NOVEL APPROACH OF PULSED ABRAXANE AND RADIOTHERAPY FOR IMPROVING AND MAINTAINING AMBULATION AFTER CANCER-RELATED CORD COMPRESSION

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Protocol Revision History

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SCHEMA

Eligible Patients

Patients with metastatic epidural spinal cord compression on MRI.

Patients selected will be in Group I and II with ≤37 points. See Table 1 for the scoring scale.

Treatment Plan

4 blocks of *nab*-paclitaxel and RT and 2 blocks of RT alone for a total of 10 fractions of RT and 4 doses of *nab*-paclitaxel

Blocks of nab-Paclitaxel and RT

	Day 1	Day 2
AM	*nab*-Paclitaxel 15 mg/m^2	3 Gy**
PM	3 Gy*	

*latest possible, ideally at least 6 hours later after the start of the *nab*-Paclitaxel infusion
**earliest possible, ideally within 24 hours from the start of the *nab*-Paclitaxel infusion the previous day
Avoid splitting Day 1 and Day 2 over a weekend.

Blocks of RT Day 1
3 Gy

Blocks can be delivered in any order. For example, treatment can start with 1 or 2 RT blocks while chemotherapy is arranged, or an RT block can be strategically placed to avoid splitting a block of pulsed nab-Paclitaxel and RT over the weekend.

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1.0 BACKGROUND AND RATIONALE

1.1 Epidural Spinal Cord Compression (ESCC)

Many cancer patients have asymptomatic or unrecognized epidural spinal cord compression (ESCC), while others present with ESCC, develop it during the course of illness, or it is detected during diagnostic imaging. For these reasons, the incidence of ESCC can only be estimated. One population-based study of spinal cord compression reported that the likelihood of a patient with cancer suffering cord compression in the five years before death was 2.5%, ranging from 0.2% in pancreatic cancer to 7.9% in myeloma **(1)**. A study of malignant spinal cord compression in hospitalized patients with cancer identified an annual incidence of 3.4% **(2)**.

Autopsy studies suggested that 5% of patients dying with cancer have ESCC **(3)**. Similar findings were noted in a Danish study based upon referrals to a regional treatment center, in which the incidence of ESCC in cancer patients rose from 4.4% to 6% between 1979 and 1985 **(4)**.

In a population-based series of over 15,000 hospitalizations for ESCC, the three most common underlying cancer diagnoses were lung cancer, breast cancer, and multiple myeloma; the highest incidence rates were seen in patients with multiple myeloma (15%), Hodgkin and non-Hodgkin lymphomas (13.9%) and prostate cancer (5.5%) **(2)**. Approximately 20% of cases of ESCC are the initial manifestation of malignancy **(5)**. ESCC most commonly arises in the thoracic spine. Approximately 60% of cases occur in the thoracic spine, 30% in the lumbosacral spine, and 10% in the cervical spine **(6)**.

ESCC can have a number of symptoms including pain, motor findings, sensory findings, bladder and bowel dysfunction, and/or ataxia. Pain is usually the first symptom of ESCC, present in 83% to 95% of patients at the time of diagnosis **(4,7)**. Weakness is present in 60% to 85% of patients with ESCC at the time of diagnosis **(7,8)**.

Conventional fractionation is routinely used to palliate the symptoms of ESCC. Most of the data on conventional radiotherapy for ESCC is retrospective in nature. Summarizing the retrospective data, 5125 patient ambulatory outcomes were described, although it is possible that in some cases, patient outcomes were described in different reports by the same authors at different time intervals. Based on the reported data, 4155 patients remained ambulatory after radiation (81%; range, 58%–100%). In the same group of papers, an average of 32% (range, 6%–67%) of patients who were nonambulatory before radiation became ambulatory after radiotherapy alone **(9)**.

Level 1 evidence shows that 60% to 74% of patients remain ambulatory after conventional radiation in the setting of cord compression, whereas 19% to 33% of nonambulatory patients are able to walk after radiation. Prospective series and retrospective data report rates of ambulation are somewhat more optimistic than the data from randomized trials, but there is no doubt that conventional radiation is able to provide ambulatory benefit to patients who undergo treatment. Ambulation status is correlated with survival.

However, ambulation status may have less to do with radiation therapy than with the ability of the patient to walk before treatment, or the timing between radiation and the onset of symptoms, as only a minority of patients who are nonambulatory before treatment are able to walk after radiation. Pain is palliated in about 50% to 70% of patients treated with conventional radiotherapy **(9)**. For multiple myeloma, 30 Gy in 10 fractions resulted in better functional outcome than short-course radiotherapy **(10)**.

A scoring system for predicting post-radiotherapy ambulatory rates was proposed taking into consideration the variables in **Table 1 (11)**. **Figure 1** illustrates the original five total score groups versus the ambulatory rate. These 5 groups were subsequently validated prospectively and simplified into 3 groups: I, II, and III which we will use in this clinical trial. **(12)**

Table 1. Significant Prognostic Factors and Corresponding Scores. **(11)**

Variable	Post-RT ambulatory rate (%)	Score
Type of primary tumor		
Breast cancer	81	8
Prostate cancer	68	7
Myeloma/lymphoma	89	9
Non–small-cell lung cancer	54	5
Small-cell lung cancer	64	6
Cancer of unknown primary	45	5
Renal cell carcinoma	62	6
Colorectal cancer	64	6
Other tumors	59	6
Interval from tumor diagnosis to MSCC		
≤15 mo	58	6
>15 mo	78	8
Visceral metastases at the time of RT		
Yes	54	5
No	77	8
Motor function before RT		
Ambulatory without aid	98	10
Ambulatory with aid	89	9
Not ambulatory	28	3
Paraplegic	7	1
Time of developing motor deficits before RT		
1–7 days	37	4
8–14 days	69	7
>14 days	88	9

Figure 1. Original scoring system. Post-radiotherapy ambulatory rates of the five patient groups formed according to the total score (A: ≤28 points; B: 29–31 points; C: 32–34 points; D: 35–37 points; E: ≥38 points) **(11)**

