esophagus received ≥2.7Gy per fraction, the rate of grade III esophagitis was 83%. Additionally, of the 7 patients that were able to receive the full prescription dose of 69Gy, the rate of grade III pneumonitis was 28%.

A recently completed Phase I institutional trial at Washington University delivering hypofractionated *proton* therapy with concurrent chemotherapy for locally advanced NSCLC demonstrated that this combination is feasible and well tolerated with promising rates of disease control.(31) On this trial, fraction number was fixed at 15, with progressively increased dose-per-fraction from 3.5 Gy to 4.0 Gy. Most patients (70%) were treated at the highest dose level (60 Gy in 15 fractions) with no serious adverse events reported by 6 months. No acute (within 6 months) non-hematologic toxicities grade 3 or higher and no late (> 6 months) grade 4 or 5 toxicity were reported after a median of 22.4 months for living patients. One patient developed a grade 3 pleurocutaneous fistula at 27 months and 4 patients developed grade 2/3 toxicity (2 pulmonary and 2 laryngeal). Two-year local and regional control rates were 93.3% and 77.1% respectively. Proton therapy has some advantages over conventional photon therapy with regard to dose distribution and OAR sparing that may account for this feasibility compared with photon-based hypofractionation trials thus far. However, proton therapy remains limited in other dose-sparing functions, including the inability to track intra-fraction tumor motion with respiration (i.e. respiratory gating). An additional disadvantage is that this study predates the use of consolidation durvalumab, now standard of care after chemoradiation for locally advanced disease, and this may further impact disease control and survival in this population with this treatment approach.

Author - Institution	Phase	n	Stage	Total dose @ dose/fx	Chemo	MFU	LC, LRC, or LPFS	OS	Toxicity
USA, U. Michigan - (Hayman, 2011; Kong, 2005)	I	106	I (29), II (9), IIIA (35), IIIB (25)	63-103 Gy / 30-49 fx @ 2.1 Gy/fx	20 (18%) neoadjuvant chemo, no concurrent.	102.7	5y LRC 29%	5y OS 13%	6 G3 esophagitis, 1 G4 esophagitis, 5 G2 pneumonitis, 2 G5 hemoptysis
South Korea, Multiple (Cho, 2009)	II	49	IIIA (18), IIIB (31)	60 Gy / 25 fx @ 2.4 Gy/fx to GTV and 1.8 Gy/fx to PTV	All weekly concurrent carboplatin / paclitaxel	36.8	3y LPFS 53.7%	3y OS 43.8%	5 G3 esophagitis, 2 G4 esophagitis, 2 G5 hemoptysis, 10 G2+ pneumonitis
China, Shanghai Medical College (Zhu, 2011)	II	34	IIIA (16), IIIB (18)	50 Gy / 20 fx @ 2.5 Gy/fx + boost 15-18 Gy / 5-6 fx @ 3 Gy/fx	All 2 cycles induction cisplatin / vinorelbine and 1-2 cycles consolidation, no concurrent	20	3y LPFS 60.9%	3y OS 32.1%	2 G3 esophagitis, 10 G2+ pneumonitis
China, Hebei Medical University (Lin, 2013)	I	13	IIIA (6), IIIB (7)	66-72 Gy / 22-24 fx @ 3 Gy/fx	All 1-2 cycles concurrent carboplatin / vinorelbine, 1-4 cycles consolidation	10	NR	NR	2 G3 esophagitis, 6 G2+ pneumonitis
Ireland, St. Lukes (Thirion, 2004)	I/II	25	I/II (9), IIIA/B (16)	72 Gy / 24 fx @ 3 Gy/fx	11 (44%) "induction chemo", no concurrent	9.7	1y LPFS 72%	1y OS 68%	2 G3 esophagitis
Netherlands, Multiple (Belderbos, 2007)	III	158 (early closure)	I (3,1%), II (4,5%), IIIA (45,30%), IIIB (47,64%), Unk (1%)	55 Gy / 20 fx @ 2.75 Gy/fx to GTV and 2 Gy/fx ENI + boost 11 Gy / 4 fx @ 2.75 Gy/fx to GTV	78 (49%) 2 cycles of induction cisplatin / gemcitabine vs. 80 (51%) concurrent daily "low dose" cisplatin	39	Raw LRC 43-46%	3y OS 21.6% vs. 29.2%	Concurrent - 9 G3 esophagitis, 2 G4 esophagitis, 1 G5 hemoptysis; Sequential - 4 G3 esophagitis, 1 G5 hemoptysis
UK, Multiple (Maguire, 2011)	III	130	IIIA (44%), IIIB (56%)	55 Gy / 20 fx @ 2.75 Gy/fx	60 (47%) 4 cycles induction cisplastin / vinorelbine vs. 67 (53%)	31	NR	3y OS 38% vs. 27%	Concurrent - 6 G3 esophagitis, 2 G5 ???; Sequential - 1 G3 esophagitis, 1 G5 ???
Italy, Sant'Andres Hospital (Osti, 2013)	?	30	IIIA (7), IIIB (17), IV (6)	60 Gy / 20 fx @ 3 Gy/fx	24 (80%) "induction chemo", no concurrent	13	2y LPFS 41.1%	2y OS 38.1%	1 G3 esophagitis, 8 G2+ pneumonitis
USA, U. Wisconsin (Cannon, 2013)	I	79	I/II (7), IIIA (21), IIIB (35), IV (10), Recurrent (6)	57 – 85.5 Gy / 25 fx @ 2.28 Gy – 3.42 Gy/fx	54 (68%) "either neoadjuvant or aduvant chemo", no concurrent	17	3y LC ~60% (estimated from figure)	3y OS 29%	12 G2 pneumonitis, 1 G4 TE fistula, 5 G5 (1 HSV/CMV, 2 hemoptysis, 1 lung abscess, 1 hemoptysis + abscess)

Table 1. Summary of hypofractionated radiotherapy and chemotherapy trials involving locally advanced NSCLC. N=number of patients, Gy=Gray, fx=fraction, MFU=median follow-up, LC=local control, LRC=locoregional control, LPFS=local progression free survival, OS=overall survival, Gx= grade x, GTV=gross tumor volume, PTV=planning target volume, ENI=elective nodal irradiation. Compiled by CG Robinson.

1.6 Role of Adaptive Radiation Therapy with Concurrent Chemotherapy in Reducing Toxicity

As described above, the anatomic characteristics of locally advanced lung cancer have historically limited the ability to administer hypofractionated therapy with concurrent chemotherapy. One technique to limit the toxicity and facilitate concurrent therapy involves adaptation of the radiation therapy plan while on treatment in order to tailor the therapy to anatomical changes of the tumor in relation to the surrounding organs at risk. Previous work at the University of Michigan demonstrated that following the delivery of 45 Gy of conventionally fractionated RT, both tumor size and metabolic activity decrease significantly on ^{18}F-fludeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT). (32) Based on this, phase I and II trials were conducted to assess the feasibility of mid-treatment FDG-PET/CT adapted radiation therapy with concurrent chemotherapy for inoperable Stage II and III NSCLC patients. (33) From these mid-treatment scans, mean tumor volume decreased by 44%. From the phase II trial, dose escalation was performed (with a median tumor dose of 83Gy, range 63-86Gy) in 30 daily fractions, and patients demonstrated promising overall local-regional tumor control of 62% (compared to historical controls of 34%). The 2- and 5-year OS rates from this phase II analysis were 52% and 30% respectively. FDG-PET/CT adapted therapy is now under investigation as a separate Phase II randomized controlled trial (RTOG 1106). Specifically, patients in this ongoing trial are randomized to conventional chemoradiation therapy (60Gy/30 fractions with concurrent carboplatin and paclitaxel) versus adaptive radiotherapy based on a mid-treatment FDG-PET/CT scan with individualized dose escalation of up to 80.4Gy/30 fractions as normal tissue constraints allow, with primary outcomes including 2-year local-regional failure rate and progression-free survival.

1.7 On-Line MR-Guided Hypofractionated Adaptive Radiation Therapy as a Method to Reduce Toxicity and Increase BED

While adaptation in RTOG 1106 is being performed with the intent of dose-escalation, there are limitations of this process that could be improved. First, while mid-treatment FDG-PET/CT adaptation has shown to safely provide dose-escalation in the initial phase II trial, due to the complexities of obtaining a PET/CT, study interpretation, recontouring, developing a new treatment plan, and providing QA on the plan, treatment adaptation to tumor changes will only occur once on study. This technique of replanning a treatment course while the patient is not actively on the treatment table has been referred to as “offline” adaptive radiation therapy. By improving the efficiency of this process with on-line adaptive therapy (adapting the plan in real time while the patient is on the treatment table), it is feasible that more than one on-treatment adaptation could be performed. Additionally, while dose-escalation with conventional fractionation is one method to increase the BED, hypofractionation (with greater dose per fraction as described above) with adaptation and real-time tumor tracking during treatment is another option to increase the BED while decreasing toxicity to surrounding OARs. To successfully and safely deliver this type of treatment involves two components: online adaptive therapy and real-time tumor tracking and gating. This technology has now become available with the development of magnetic resonance-image guided radiation therapy (MR-IGRT) mounted on a linear accelerator for treatment delivery. MR-image guidance is ideal, as MR offers superior soft tissue resolution to identify both the tumor target as well as the surrounding organs at risk, compared to conventional on-board cone beam CT or 2D imaging.

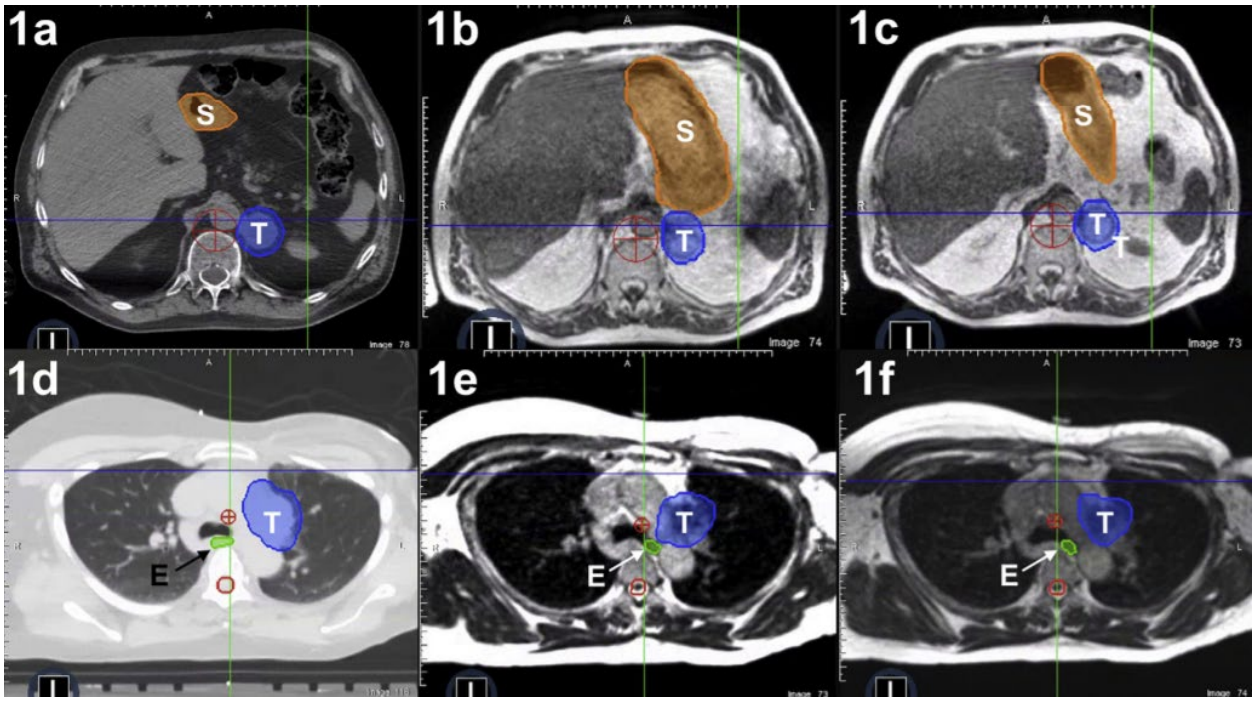


Figure 1. 1a) CT simulation of an adrenal metastasis shown in blue (T) and the stomach shown in orange (S). This CT was used for treatment planning. 1b-c) On treatment, MR imaging demonstrates the variability in the stomach anatomy during fractions 1 and 2, respectively. In 1b it can be seen that the distance between the tumor and the OAR has decreased compared to the time of simulation. 1d) CT simulation of a left upper lobe tumor (blue, T) and the esophagus (E), shown in green. 1e-f) Interfraction variability in the distance between the tumor and esophagus is again visualized in the on-treatment MR imaging seen in the first two fractions. (34)

At Washington University, our institution was one of the first to demonstrate that MR-guided adaptive radiation therapy could increase PTV coverage and prevent OAR violations. (34) In our first report on the impact of MR-guided therapy on daily treatment plans, a series of 10 patients being treated for central thorax or non-liver abdominal malignancies (conventionally planned and treated) also received daily imaging on the MR-IGRT system to assess changes in daily anatomy and tumor coverage. Although each patient's initial plan (from conventional CT simulation) met all OAR constraints, over 60% of subsequent daily treatment plans violated OAR constraints based on daily MR images. Additionally, all patients had ≥ 1 fraction with ≥1 OAR constraint violation. When virtual (*in silico*) planning was performed on each of the MR image sets, all OAR violations were resolved by adaptive planning. This was seen for both the thoracic cases (with the most common OAR violations being the trachea and esophagus) as well as the abdominal cases (duodenum and stomach OAR violations). Representative examples of how on-treatment anatomical changes can affect the proximity of OARs to the target can be seen in Figure 1.

Additionally, increased PTV dose coverage was obtained even with increased OAR avoidance in 63% of thoracic fractions and 80% of abdominal fractions (Figure 2).

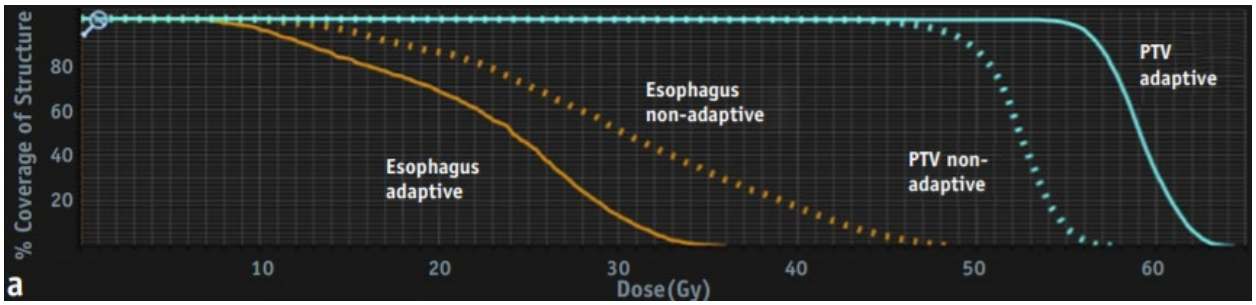


Figure 2. Dose-volume histogram comparing esophageal (orange) and PTV (teal) dose distributions between non-adapted (dashed line) and adapted (solid line) plans. For this patient, dose to the esophagus was decreased, while increasing coverage and dose to the PTV.

Based on the early results of this *in silico* analysis, it was concluded that OAR constraint violations due to anatomical changes and target movement could be identified with daily MR imaging, and that resolution with adaptive planning could be achieved while optimizing prescription dose to the PTV.

From this, two phase I trials at Washington University for online adaptive radiation therapy have been completed. The first was a Phase I trial of stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of unresectable primary abdominal malignancies or abdominal oligometastases, with a primary endpoint of feasibility. (35) As with the *in silico* modeling trial previously mentioned, all initial plans from CT and MR simulation met OAR constraints. In these stereotactic plans, a daily online adaptive plan was found to be superior to the initial plan (or previously adapted fraction) for 83.5% of all fractions. Therefore, online adaptation showed improvements not just from the original simulation, but also from fraction-to-fraction. Of the adapted fractions, it was found that the majority (75%) were adapted to meet an OAR constraint. Again, adaptive planning successfully reversed 100% of OAR violations. In over half of the plans where adaptive planning was needed to meet OAR constraints, improved PTV coverage was also achieved as a result. Though there were some cases that required PTV dose reduction to meet OAR constraints, overall, both mean and median cumulative PTV coverage was higher with online adaptive radiotherapy than the non-adapted SBRT plans.

To further test other clinical scenarios where adaptive radiation therapy could be advantageous in maximizing treatment coverage and reducing OAR dose, our institution performed another *in silico* trial of MR-guided mid-treatment adaptive planning for hypofractionated stereotactic radiotherapy for central thorax malignancies. (36) In this analysis, 12 patients with unresectable primary or recurrent NSCLC or oligometastatic disease to the chest were treated with hypofractionated MR-IGRT (60Gy/10 fractions), but with virtual adaptation only. Analysis of each of the 120 tumor volumes (12 patients, each with 10 treatment fractions) demonstrated that all patients had reduction in gross tumor volumes while on treatment. At fraction 6, the median reduction in tumor volume was 27% and by fraction 10 decreased further to 41.8%. Although each of the initial 12 plans met OAR constraints for the first fraction, by fraction 6, OAR violations were detected in 40% of the patients. Application of the initial plan to the last treatment (fraction 10), saw OAR constraint violations in half of the patients, most commonly involving the heart and esophagus. When simulated mid-treatment online adaptive planning was performed based on the MR images at fraction 6, 100% of the OAR violations were successfully resolved. When the mid-treatment online adaptive plan was then applied to the final fraction, OAR violations were still detected, although decreased in magnitude, suggesting the need for additional adaptation during the treatment course. Additionally, measurable improvements in the PTV coverage were also accomplished.

With this *in silico* experience, a phase I trial with five patients having either ultracentral thoracic oligometastatic or unresectable primaries clinically and technically appropriate for SBRT were treated with online MR-IGRT adaptive therapy at a prescription dose of 50Gy/5 fractions. (37) In this series, half of all fractions required online adaptation, with the reason being improved PTV

coverage for half, and for reversal of ≥1 OAR violations in the other half. In these instances, OAR adjustments occurred in the esophagus, trachea, and stomach (example in Figure 3). In this series, the mean and median cumulative GTV and PTV coverage were increased with online adaptive radiotherapy compared to what the non-adaptive plans would have delivered. Additionally, no acute grade ≥3 CTCAE treatment related toxicities (within 6 months) occurred. Local control of the treated lesion (defined as stable disease, partial response, or complete response by RECIST criteria), was 100% at three and six months. Local progression free survival was 100% at 6 months and 80% at 12 months.

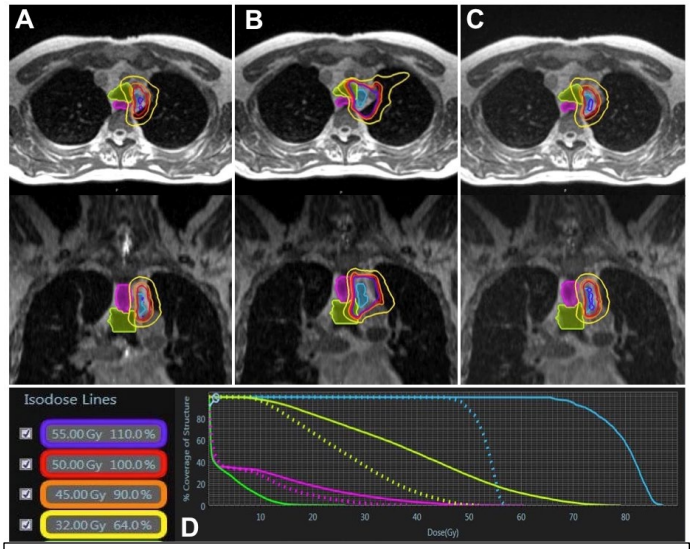


Figure 3. A) MR Images of the patient's plan for the first fraction of treatment met all OAR constraints. Upper paratracheal tumor is shown in blue colorwash. Prescription dose = 50Gy/5 fractions. B) By fraction 2, application of the fraction 1 plan resulted in dose constraint violation to the esophagus (magenta colorwash) and trachea (green colorwash). C) By performing adaptation, the second fraction plan could be modified to meet OAR constraints while preserving target coverage. D) Dose-volume histogram showing improved OAR sparing in fraction 2, with planned treatment (solid lines) and adapted treatment (dashed lines).

Based on these promising results, our department has implemented the MR-IGRT with online adaptive planning as needed for select ultracentral and central stereotactic thoracic cases, where OAR proximity is a significant concern. Recently, Washington University has acquired its second integrated MRI-radiation therapy unit, consisting of a linear accelerator for photon therapy with an open, split solenoid 0.35 Tesla (T) MRI scanner capable of parallel imaging. The low-field strength of the MRI component is designed to provide sufficient soft-tissue definition for target and OAR identification and tracking, but not cause electromagnetic disruptions in dose distribution during radiation delivery. Additionally, based on the cine images that can be acquired every 0.25 seconds, this technology allows for treatment gating, meaning that once the tumor volume has appreciably moved outside the target area (i.e. due to respiratory motion), the radiation beam is turned off automatically until the target moves back into the treatment field. Therefore, the most significant issues in delivering high doses of radiation to lung tumors – tumor movement, tumor vs OAR delineation, and tumor volume changes – can each be addressed using MR-IGRT with online adaptive planning.

1.8 Circulating Tumor DNA as a Biomarker for Monitoring Responses to Radiotherapy and Immunotherapy

Physiologic cell-free DNA (cfDNA) in the blood is thought to arise from cell death due to necrosis, apoptosis, and phagocytosis (38, 39). Malignant tumors also continually shed DNA into circulation, where it can be isolated, quantitated and sequenced as circulating tumor DNA (ctDNA) (40). Studies from our group have demonstrated that ctDNA levels during and after tumor-directed therapy for lung cancer may be an early predictor of treatment response (39, 41, 42).

Experimental approaches to identify and isolate ctDNA separately from cfDNA at both the population- and individual-level are varied and remain a critical component of ctDNA analysis (39, 43). Next-generation sequencing (NGS) has been successfully applied to many types of cancer to elucidate novel genetic/genomic alterations (44) and several NGS-based approaches for detecting ctDNA have been developed (39, 43, 45). The first class of NGS approaches involves amplifying regions of interest using PCR, and quantifying the fraction of mutant alleles at each position using NGS (45-49). Key limitations of the amplicon-based methods published to date include requirement for patient-specific assay customization, and inability to detect mutations in plasma not known *a priori* (39, 45). The second approach is direct whole exome sequencing (WES) of cfDNA. This approach is limited by high per sample costs, and requirement for a high ctDNA mutant allele fraction (>5%) for detection, making it difficult to apply to non-metastatic cancer patients (39). Finally, some groups have performed whole genome sequencing directly on cfDNA, an approach that can reveal copy number changes but is not practical for providing mutation data (50, 51). Given the limitations of the above methods, the Diehn laboratory at Stanford developed a method called Cancer Personalized Profiling by Deep Sequencing (CAPP-Seq) (Figure 4), which allows highly sensitive quantitation of ctDNA (detection limit=~0.0015%) and is applicable to >95% NSCLC patients without need for patient-specific optimization, with the ability to detect single nucleotide variants, insertions, deletions, rearrangements and copy number variations noninvasively from plasma at a reasonable cost (41, 52, 53).

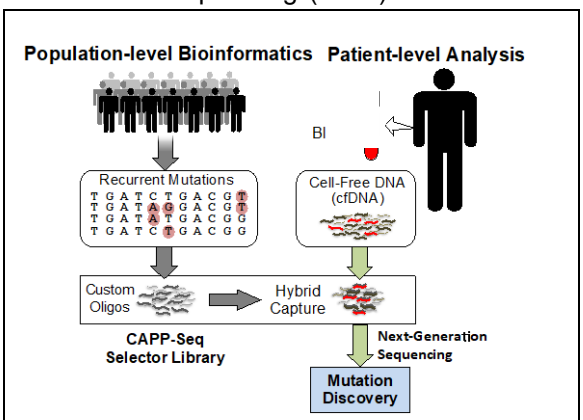


Figure 4. Design and Implementation of CAPP-Seq ctDNA analysis.

To determine if CAPP-Seq can be used to assess minimal residual disease (MRD) in blood plasma after treatment, Chaudhuri et al. applied this test retrospectively to 40 non-metastatic lung cancer patients treated with definitive intent. (41) Specifically, 93% of the patients were treated with radiotherapy (typically chemoradiation or SBRT) and the remaining 7% treated with surgery. The authors measured ctDNA within 4 months after treatment completion and found that ctDNA MRD detection was highly prognostic, with 95% sensitivity and 100% specificity of predicting clinical/radiographic progression, which correlated with significantly worse survival (Figure 5) (41). They also found that post-treatment ctDNA detected recurrence earlier than CT imaging in 72% of patients with a median lead-time of 5.2 months (41).

To determine if CAPP-Seq ctDNA analysis can be used to assess treatment response mid-treatment , Chaudhuri and colleagues applied this test retrospectively to 13 patients during chemoradiation (66 Gy delivered over 6 weeks) (42). The authors measured mid-treatment ctDNA levels on average 3 weeks after treatment start (range 1.4-3.7). Mid-treatment ctDNA levels correlated significantly with eventual disease progression by Cox regression (HR 2.7; P=0.006). Patients with ≥0.1% ctDNA at the mid-treatment timepoint displayed significantly inferior 2-year freedom from progression than patients with <0.1% mid-treatment ctDNA (0% vs. 60%; HR 4.4; P=0.037). All patients with ≥0.1% ctDNA during treatment demonstrated progression within 18 months (Figure 6).

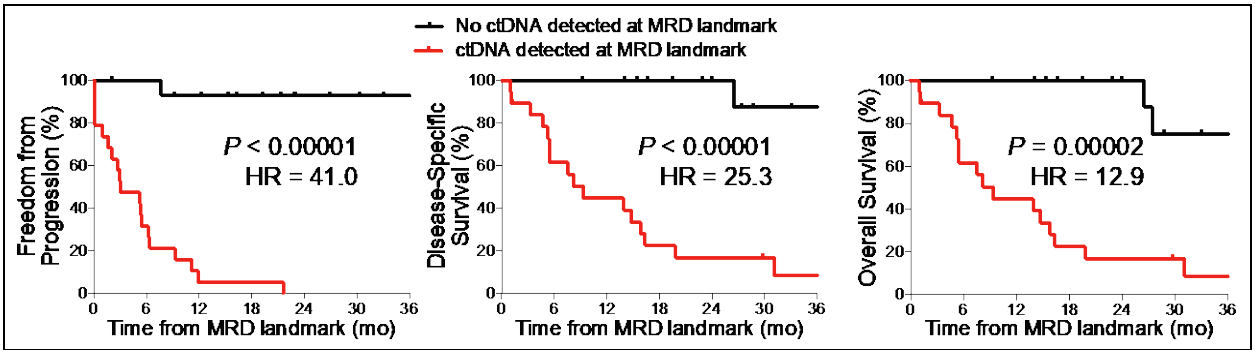


Figure 5. ctDNA MRD detection was prognostic for lung cancer patients on retrospective analysis.

Chaudhuri and colleagues also retrospectively performed ctDNA analysis for 27 patients treated with immune checkpoint inhibitors as 2nd line therapy for metastatic non-small cell lung cancer, and observed that ctDNA levels decrease by >5-fold within 8 weeks of starting immune checkpoint blockade in responders who achieve durable clinical benefit, but remained elevated in progressors (Figure 7) (54). Similar to what has been observed for melanoma (55), they observed that earlier assessment of responders could make stratification by ctDNA challenging because these patients may have a ctDNA spike at 2-4 weeks after starting treatment, which is likely related to the increased cell kill from immune checkpoint blockade which can be difficult to distinguish from progression (Figure 8).

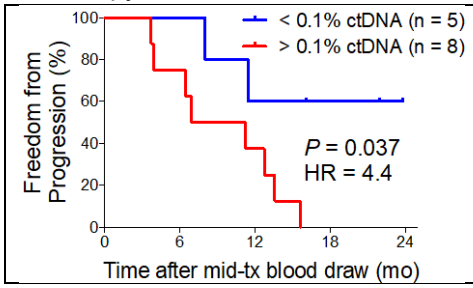


Figure 6: Mid-treatment ctDNA levels were prognostic on retrospective subset analysis.

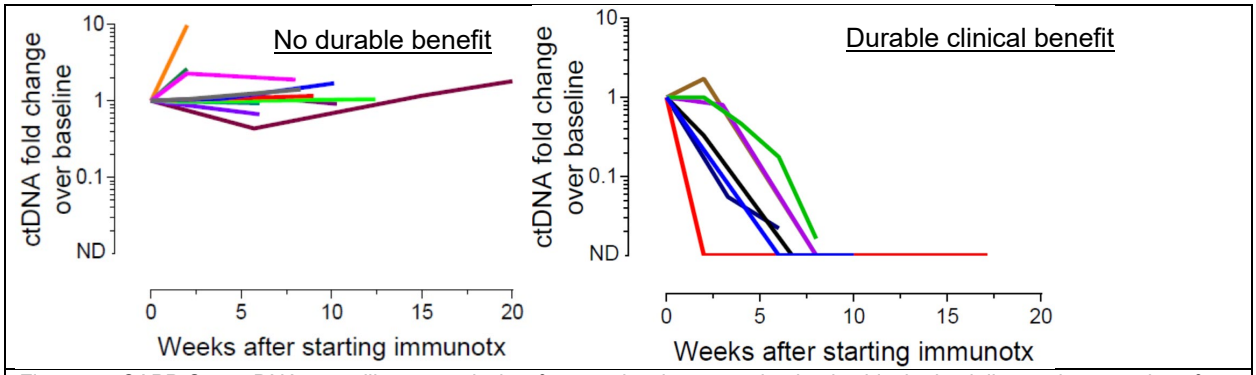


Figure 7: CAPP-Seq ctDNA surveillance analysis after starting immune checkpoint blockade delineated responders from progressors within 8 weeks on retrospective analysis.

Given these data, we believe it will be important to measure ctDNA before, during and after hypofractionated radiotherapy and immunotherapy in a prospective fashion, and correlate the absence/presence and levels of ctDNA with therapeutic response and patient outcomes. *In combination with MRI-guided adaptive chemoradiation and immune checkpoint blockade, circulating tumor DNA has strong potential for guiding treatment in a personalized and precise manner.*

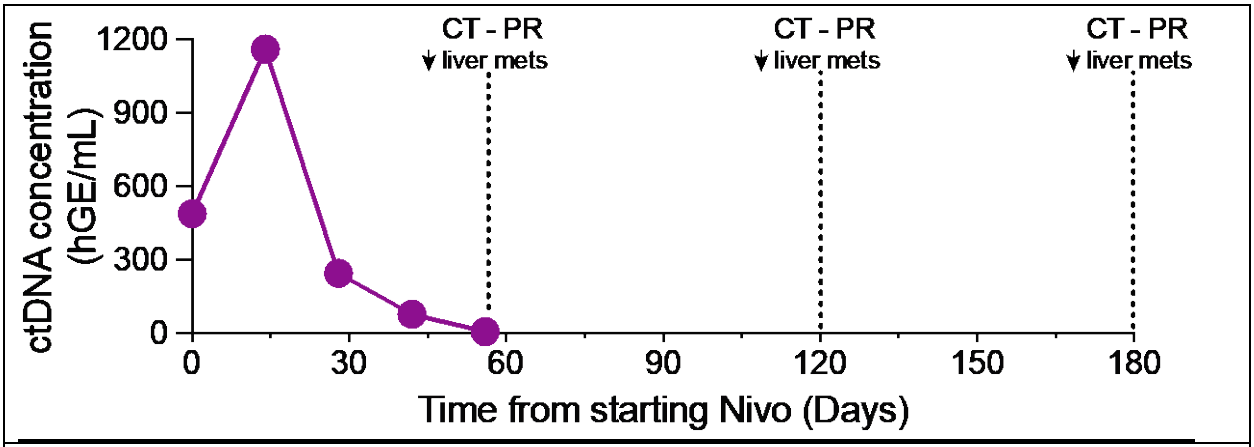


Figure 8: Patient with durable clinical benefit on immune checkpoint blockade who had an early ctDNA spike.

1.9 Cardiac Biomarkers

While radiation therapy can improve the local control and survival of locally-advanced lung cancer patients, there are a number of long-term toxicities that can occur in cancer survivors. For patients who receive chest irradiation, cardiac radiation exposure can cause severe toxicities. While cardiac exposure in left-sided breast cancer patients has been minimized due to technical advances in radiation therapy, significant radiation exposure occurs in many patients with lung cancers. Recent studies show that radiation-induced cardiotoxicity could manifest within 2 years of completing radiation for lung cancer (56-58) and studies in lung cancer patients have found that mortality correlates mean heart dose (56), or with the percent of the heart receiving 5 Gy (58), 30 Gy (58), 50 Gy (57).

While radiation remains a mainstay of cancer treatment, identifying those at higher risk of increased cardiac side effects can alter surveillance and allow earlier treatment of sub-clinical dysfunction. Currently, there is no way to predict who is at higher or lower risk of cardiac toxicity from radiation, and the critical factors that alter radiation-induced cardiotoxicity are not completely clear. This leads to a one-size-fits-all approach to limiting cardiac doses for radiation treatments, which is suboptimal. Our goal is to allow personalization of radiation treatment by identifying biomarkers that would prediction of patients at increased risk of radiation-induced cardiotoxicity and may lead to the development of therapies to prevent and/or mitigate cardiotoxicity after radiation. Identifying new markers or imaging modalities capable of early detection and localization of subclinical cardiac dysfunction will enable risk stratification, closer surveillance, and more prompt initiation of cardioprotective therapy to avoid development of heart failure.

Cardiac serum biomarkers, including troponin I/T and NT B-type natriuretic peptide NT-proBNP are well-established markers of cardiac dysfunction (59, 60), can be helpful in predicting the development of a cardiovascular adverse event during cancer therapy (61-63), their value for predicting radiation-induced cardiotoxicity has not been uniformly demonstrated. For radiation-induced cardiotoxicity, there are conflicting results from studies of these biomarkers (64-67), but many of the studies are small and many only examine very early timepoints during and after radiation therapy. In addition, not many studies have examined the use of *high sensitivity* troponins as biomarkers for radiation-induced cardiac dysfunction. Because the mechanisms of cardiac injury after radiation are not solely dependent upon cardiac myocyte injury, the role of biomarkers related to vascular injury, inflammation, and fibrosis may be more informative than markers such as troponins and NT-proBNP. Studies have recently begun to examine such biomarkers in clinical and pre-clinical studies (68-71). Embedding biomarker studies within prospective studies is ideal since this allows more unbiased capturing of outcomes and adverse effects than retrospective review of such events. Identifying biomarkers that predict patients at

higher risk of cardiac side effects would allow better personalization of patient treatment and follow-up.

1.10 Summary

The improvement of local control with hypofractionated radiation therapy has been well known and accepted from a radiobiological standpoint, but its application to clinical practice has been limited for locally advanced disease. The primary barrier has been the increased risk of irreversible late toxicity with higher dose-per-fraction and technical limitations in accurate OAR delineation, patient setup, and treatment delivery. However, with recent technologic enhancements in imaging and radiation delivery and key clinical trials demonstrating the feasibility of high dose-per-fraction therapy, hypofractionation has now gained prominence in early stage NSCLC where target volumes are unifocal and often small in size. For larger and/or multifocal disease, however, concerns for limiting toxicities remain and conventional photon based systems remain largely inadequate to address these concerns. The application of MRI-based radiation therapy is a novel approach to address these limitations and achieve effective tumor coverage with hypofractionation while utilizing on-board MRI capabilities to account for both *intra*-fraction and *inter*-fraction variability to minimize dose to surrounding normal structures. The parallel analysis of cell-free DNA to identify and track ctDNA may enable more precise response assessment than imaging alone during definitive chemoradiation and consolidation immunotherapy. Additional studies of biomarkers that may predict toxicities, most notably cardiotoxicity, may also lead to studies of ways in which to minimize radiation-induced side effects.

Building upon our clinical experience with the MR-guided radiation therapy system and applying principals of hypofractionation toward the current treatment paradigm of concurrent chemoradiation and consolidation immunotherapy for locally advanced NSCLC, this prospective, single-arm Phase II clinical trial with safety lead-in will test the feasibility and outcomes of this approach. Additional post-treatment analysis of tumor response, OAR dose compliance, the extent of adaptation, and changes in biomarkers of radiation toxicity and circulating tumor DNA levels will further quantify the utility and necessity of this approach to safely and effectively deliver hypofractionated radiation therapy with concurrent chemotherapy.

1.11 Trial Design

After completion of all regulatory requirements including IRB and Protocol Review and Monitoring Committee (PRMC) approval, patients would be enrolled on this phase II trial with safety lead-in in a prospective manner following informed consent based on their protocol-determined eligibility. This would include patients ≥18 years of age with inoperable clinical stage IIB, IIIA, and select IIIB and IIIC NSCLC who are eligible for concurrent chemotherapy and consolidation immunotherapy based on pre-determined criteria (e.g. performance status, adequate renal and hepatic function), have no history of prior radiation therapy to the chest (with the exception of non-overlapping SBRT), and have no contraindication to MRI.

Concurrent chemoradiation therapy (with weekly carboplatin and paclitaxel) will constitute the first phase of definitive treatment. The radiation prescription dose for each patient will be 60Gy/15 daily fractions, delivered on the ViewRay MRIdian® linear accelerator. MRI-gating will be utilized for each daily fraction to minimize dose delivery when the tumor target moves out of the delineated treatment field. Planned online adaptations will be performed at fractions 6, 9, and 12. These timepoints for online adaptation were selected as our institutional retrospective data of *in silico* centrally-located lung tumors found that tumor volume does not change significantly prior to fraction 6. (36) Prior to the patient's radiation treatment at fractions 6, 9, and 12, the PTV and OAR contours will be revised based on that days imaging and the treating physician will review the treatment plan and determine if adaptation is required based on predefined criteria (section 5.1.7). If necessary, online adaptation will occur with the required re-contouring, replanning, and quality assurance assessments.

During this phase of the study, toxicities will be assessed and graded by a trial physician and/or certified research coordinator (CRC) on a weekly basis during on-treatment visits. For safety assessment in the lead-in cohort, a total of 6 patients will be closely monitored for adverse events to confirm the safety of the concurrent chemoradiation approach. After the 6th patient has been enrolled on study, further enrollment will be suspended until 6 months after completion of the chemoradiation component to assess for limiting toxicities. If predetermined stopping criteria are *not* met, enrollment will resume. One month after the completion of definitive chemoradiation therapy (lead-in cohort included), patients will begin immunotherapy (durvalumab), if clinically stable, every 2 weeks or 4 weeks (timeline at the discretion of the treating physician) for up to 12 months, per the current standard of care. Treatment response will be assessed every 12 weeks by CT and durvalumab therapy will continue for a total of 12 months if there is no disease progression. Toxicity assessment during the immunotherapy portion of the study will be performed every 4 weeks by a trial physician and/or CRC. Patients will then follow up with a physician with history and physical with toxicity assessment and chest CT ± contrast q 6 months x 1 year (assuming 12 months of durvalumab have been completed, if <12 months from discontinuation of durvalumab for toxicity, then up to 2 years after completion of chemoradiation), with subsequent follow up at the physician's discretion. Pre-treatment, during treatment and post-treatment, blood will also be drawn for CAPP-Seq ctDNA analysis in order to monitor disease and track therapeutic response.

2.0 OBJECTIVES

Objectives	Endpoints	Justification for Endpoints
Primary		
Safety lead-in - Confirm safety of hypofractionated MRI-guided adaptive radiotherapy (60Gy/15 fractions) with concurrent chemotherapy (carboplatin and paclitaxel) and consolidation durvalumab	Number of patients experiencing dose limiting toxicities. See section 5.3 for definition of dose limiting toxicities.	To confirm the safety and feasibility of this dose and fractionation using MR-guided radiotherapy (previously established using protons) before expanding to the Phase II component
Phase II - Assess local and regional control with hypofractionated MRI-guided adaptive radiotherapy (60Gy/15 fractions) with concurrent chemotherapy (carboplatin and paclitaxel), followed by consolidation durvalumab for up to 12 months in patients with inoperable IIB, IIIA, and select IIIB and IIIC non-small cell lung cancer.	Local control: clinical and/or radiographic evidence of progression of disease at the primary (local) site Regional control: clinical and/or radiographic evidence of progression of disease at the previously involved or uninvolved hilar and/or mediastinal nodal (regional) sites	Hypofractionation is anticipated to improve local and regional control over conventional fractionation and is the primary rationale for this study.
Secondary		
Assess acute and late toxicities of hypofractionated MRI-guided adaptive radiotherapy with concurrent carboplatin and paclitaxel, followed by consolidation durvalumab	Acute toxicity timeframe: 60 days from start of chemoRT and possibly/probably/definitely related to RT or chemoRT Late toxicity timeframe: 60 days from start of chemoRT to 2 years	Hypofractionation can be associated with increased risk of toxicity over conventional fractionation and systematically tracking acute and late toxicity will allow for a comparison to historical controls (i.e. conventional chemoradiaton and consolidation durvalumab)

Objectives	Endpoints	Justification for Endpoints
	and possibly/probably/definitely related to RT or chemoRT	
Report preliminary estimates of other disease control parameters	Secondary Endpoints: Tumor response rate is defined as achieving a partial or complete response per RECIST criteria. Distant recurrence rate is defined as development of metastatic, non-local and non-regional disease. Incidence of brain metastasis is defined as development of brain metastasis. Progression free survival is defined as survival with no evidence of disease progression (local, regional, or distant) or death. Disease-free survival is defined as survival with no evidence of recurrent (local, regional, or distant) disease or death. Overall survival is defined as survival with no evidence of death.	Improvement in locoregional control is anticipated to improve other disease outcomes such as overall survival and recurrence or progression to metastatic disease. These secondary endpoints will be compared to historical controls (i.e. conventional chemoradiaton and consolidation durvalumab).
Exploratory		
Collect ctDNA at defined timepoints before, during, and after therapy and correlate with time to radiographic progression, progression-free survival, and overall survival.	Serum minimum residual disease (MRD) assessment pre, during, and post treatment.	To determine if serum MRD can independently predict for treatment response or recurrence and, if so, integrate this into future therapeutic studies.
Examine levels of biomarkers that may predict toxicity, most notably cardiac toxicity, including high sensitivity troponin and NT-proBNP, in addition to other potential biomarkers.	Serum cardiac biomarker level assessment pre, during, and post treatment.	To determine if serum cardiac biomarker levels can independently predict for cardiac toxicity and, if so, integrate this into future therapeutic studies to help predict or prevent adverse outcomes.
Analyze post-treatment dosimetric parameters to assess the magnitude of adaptation and organ-at-risk (OAR) (normal tissue) sparing with MRI-guided adaptive treatment. We will determine the extent of target volume dose coverage and OAR dose reduction and correlate these values with the incidence and grade of acute and late toxicities.	Dosimetric assessment (including dose-per-volume assessment) of tumor and OAR radiation dose from the initial plan, and adaptive fractions 6, 9, and 12.	To evaluate if adaptive treatment is indicated or necessary to account for tumor response and/or OAR dose reduction.

Objectives	Endpoints	Justification for Endpoints
Collect DVH data for correlation with esophageal and pulmonary toxicity in the setting of concurrent hypofractionated chemoradiation.	Dosimetric assessment (including dose-per-volume assessment) of lung and esophageal dose between patients with or without grade 3 or higher esophageal or pulmonary toxicity	To determine if there are clear dosimetric values associated with high grade esophageal or pulmonary toxicity to account for in future studies

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Histologically or cytologically proven diagnosis of non-small cell lung cancer.

2. Inoperable or patient has refused surgery.

3. Clinical AJCC stage IIB or IIIA (AJCC, 8th ed.) with plans to be treated with concurrent chemoradiotherapy.
   a. Recurrent non–small cell lung cancer is allowed, provided the intent of the current treatment is curative and there has been no prior radiation to the thorax (except prior SBRT as detailed in Section 3.2).
   b. Prior chemotherapy, immunotherapy, or targeted therapy is permitted as long as patients have recovered from prior toxicities to grade ≤ 1
   c. Clinical AJCC stage IIIB with plans to be treated with concurrent chemoradiotherapy are eligible if <u>any</u> of the following apply: (1) T3N2M0, (2) T4N2M0 with T4 by size criteria (> 7 cm); T4 due to invasion or nodules in other ipsilateral lobe are excluded, (3) T1-2N3M0 where N3 disease is confined to no more than 2 contiguous nodal stations in the contralateral mediastinum. N3 disease with either contralateral hilar adenopathy, multistation contralateral mediastinal adenopathy that is either non-contiguous or >2 contiguous nodal stations, or any scalene or supraclavicular adenopathy are not eligible.
   d. Clinical AJCC stage IIIC (T3-4N3M0) are eligible if N3 disease is confined to no more than 2 contiguous nodal stations in the contralateral mediastinum as above and, if applicable, T4 is due only to size >7 cm as above.

4. Appropriate stage for protocol entry based upon the following minimum diagnostic workup:
   a. History/physical examination within 30 days prior to registration
   b. FDG-PET/CT scan and CT chest with or without contrast for staging within 60 days prior to registration
   c. MRI scan with contrast of the brain (preferred) or CT scan of the brain with contrast within 60 days prior to registration

5. Zubrod Performance Status 0-2 within 30 days prior to registration.

6. Age ≥ 18 years.

7. CBC/differential obtained within 30 days prior to registration, with adequate bone marrow function defined as follows:
   a. Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3
   b. Platelets ≥ 100,000 cells/mm^3
   c. Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.)

8. AST and ALT ≤ 1.5 upper limit of normal within 30 days prior to registration.

9. Total bilirubin ≤ 1.5 upper limit of normal within 30 days prior to registration.

10. Serum creatinine < 1.5 mg/dL or calculated creatinine clearance ≥ 50 mL/min within 30 days prior to registration estimated by the Cockcroft-Gault formula:

    Creatinine Clearance (male) = [(140 – age) x (wt in kg)] / [(Serum Creatinine mg/dl) x (72)]
    Creatinine Clearance (female) = 0.85 x Creatinine Clearance (male)

11. Peripheral neuropathy ≤ grade 1 at the time of registration.

12. Presence of measurable or evaluable disease by RECIST 1.1.

13. Negative serum or urine pregnancy test within 2 weeks prior to registration for women of childbearing potential.

14. Women of childbearing potential and male participants must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study.

15. Able to understand and willing to sign an IRB-approved informed consent document. Patients without capacity to make an informed consent decision must have a legally authorized representative sign the IRB-approved informed consent document on their behalf.

3.2 Exclusion Criteria

1. Severe, active comorbidity, defined as follows:
   a. Unstable angina, history of myocardial infarction and/or congestive heart failure requiring hospitalization within the last 6 months
   b. Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;
   c. Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration
   d. Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for liver function and coagulation parameters are not required for entry into this protocol
   e. Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients

2. Prior radiotherapy to the thorax. An exception can be made for prior stereotactic body radiation therapy (SBRT) if there is no overlap with the protocol PTV and OAR constraints can still be achieved with a composite plan.

3. Evidence of a concurrent primary malignancy, or any history of metastatic cancer.

4. Currently receiving any other investigational agents.

5. Pregnant or breastfeeding.

6. Medical contraindication to receiving MRI imaging (including presence of a cardiac pacemaker).

7. Autoimmune disease requiring active treatment, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis. Specific instances of autoimmune disease are eligible and allowed on study, as below:
    a. Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone
    b. Patients with controlled type 1 diabetes mellitus on a stable insulin regimen.
    c. Patients with eczema or psoriasis with dermatologic manifestations only, provided that the disease is well controlled at baseline and only requiring topical steroids, with no acute exacerbations within the last 12 months (requiring psoralen, ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, high potency or oral steroids

8. History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest CT scan.

9. Chronic oral steroid use (greater than prednisone 10 mg orally once daily, or its equivalent) for any indication.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility collecting the information listed below:

1. Registering MD's name
2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

5.0 STUDY TREATMENT

Consenting and eligible patients will receive concurrent chemoradiation over the course of 3 weeks (15 fractions of radiation with online adaptive treatment planning at fractions 6, 9, and 12 and weekly carboplatin + paclitaxel). Four to 6 weeks after the end of chemoradiation, durvalumab immunotherapy will be administered every two or four weeks (timing at the discretion of the treating physician) for up to 12 months.

The first 6 patients enrolled on study will comprise the Safety Lead-In cohort and will be closely monitored for toxicity related specifically to the experimental chemoradiation portion of the study treatment. After these 6 patients have been enrolled, accrual will temporarily be suspended for a minimum of 6 months after completion of chemoradiation to allow for the evaluation of adverse events. If 2 or more patients experience DLTs, the study will be stopped and the initial treatment plan re-evaluated. If 1 or fewer patients experience a DLT, an additional 21 patients will be enrolled for treatment (for a total of 27 evaluable patients). If 1 or fewer patients experience DLTs due to chemoradiation, enrollment will commence potentially as patients in the Safety lead-in cohort are still receiving durvalumab.

5.1 Radiation Therapy Guidelines

5.1.1 Dose, Fractionation

All patients will be planned for radiation therapy to 60Gy in 15 fractions to the PTV, with treatment plans subject to the OAR constraints listed in Section 5.1.5. These fractions will be delivered once-daily over a three week period on the ViewRay MR-Linear Accelerator.

5.1.2 Simulation Procedures/Patient Positioning

All patients will undergo both CT and Viewray MRI simulation in the supine position, with arms over head. If patients cannot tolerate having both arms over head, then simulation may be performed with the contralateral arm down. The CT simulation will include both an end-exhale CT and four-dimensional (4D) CT to assess respiratory motion. Viewray simulation will include an end-exhale scan and a cine evaluation. The end-exhale ViewRay image will be the primary planning dataset, with the helical end-exhale CT image providing relative electron density information (secondary image set). CT slice thickness will be no greater than 3mm. Use of IV contrast is optional, and should be used if not medically contraindicated. CT imaging will be performed from the level of the cricoid cartilage extending inferiorly through the entire liver volume. If Viewray MRI simulation is not possible for any reason (e.g. scheduling conflict causing prolonged delay in treatment start), MR simulation with the 1.5 T MR simulator is an acceptable alternative as is no MR simulation and only CT simulation as above. In both of these instances, the CT imaging will become the primary data set and a physician may need to review alignment and respiratory gating at 1st fraction on the Viewray at the discretion of the treating physician and/or physics.

5.1.3 Clinical Target Volume (CTV) and Planning Target Volume (PTV) Definitions

Definition of the GTV: The primary tumor (GTV-P) and clinically positive lymph nodes (GTV-N, defined as >1cm short axis diameter on CT or SUV >3 on PET) will be contoured separately as they may be in different anatomical locations in locally advanced NSCLC. In the presence of associated collapsed lung tissue, PET images fused to the CT simulation study should be used to distinguish tumor from consolidation.

Definition of the ITV-N: An ITV will only be generated from the nodal volume (GTV-N) since the nodal volume will not be tracked for respiratory gating. There will be **NO** ITV-P generated. The ITV-N will include the area that encompasses GTV-N motion during a complete respiratory cycle as visualized on the 4D-CT and confirmed on the ViewRay cine preview. In creating the ITV-N structure, a manual contour will first be generated from 4D-CT data. However, the ITV-N ultimately used in planning will be a faithful approximation of this initial manual contour with specific numerical expansions in anterior, posterior, left, right, superior, and inferior directions. For example, if the manual ITV-N generated from the 4D-CT is mostly closely approximated by a 0.3 cm isometric expansion of the GTV-N, then an isometric 0.3 cm expansion of the GTV-N will serve as the ITV-N for planning. The reason for using this close approximation up front is to improve reproducibility with adaptive fractions as is explained in more detail in Section 5.1.7.

Definition of the CTV: The CTV includes areas of microscopic extension, and a CTV-P will be defined as the GTV-P + 0.5 cm, and may be modified for anatomical barriers to tumor spread. Given the proximity to OARs in the mediastinum, no CTV expansion will be done for the lymph node volume, and therefore CTV-N = ITV-N. There will be no elective treatment of clinically uninvolved nodes.

Definition of the PTV: The PTV margin accounts for setup uncertainties, and will be a 0.5 cm expansion on the CTV-P and CTV-N to create the PTV. The ViewRay gating boundary used for real-time, anatomy-based motion management (see section 5.1.6) will be defined as a 0.7-cm expansion around the GTV-P as visualized on the ViewRay volumetric image (and will therefore be within the boundary of the PTV).

Definition of the PTV_OPT: The PTV_OPT is a structure to be utilized for planning purposes if necessary. In particular, if the PTV overlaps or comes into close proximity (less than 3-5 mm) with the esophagus and/or heart. This structure will be generated by creating a 3 mm expansion on the heart and a 5 mm expansion on the esophagus and subtracting these volumes from the PTV volume. The outcome is creating a PTV substructure subtracting out these expanded esophagus and heart contours to allow for adequate PTV dose coverage while respecting OAR constraints/priorities (see below).

5.1.4 Initial Treatment Planning

All patients will be planned to receive 60 Gy in 15 fractions to the PTV, subject to the dose constraints listed in Section 5.1.5. For the initial plan, dose volume histograms will be generated to provide quantitative assessment of both target coverage by the prescription dose and dose to the surrounding critical structures/OARs. The PTV coverage goal will be for 95% of the volume to be covered by 95% of the prescription dose. If a PTV_OPT is necessary, coverage goal will be for 95% of the volume to be covered by 95% of the prescription dose to this structure. If a critical structure is violated, reduction of dose will be allowed in the area of overlap. However, minimum acceptable PTV coverage (whether or not a PTV_OPT is necessary) will be 51 Gy (85% of prescription dose) to ≥95% of the PTV. An acceptable variation would be a minimum dose of 48 Gy (80% of prescription dose) to ≥95% of the PTV if 51 Gy cannot be met. Maximum PTV point dose (point dose defined as 0.5cc or less) goal will be <130% of prescription (or <7800cGy) with acceptable variation of <140% (or <8400 cGy). Maximum PTV point dose should be targeted to within

the GTV volume when possible. Additionally, PTV volume receiving 125% of prescription dose (or 7500 cGy) should be 1 cc or less. If maximum PTV point dose exceeds 130% (per acceptable variation above), an acceptable variation for this PTV volume constraint is 130% to 1 cc or less.

To minimize the risk of toxicity in this hypofractionated regimen, the following prioritization rank will be used for treatment planning:

Priority	Definition
1	Obey spinal cord and esophagus constraints. No deviations allowed.
2	Respect tumor coverage requirements.
3	Obey normal tissue guideline constraints of OARs other than spinal cord and esophagus.

5.1.5 Hypofractionated Dose Constraints and OAR Contouring

Instructions for OAR contouring, with the associated dose constraints for that OAR, are detailed in the table below. An OAR may be omitted from contouring if it is greater than 10cm from the PTV, or at the discretion of the treating radiation oncologist if it is determined that no clinically meaningful dose would be received by the OAR based on tumor anatomy. If minimum PTV coverage described above still results in constraint violations in one or more OARs (not including the spinal cord or esophagus) per the table below, then a maximum point dose (0.5 cc) of 63 Gy (105% of prescription) to this OAR is an acceptable variation.

Serial Tissue	Contouring Instructions	Volume (cc)	Volume Maximum Dose (Gy)	Maximum Point Dose (Gy)**
Spinal Cord	Entire bony canal including at least 10 cm superior and inferior to PTV	<5 cc	39	42
Esophagus*	Include the mucosal, submucosa, and all muscular layers out to the fatty adventitia at least 10 cm superior and inferior to PTV	<5 cc	51.3	55.3
		Mean dose <28.5 Gy		
Brachial Plexus	Separately from the spinal nerves exiting the neuroforamina from around C5 to T2 to include only the major trunks of the brachial plexus using the subclavian and axillary vessels as a surrogate for identifying its location extending proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib.	<3cc	48	52.5
Heart/Pericardium	Contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aorto-pulmonary window) and extend inferiorly to the apex of the heart.	<15cc	42	48.9
		≤50%	>30	
		≤35%	>40.5	
Great Vessels	The wall and lumen of the named vessel at least 10 cm superior and inferior to PTV	<10cc	48.9	54.3

Trachea and Large Bronchus*	Contour the trachea and cartilage rings starting 10 cm superior to the PTV extending inferiorly to the bronchi ending at the first bifurcation of the named lobar bronchus.	<3cc	54	60
Skin	The outer 0.5 cm of the body surface anywhere within the whole body contour.	<10cc	54	57
Stomach	The entire stomach wall and the gastric contents included from the GE junction to the proximal duodenum at the pyloris.	<50cc	40.5	50
Duodenum*	The entire duodenal wall and lumen from the pyloris to the duodenojejunal flexure.	<5cc	37.5	40.5
Jejunum/Ileum*	Any and all loops of small bowel as one structure within 10 cm of the PTV in any direction.	<120cc	40.5	46.5
Colon*	One structure including wall and contents of lumen starting 10 cm superior to PTV and ending 10 cm below PTV.	<20cc	47	53

Parallel Tissue	**Contouring Instructions**	**Volume (cc)**	**Volume Maximum Dose (Gy)**	**Maximum Point Dose (Gy)****
Lung (Right and Left) minus GTV	Contour right and left lung as one structure including all parenchymal lung tissue but excluding the GTV and major airways (trachea and main/lobar bronchi)	1000†	13.5	
		Mean dose <18Gy V18Gy <37%		
Liver minus GTV	Contour right and left lobes as one structure including all parenchymal liver tissue but excluding the GTV and major draining ducts, extrahepatic portal vein, and gall bladder.	700	25	
Renal cortex (Right and Left)	Contour right and left kidney as one structure including all parenchymal capsular tissue but excluding the renal hilum/vascular trunk (see above)	200	19	

*Avoid circumferential irradiation
**Point dose defined as 0.5cc or less
†When PTV coverage cannot be further modified to achieve this constraint due to large-volume disease, a Lung-minus-GTV volume of up to 1250 cc will be an acceptable variation if remaining lung and other OAR constraints can still be achieved.

5.1.6 Respiratory Gating

Respiratory gating will be performed for each fraction and gating will be performed on the primary tumor only. A gating boundary of 0.7 cm will be generated around the GTV-P. When the GTV-P is within this gating boundary during the respiratory cycle, this will correspond to “beam-on” time. Beam-on time will be planned for the end-expiratory phase of the respiratory cycle. However, if the inspiratory phase would result in enhanced OAR sparing, this phase can be used for the beam-on portion. Tumor motion will be tracked in real-time on a pre-selected sagittal plane where the GTV-P can be adequately monitored and distinguished from surrounding structures. If 2-D shifting is indicated during treatment as determined in the gating window, shifts of 0.3 cm or less are acceptable without additional imaging. If there are 2-D shifts >0.3 cm, a 3D confirmatory scan is required to confirm the non-gated GTV-N structures are still within the PTV.

5.1.7 Adaptive Treatment Planning and Evaluation

Evaluation for online adaptive treatment planning will occur at fractions 6, 9, and 12 to account for changes in both primary tumor volumes and OAR anatomy. OAR violations can occur if changes in the tumor dimensions alter the proximity of OARs to the target volume. Once the patient has received their daily MR-localization imaging, GTV-P and GTV-N contours will be modified to account for any treatment effect and the appropriate expansions will be made to generate an adapted PTV (and adapted PTV_OPT if necessary). The expansions will be performed as described in section 5.1.3. Since 4D data cannot be obtained at the time of adaptive planning due to limitation in the MRI-guided system and the absence of correlative CT imaging for adaptive treatments, the adapted ITV-N will be a reapplication of the approximated expansion margin of the original ITV-N. For example, if the ITV-N was initially best approximated by a 0.3 cm isometric expansion of the GTV-N, the adapted ITV-N will also be a 0.3 cm isometric expansion of adapted GTV-N. The OARs will also be re-contoured within a 5cm-ring of the PTV before fractions 6, 9, and 12. The estimated delivered dose for these specific fractions to both the PTV (and PTV_OPT if necessary) and the OARs will be calculated using the console dosimetry software. An adapted radiation therapy plan will be generated for each of these adaptive fractions, regardless of the subjective or objective assessment of change in GTV volume.

Guidelines for adaptation for individual patients will be put in the fraction note in Aria. This fraction note will also include specific values on the ITV expansion for the GTV-N based on the initial approximation (see Section 5.1.3).

Once OAR recontouring and PTV adjustment is completed, the newly optimized plan for that day's anatomy will be immediately evaluated for OAR violations as detailed above, as well as confirm appropriate target coverage of the PTV (and PTV_OPT if necessary). Priority for PTV coverage and OAR constraints for adaptive plans will be similar to the initial plan (see Section 5.1.4) and these priorities should be utilized by the covering physician if not all coverage and constraint requirements are met. Specifically, top priority will be respecting spinal cord and esophagus constraints, followed by PTV coverage, followed by the other OAR constraints. Once the new plan is approved by the physician and physicist, online QA will be performed by the physicist prior to delivery of the adapted plan. Fraction 9 will be adapted from the sixth fraction, and fraction 12 from the ninth fraction. Each of the other, non-online adaptive treatment days will receive MR-Imaging to confirm localization of the tumor volume, as well as real-time gating of the tumor during the radiation treatment.

5.2 Drug Therapy

5.2.1 Premedication Administration

Standard premedications for concurrent carboplatin/paclitaxel are to be administered per institutional guidelines. No premedications are recommended for durvalumab.

5.2.2 Concurrent Chemotherapy

Paclitaxel and carboplatin doublet chemotherapy regimen is to be administered weekly (every 7 days) during the 3 week course of radiotherapy:

- Paclitaxel 50 mg/m^2 intravenous over 1 hour followed by
- Carboplatin AUC = 2 mg/mL/min intravenous over 30 minutes
- Every week for 3 weeks

Carboplatin dose (mg) = target AUC (mg/mL/min) x (CrCl + 25)(mL/min). Creatinine clearance will be determined with the Cockcroft-Gault formula using actual body weight. (72)

Creatinine clearance will be capped at a maximum CrCl of 125 mL/min for dosing.

Chemotherapy dosing for all patients will be based on actual body weight as per institutional standard of care, in accordance with ASCO guidelines.

Chemotherapy scheduling modifications of +/- 72 hours are allowed due to weekends and holidays.

CBC with differential (including Absolute Neutrophil Count (ANC), Hemoglobin, Platelets) and serum creatinine is required within 72 hours prior to each dose of carboplatin and paclitaxel.

5.2.3 Consolidation Immunotherapy

Durvalumab immunotherapy will administered every two to four weeks (timeline at the discretion of the treating physician) within 4-6 weeks of completing chemoradiation therapy, and continue for 12 months, or until documented disease progression or if unacceptable toxicity occurs.

For q2 week dosing the dosage of durvalumab will be 10mg/kg, per the PACIFIC trial. Durvalumab dosing will be based on actual body weight on day 1 of consolidation and will be recalculated for subsequent doses only when weight has changed ≥10% from baseline at day 1. (4) For q4 week dosing, durvalumab will be administered at a 1500mg fixed dose.

Durvalumab scheduling modifications of +/- 72 hours are allowed due to weekends and holidays.

CMP will be required within 72 hours prior to each dose of durvalumab. Thyroid stimulating hormone (TSH) and CBC will not be routinely required during durvalumab therapy and can be performed as needed at the treating physician's discretion/Standard of Care guidelines.

5.3 Definitions of Dose Limiting Toxicity (DLT) and Evaluability

5.3.1 Dose Limiting Toxicities (DLTs)

DLT is defined as any possibly, probably, or definitely related to concurrent chemoradiation grade 3 toxicity that cannot be managed with maximal supportive care within 2 weeks, or any grade > 4 toxicity that occurs during treatment. As the safety assessment is specifically related to the use of hypofractionated radiation with a standard, well-established concurrent chemotherapy regimen, DLTs will *not* include grade 3 or 4 toxicities based on laboratory values alone. Patients enrolled in the Safety Lead-In cohort will be evaluated for DLT from first receiving study treatment until 6 months after completion of concurrent chemoradiation.

5.3.2 Definitions of Evaluability

Endpoint	Definition of Evaluability
Number of patients experiencing dose limiting toxicities. See section 5.3 for definition of dose limiting toxicities.	Only safety lead-in patients are evaluable for this endpoint
Local control: clinical and/or radiographic evidence of progression of disease at the primary (local) site or Regional control: clinical and/or radiographic evidence of progression of	Patients are only evaluable if they have completed the course of chemoRT.

disease at the previously involved or uninvolved hilar and/or mediastinal nodal (regional) sites	
Acute toxicity timeframe: 60 days from start of chemoRT and possibly/probably/definitely related to RT or chemoRT Late toxicity timeframe: 60 days from start of chemoRT to 2 years and possibly/probably/definitely related to RT or chemoRT	Patients are evaluable for toxicity provided they received at least 1 fraction of radiation.
Secondary Endpoints: Tumor response rate Distant recurrence rate Incidence of brain metastasis Progression free survival Disease-free survival Overall survival	Patients are evaluable provided they received at least 1 fraction of radiation.
Serum minimum residual disease (MRD) assessment pre, during, and post treatment.	Patients are evaluable if they completed chemoRT per protocol and had pre- and at least one mid- or post-treatment draw.
Serum cardiac biomarker level assessment pre, during, and post treatment.	Patients are evaluable if they completed chemoRT per protocol and had pre- and at least one mid- or post-treatment draw and had at least 1 late toxicity assessment.
Dosimetric assessment (including dose-per-volume assessment) of tumor and OAR radiation dose from the initial plan, and adaptive fractions 6, 9, and 12.	Patients are evaluable if they completed chemoRT.
Dosimetric assessment (including dose-per-volume assessment) of lung and esophageal dose between patients with or without grade 3 or higher esophageal or pulmonary toxicity	Patient are evaluable if they completed chemoRT and had at least 1 late toxicity assessment.

5.4 General Concomitant Medication and Supportive Care Guidelines

A significant portion of patients is expected to experience grade 2 esophagitis. Treatment of esophagitis varies with the severity of the patient's symptoms; for example, diet adjustment and narcotic management may be sufficient for grade 2 esophagitis. Nutritional support via gastric tube or jejunostomy tube may be initiated upon development of grade 3-4 esophagitis, per mutual preference of the treating physician and patient. Filgrastim, pegfilgrastim, and erythropoiesis-stimulating agents (epoetin alfa, darbepoietin alfa) are not permitted during concurrent chemoradiotherapy.

Premedication regimens for chemotherapy administration will be employed as noted in Section 5.2 per standard of care guidelines and institutional standards.

5.5 Women of Childbearing Potential

Women of childbearing potential (defined as women with regular menses, women with amenorrhea, women with irregular cycles, women using a contraceptive method that precludes withdrawal bleeding, or women who have had a tubal ligation) are required to have a negative serum or urine pregnancy test within 14 days prior to study registration.

Female and male patients (along with their female partners) are required to use two forms of acceptable contraception, including one barrier method, during participation in the study.

If a patient is suspected to be pregnant, study treatment should be immediately discontinued. In addition a positive urine test must be confirmed by a serum pregnancy test. If it is confirmed that the patient is not pregnant, the patient may resume dosing.

If a female patient or female partner of a male patient becomes pregnant during therapy, the investigator must be notified in order to facilitate outcome follow-up.

5.6 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, treatment may continue for the full dose of radiation and intended chemotherapy (3 weeks) and consolidation immunotherapy (12 months) or until one of the following criteria applies:

- Documented and confirmed disease progression
- Death
- Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Suspected pregnancy
- Serious noncompliance with the study protocol
- Lost to follow-up
- Patient withdraws consent
- Investigator removes the patient from study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will be followed as indicated in the study calendar.

5.7 Duration of Follow-up

Patients will be followed on protocol every 6 months x 1 year following the completion of consolidation immunotherapy (or until death, whichever occurs first), with a history and physical and chest CT ± contrast. Patients who receive < 12 months of durvalumab due to discontinuation for toxicity will be followed every 3-6 months from last durvalumab for a total of 2 years after the start of chemoradiation. Total follow-up for patients will be 2 years after the start of chemoradiation. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Other clinical follow-up and imaging (PET/CT, brain MRI) will be at the discretion of the medical oncologist and/or radiation oncologist.

5.8 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study team.

The following actions must be taken if the participant fails to return to clinic for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit within 6 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6.0 BLOOD COLLECTION AND ANALYSIS FOR ctDNA AND BIOMARKER STUDIES

Thirty mL of blood will be drawn at the following time points:

- pre-treatment (anytime between consent and start of chemoradiation, with preferred timing being at or around the time of radiotherapy simulation)
- during chemoradiation (with Week 3 chemotherapy labs +/- 2 days)
- post-chemoradiation/pre-durvalumab (with Cycle 1 durvalumab labs +/- 3 weeks)
- after 3 months of initiating durvalumab (+/- 5weeks)
- end of treatment (at 3-month medical oncology follow up +/- 4 weeks)
- at 6-month follow-up visit (+/- 8 weeks)

These research blood collections will be coordinated with clinical collections where possible, to minimize extra needle sticks. For each blood draw, plasma will be separated from peripheral blood mononuclear cells and both phases will be stored at -80°C or under liquid Nitrogen vapor until CAPP-Seq ctDNA analysis is performed in the Chaudhuri lab or biomarker measurement is performed in the Bergom lab.. CAPP-Seq will be as previously described (41, 52, 53), with barcoded adapters for library preparation, targeted DNA hybrid capture, and next-generation sequencing followed by bioinformatic correction of stereotypic errors. Please refer to the lab manual for additional information.

7.0 DOSE MODIFICATIONS

7.1 Radiation Therapy Dose Modifications

There are no planned reductions for radiation therapy. Patients whose chemotherapy doses are held will still receive their daily radiation therapy.

7.2 Dose Modifications during Concurrent Chemoradiotherapy

If carboplatin or paclitaxel doses are reduced, all future weekly doses are reduced. Dose re-escalation is not permitted. Doses for carboplatin should be adjusted to the specified percentage of the previous AUC.

7.2.1 Hematologic Toxicity

ANC and platelet count must be obtained within 72 hours prior to each dose of carboplatin and paclitaxel. If ANC < 1000 or platelet count < 75,000, omit weekly carboplatin and

paclitaxel. Restart weekly carboplatin and paclitaxel at same dose if ANC > 1000 and platelets > 75,000. Doses that are omitted are not made up.

7.2.2 Dysphagia/Radiation Esophagitis

If radiation is interrupted for grade 3 or 4 dysphagia or radiation esophagitis, hold weekly carboplatin and paclitaxel. If radiation is interrupted for grade 3 dysphagia or radiation esophagitis and radiation is to be restarted, it is the investigator's decision whether or not to restart chemotherapy. If radiation is interrupted for grade 4 dysphagia or radiation esophagitis, do not restart chemotherapy even if radiation is restarted.

7.2.3 Neurologic Toxicity

Carboplatin and paclitaxel doses will be modified for neurologic toxicity:

- If grade 1 neurologic toxicity, no dose modification.
- If grade 2 neurologic toxicity, reduce dose to 75%.
- If grade > 2 neurologic toxicity, hold chemotherapy until neurologic toxicity improves to grade ≤ 2, then either reduce dose to 50% or discontinue chemotherapy, at the physician's discretion.

7.2.4 Renal Toxicity

Carboplatin dose may be modified for renal toxicity attributed to carboplatin. Dose holds or reductions are permitted per investigator discretion as per standard of care.

7.2.5 Neutropenic Fever

Neutropenic fever is defined as temperature ≥ 38.3 C (101 F) and ANC < 500. If neutropenic fever occurs and the patient subsequently meets criteria for further chemotherapy, the doses of both agents are reduced to 75% of the previous dose administered.

7.2.6 Other Toxicities Not Defined Above

- If toxicities ≤ grade 2, then manage symptomatically, if possible, and retreat without dose reduction.
- If toxicities ≥ grade 3, dose hold or reductions are allowed per standard of care in line with package inserts.

7.3 Dose Modifications for Consolidation Durvalumab

Refer to package insert for detailed indications for holding or discontinuing durvalumab therapy and managing associated immune mediated toxicities. Dose reductions of durvalumab are not permitted.

8.0 PHARMACEUTICAL INFORMATION

8.1 Carboplatin Agent Information

Refer to package insert for detailed pharmacologic and safety information.

8.1.1 Formulation

Carboplatin is available as a sterile lyophilized powder in single-dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin. Each vial contains equal parts by weight of

carboplatin and mannitol. Carboplatin also is available as a 10 mg/mL solution in 50, 150, and 450 mg vials.

8.1.2 Preparation

When available, prediluted vials of carboplatin should be utilized. Otherwise, the preparation of carboplatin should proceed as described below:

Immediately before use, the contents of a carboplatin vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP. The following shows the proper diluent volumes to be used to obtain a carboplatin concentration of 10 mg/mL:

Vial Size	Diluent
50 mg	5 mL
150 mg	15 mL
450 mg	45 mL

Carboplatin reacts with aluminum to form a precipitate and cause a loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

8.1.3 Storage and Stability

Intact vials of carboplatin are stable for the period indicated on the package when stored at room temperature (15-30˚C or 59-86˚F) and protected from light. When prepared as described above, carboplatin solutions are stable for 8 hours at room temperature if protected from light. The solution should be discarded after 8 hours since no antibacterial preservative is contained in the formulation.

8.1.4 Adverse Effects of Carboplatin

Hematologic: Myelosuppression is the major dose-limiting toxicity. Thrombocytopenia, neutropenia, leucopenia, and anemia are common but typically resolve by day 28 when carboplatin is given as a single agent.
Allergic Reactions: Hypersensitivity to carboplatin has been reported in 2% of patients receiving the drug. Symptoms include rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. The reactions can be successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy. Desensitization per the allergy team is allowed.
Neurologic: Peripheral neuropathies have been observed in 4% of patients receiving carboplatin with mild paresthesia being the most common.
Gastrointestinal: Nausea and vomiting are the most common gastrointestinal events; both usually resolve within 24 hours and respond to antiemetics. Other gastrointestinal events include diarrhea, weight loss, constipation, and gastrointestinal pain.
Hepatic: Elevated alkaline phosphatase, total bilirubin, and SGOT have been reported.
Other: Pain and asthenia are the most common miscellaneous adverse events. Alopecia has been reported in 3% of the patients taking carboplatin.

8.1.5 Supply

Commercially available.

8.2 Paclitaxel Agent Information

Refer to package insert for detailed pharmacologic and safety information.

8.2.1 Preparation

Paclitaxel injection is a sterile solution concentrate, 6 mg/ml in 5, 16.7, and 50 ml vials (30, 100, and 300 mg/vial) in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol, USP, 50%. Paclitaxel will be diluted to a final concentration of 0.3 to 1.2 mg/ml in D5W, NS, or D5NS , in glass or polyolefin containers due to leaching of diethylhexphthalate (DEHP) plasticizer from polyvinyl chloride (PVC) bags and intravenous tubing by the Cremophor vehicle in which paclitaxel is solubilized. Each bag/bottle should be prepared immediately before administration. NOTE: Formation of a small number of fibers in solution (NOTE: acceptable limits established by the USP Particular Matter Test for LVPs) have been observed after preparation of paclitaxel. Therefore, in-line filtration is necessary for administration of paclitaxel solutions. In-line filtration should be accomplished by incorporating a hydrophilic, microporous filter of pore size not greater than 0.22 microns (e.g.: Millex-GV Millipore Products) into the intravenous fluid pathway distal to the infusion pump. Although particulate formation does not indicate loss of drug potency, solutions exhibiting excessive particulate matter formation should not be used.

8.2.2 Storage

Paclitaxel vials should be stored between 20º-25ºC (68°-77°F).

8.2.3 Adverse Effects of Paclitaxel

Hematologic: Myelosuppression;
Gastrointestinal: Nausea, diarrhea, vomiting, abdominal pain;
Heart: Arrhythmias, heart block, hypertension;
Neurological: Sensory and peripheral neuropathy
Allergy: Severe anaphylactic reactions;
Other: Alopecia, fatigue, arthralgia, myopathy, myalgia, infiltration (erythema, induration, tenderness, rarely ulceration), hypotension, irritation to the injection site, mucositis

8.2.4 Supply

Commercially available.

8.3 Durvalumab Agent Information

Refer to package insert for detailed pharmacologic and safety information.

8.3.1 Preparation

Doses of 10 mg/kg (q2 week dosing) or 1500 mg fixed dose (4q week dosing) will be administered using a 250 mL IV bag containing 0.9% (weight/volume) saline and delivered through an IV administration set with a 0.2-µm in-line filter. When applicable, patient weight at baseline (day 1 of durvalumab) should be used for dosing calculations unless there is a ≥10% change in weight. An additional volume of 0.9% (weight/volume) saline equal to the calculated volume of durvalumab to be added to the IV bag must be removed from the bag prior to addition of durvalumab. The calculated volume of durvalumab is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

8.3.2 Storage

Total in-use storage time from reconstitution of durvalumab to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2 to 8°C (36 to 46°F). If the

in-use storage time exceeds these limits, a new dose must be prepared from new vials. Durvalumab does not contain preservatives and any unused portion must be discarded.

8.3.3 Adverse Effects of Durvalumab

Pulmonary: Immune-mediated pneumonitis, cough, dyspnea
Endocrine: Immune-mediated endocrinopathies including thyroid disorders, adrenal insufficiency, Type 1 diabetes mellitus, and hypophysitis/hypopituitarism
Dermatologic: Immune-mediated rash, bullous dermatitis, Stevens Johnson syndrome/toxic epidermal necrolysis
Hepatic: Immune mediated hepatitis, elevated transaminases, inflammatory hepatitis.
Gastrointestinal: Immune-mediated colitis, diarrhea, abdominal pain
Renal: Immune-mediated nephritis
Allergic: Hypersensitivity reactions, including anaphylaxis
Other: Fatigue, other immune-mediated reactions, which can be severe or fatal, infections, pyrexia

8.3.4 Supply

Commercially available.

9.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix A for definitions and Appendix B for a grid of reporting timelines.

Grade 2 and above adverse events will be tracked from start of chemoRT through 30 days after completion of all study treatment. Acute toxicities are those that are possibly/probably/definitely related to RT or chemoRT and are followed from start of treatment through 60 days. Late toxicities are those that are possibly/probably/definitely related to RT or chemoRT and are followed from 60 days from start of chemoRT to 2 years. Adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF

Refer to the data submission schedule in Section 11 for instructions on the collection of AEs in the EDC.

Reporting requirements for Washington University study team may be found in section 9.1.

9.1 WU PI Reporting Requirements

9.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

9.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems

reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within 10 days of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

9.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 1.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

10.0 PATIENT ASSESSMENTS

	Pre-treatment	Chemoradiation	Consolidation Durvalumab[1]	End of Therapy[12]	Follow-Up[2]
Informed consent	X				
H&P	X[4]	X[5]	X[7]	X	X
FDG-PET/CT [13]	X				
MRI brain with contrast or CT head	X				
CBC w/diff	X[4]	X[5]			
CMP	X[4]	X[5]	X[8]		
TSH			X[9]		
Pregnancy test[11]	X				
CT chest +/- contrast	X		X[10]	X	X
Blood for ctDNA/biomarkers	X[14]	X[14]	X[14]	X[14]	X[14]
Radiation Therapy		X[6]			
Paclitaxel		X[5]			
Carboplatin		X[5]			
Durvalumab			X[8]		
Adverse Events		X[5]	X[7]	X	X
Clinical Outcomes					X[3]

1. Should start within 4-6 weeks after completion of chemoradiation therapy.
2. Follow-up after completion of durvalumab will take place every 3-6 months x 1 year. If the duration of durvalumab is <12 months, then follow up will continue until 2 years after start of chemoradiation. Please refer to Section 9.0 for adverse event reporting follow-up timeframes.
3. Patients will be followed as per routine clinical practice, with data being collected from the medical record on outcomes and recurrence for up to 2 years from start of chemoradiation.
4. No more than 30 days prior to registration.
5. Weekly (H&P with both Rad Onc and Med Onc)
6. 15 daily fractions over 3 weeks
7. While on Durvalumab, patients will follow-up with radiation oncology q3-6 months x 1 year, AE assessments will occur at these appointments. Follow-up with medical oncology during durvalumab will also occur, per routine clinical practice (typically Q2W or Q4W), with AE assessment at each medical oncology visit.
8. Every two or four weeks (timing is at the discretion of the treating physician). CMP drawn prior to each cycle (± 72 hours)
9. Per SOC guidelines and before starting treatment with durvalumab.
10. Q3 months while on durvalumab.
11. For women of childbearing potential.
12. End of treatment refers to the end of consolidation durvalumab therapy whether due to completion of a full 12 months of durvalumab or discontinuation due to toxicity or progression of disease prior to 12 months.
13. A pre-treatment FDG-PET/CT will be required pre-treatment, post-treatment FDG-PET may be obtained per clinical practice of the medical oncologist and radiation oncologist.
14. ctDNA/biomarker labs will be drawn at the following time points: pre-treatment, during chemoradiation (with Week 3 labs +/- 2 days), post-chemoradiation/pre-durvalumab (with Cycle 1 durvalumab labs +/- 3 weeks), after 3 months of durvalumab (+/- 5 weeks), end of treatment (with 3 month medical oncology follow up +/- 4 weeks), and at 6-month follow-up visit (+/- 8 weeks). If durvalumab is stopped earlier than 3 months due to toxicity or progression, this timepoint will be eliminated. These research draws will occur with regularly scheduled blood draws whenever possible, and not require separate phlebotomy or access.

11.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Form	Completion Schedule
On Study Form Cohort Form	At the time of Study Entry
Chemoradiation Form	After RT is finished
Durvalumab Form	After each cycle of durvalumab
Response Form	Baseline, every 3 months while on durvalumab, end of treatment, coinciding with follow-up schedule
Research Blood Form	Pre-treatment, during chemoradiation, post-chemoradiation/pre-durvalumab, after 3 months of durvalumab, end of treatment, 6-month follow-up visit
Follow-Up Form	Every 3-6 months for 1 year following completion of treatment (or 2 years after start of chemoradiation if participant receives < 12 months of durvalumab). Total follow-up for up to 2 years after start of chemoradiation.
Adverse Event Assessment	Please see section 9.0.
Progression Form	Time of progression
Death Form	Time of death

11.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 7.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

12.0 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, scans will be obtained per protocol as described in Section 10.1, but formal disease control assessments will be batched at the end of the study. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm

with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

12.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory

to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

12.4 Response Criteria

12.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

12.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	>4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	>4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once >4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.4.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

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

12.4.5 Progression-Free Survival

Progression-free survival is defined as survival with no evidence of disease progression (local, regional, or distant) or death.

12.4.6 Response Review

It is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

13.0 DATA SAFETY AND MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually beginning six months after accrual has opened (if at least one patient has been enrolled) or one year after accrual has opened (if no patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every 6 months, and provide a semi-annual report to the QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual.
- Protocol activation date.
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities with the number of dose-limiting toxicities indicated
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

The study principal investigator and Research Patient Coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

14.0 STATISTICAL CONSIDERATIONS

14.1 Stopping Criteria

If at any point during the safety lead-in phase, if 2 or more patients experience a DLT (as defined in section 5.3.1), the trial will be suspended. Additionally, if at any point during the trial enrollment period after expansion into the Phase II component, >3 of the first 10 patients experience grade 3 or greater toxicity (exclusive of laboratory only toxicity) that is probably or definitely attributable to the treatment, and did not predate the initiation of definitive chemoradiation therapy, the trial will be suspended. Symptoms that pre-dated definitive chemoradiation therapy will not count towards the stopping criteria.

If at any time a grade 5 toxicity (death) is observed that is probably or definitely attributable to treatment, accrual will be suspended and the event will be reviewed by the principal investigator. Death that is felt to be due to disease progression or patient comorbidity will not be scored as a grade 5 toxicity and will not result in trial suspension.

14.2 Definition of Primary Endpoint

1. **Safety Lead-in** – Dose limiting toxicities, defined as grade 3 toxicity that cannot be managed with maximal supportive care within 2 weeks, or any grade > 4 toxicity that occurs during treatment.

2. **Phase II** - Rate of local and regional control with MR-guided hypofractionated radiation therapy with concurrent carboplatin/paclitaxel and consolidation durvalumab. Local and/or regional failure will be defined as clinical and/or radiographic evidence of progression of disease at the primary (local) site or previously involved or uninvolved hilar and/or mediastinal nodal (regional) sites. Radiographic progression will be determined per RECIST 1.1 criteria (section 12.0). Disease control assessments will be batched at completion of the study.

14.3 Definition of Secondary and Exploratory Endpoints

The development of adverse events from MR-guided hypofractionated radiation therapy with concurrent carboplatin/paclitaxel and consolidation durvalumab as defined by CTCAE v5 criteria determined to be possibly, probably or definitely related to treatment, and is related to the following specific grades and symptoms:

<u>Grade 3-5 cardiac arrhythmia/cardiac general</u>
- Pericardial effusion
- Pericarditis
- Restrictive cardiomyopathy

<u>Grade 3-5 hemorrhage/bleeding</u>
- Hemorrhage (pulmonary or upper respiratory), excluding nose, larynx, or pharynx

<u>Grade 3-5 neurologic</u>
- Brachial plexopathy
- Laryngeal nerve dysfunction
- Myelitis

- Phrenic nerve dysfunction

Grade 3-5 pulmonary/upper respiratory (except grade 4-5 atelectasis only)

- Atelectasis (grade 4-5 only)
- Fistula
- Hypoxia (provided grade 3 is worse than baseline)
- Obstruction/stenosis of the airway
- Pleural effusion
- Pneumonitis
- Pulmonary fibrosis

Grade 4-5 gastrointestinal

- Dysphagia
- Esophagitis
- Fistula (esophagus)
- Obstruction (esophagus)
- Perforation (esophagus)
- Stricture/stenosis (esophagus)
- Ulcer (esophagus)
- Hemorrhage (esophagus)

Grade 4-5 skin

Any grade 5

Determine likelihood of meeting BED-derived dose constraints for organs at risk (OARs) with MRI-guided hypofractionated radiation therapy, as defined by the proportion of OARs for which planning objectives were met versus violated.

Report preliminary estimates of additional metrics of disease control (tumor response, distant recurrence rate, incidence of brain metastasis, disease-free survival, progression-free survival) and overall survival. Tumor response is defined as achieving a partial or complete response per RECIST criteria. Distant recurrence is defined as development of metastatic, non-local and non-regional disease. Disease free-survival is defined as survival with no evidence of recurrent (local, regional, or distant) disease or death. Progression-free survival is defined as survival with no evidence of disease progression (local, regional, or distant) or death.

Compare dosimetry between the adapted, delivered plans and the original treatment plan, defined by the differences in PTV coverage and doses to OARs between the two treatment modalities.

Collect preliminary dose-volume data for correlation with esophageal, cardiac, and pulmonary toxicity.

Calculate pre-treatment sensitivity of ctDNA/biomarker detection.

Correlate ctDNA levels with radiographically measured tumor burden before and during MRI-guided radiotherapy, and on follow-up imaging.

Correlate ctDNA (detection and levels) with therapeutic response to chemoRT and to immunotherapy.

Correlate biomarker levels with cardiac and pulmonary side effects, as well as with dosimetric values to heart and lungs and other patient characteristics.

Determine lead-time of post-treatment ctDNA detection compared to CT based imaging for identifying recurrent disease.

14.4 Analytic Plan for Primary Endpoint

14.4.1 Safety Lead-in

Safety will be defined as <2/6 patients experiencing DLTs

14.4.2 Sample Size and Study Power

While this study does have a safety lead-in component to determine tolerance to treatment, the sample size for this study is based on the proportion of patients achieving one-year progression free survival which will be compared with the current expected value in the medical literature. Currently, there is no data that exists for concurrent chemotherapy and hypofractionated radiation therapy with online, MR-guided adaptation for locally advanced lung cancer with consolidation immunotherapy. In the PACIFIC trial, Anotonia et al. reported that the 12-month progression-free survival rate for locally advanced NSCLC patients randomized to adjuvant durvalumab was 55.9%. As these results represent the most contemporary treatment paradigm for non-operative locally advanced NSCLC per NCCN guidelines, this represents the current standard for efficacy. MR-guided adaptation with hypofractionated RT with concurrent chemotherapy and adjuvant durvalumab will be considered worthy of further investigation if 1) the treatment-related Grade ≥3 toxicity rate is less than 30% and 2) the 12-month progression free survival is not significantly less than 10% lower than that reported in PACIFIC, which is 45.9%. Assuming the 12-month progression-free survival rate for our treatment is 65.9%, with accrual of 27 patients, a one-sample non-inferiority exact test would have an 80% power and alpha of 0.1 to determine if MR-guided hypofractionated RT would be non-inferior to conventionally fractionated radiation for locally advanced NSCLC patients.

14.4.3 Statistical Analysis for Primary Endpoints

Analysis of the safety lead-in cohort is as described previously and consists of determining the absence or presence of DLTs within the defined time interval (time 0 (defined below) to 6 months after completion of chemoradiation). For time-to-event analysis for local and regional control, time 0 is defined as the initiation (day 1) of chemoradiation. Patients will be censored based on last follow-up if observed no event. An event will be defined as local and/or regional progression (as described in section 14.2) that occurs within our follow-up period. Kaplan-Meier estimates will be used to describe preliminary estimates of local and regional control.

14.5 Analytic Plan for Secondary and Exploratory Endpoints

Adverse events (acute and late toxicities) will be tabulated by type and grade. Acute toxicity timeframe is defined as 60 days from start of chemoRT and possibly/probably/definitely related to RT or chemoRT. Late toxicity timeframe is defined as 60 days from start of chemoRT to 2 years and possibly/probably/definitely related to RT or chemoRT

For estimates of disease control and progression free survival/survival, time 0 for time-to-event analysis is defined as the initiation (day 1) of chemoradiation. Patients will be censored based on last follow up if observed no event. Events will be determined within our follow-up period and based on secondary endpoints as defined in section 14.3. Kaplan-Meier estimates will be used to describe preliminary estimates of disease control and survival, as well as adverse effects. Subgroup estimates will be compared using log-rank tests.

Descriptive statistics will be used to describe the proportion of OARs for which planning objectives were met vs. violated, and compare differences in PTV coverage and OAR doses from the initial, pre-treatment plan to each of the adapted fractions (at treatments 6, 9, and 12). Analysis on the extent of adaptation and its impact on PTV coverage and OAR sparing will then be performed by fusing fraction 6, 9, 12, and 15 MRIs to the initial planning MRI and recreating the initial plan on imaging from these subsequent fractions. Specific assessments will include the percentage volume of the PTV receiving at least 95% of the prescription dose, and changes in PTV coverage, violation of OAR constraints, and frequency and extent of such violations at fraction 6, 9, 12, and 15. These comparisons will be performed using Fisher's Exact Test to evaluate the proportion of fractions with violations and Wilcoxon signed-rank for dosimetry paired comparisons. Additionally, changes in tumor volume will be compared between fractions using the Friedman's Two-Way Analysis of Variance by Ranks.

Dose-volume parameters to esophagus, cardiac, and pulmonary structures will be correlated with the development of toxicity through descriptive statistics and Cox regression.

Plasma-based ctDNA detection sensitivity will be calculated pre-treatment. Conglomerate ctDNA levels (mutant allele fraction) will be calculated by averaging variant allele fractions as previously described (41, 52, 53). Progression-free and overall survival with detectable vs. undetectable ctDNA MRD after chemoRT will be compared by log-rank test as landmark analyses to minimize guarantee-time bias (73). Similar analyses will be performed using ctDNA MRD data from the mid-chemoradiation timepoint and the post-immunotherapy timepoint. Post-treatment ctDNA detection will be compared to CT-based recurrence (assessed by RECIST 1.1 criteria (74)), with lead-time reported as the median and mean of raw time differences, as well as the difference in median estimates from Kaplan-Meier curves.

A nonlinear mixed-effect model will be used to assess longitudinal per-patient trends and to compare differences in biomarkers between the CAE groups, accounting for associations between repeated measurements in the same subjects. Random intercepts and slopes will be included to model intra-patient longitudinal changes, and significance assessed by likelihood ratio. The Kruskal-Wallis test will be used for quantitative biomarker comparisons among patient groups are baseline or a specific timepoint. Spearman correlations will be used to analyze correlations between heart dose variables and biomarker changes. For time-to-event analyses, Cox proportional hazard models will be used to analyze the potential association of biomarkers with clinical characteristics. Clinical covariates will undergo stepwise forward selection (P<0.1 for entry).

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APPENDIX A: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website: http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term “research” encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX B: Reporting Timelines

Expedited Reporting Timelines		
Event	**HRPO**	**QASMC**
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.	
Protocol exception	Approval must be obtained prior to implementing the change	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Breach of confidentiality	Within 10 working days.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.
Minor deviation	Report summary information at the time of continuing review.	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

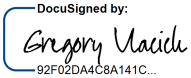
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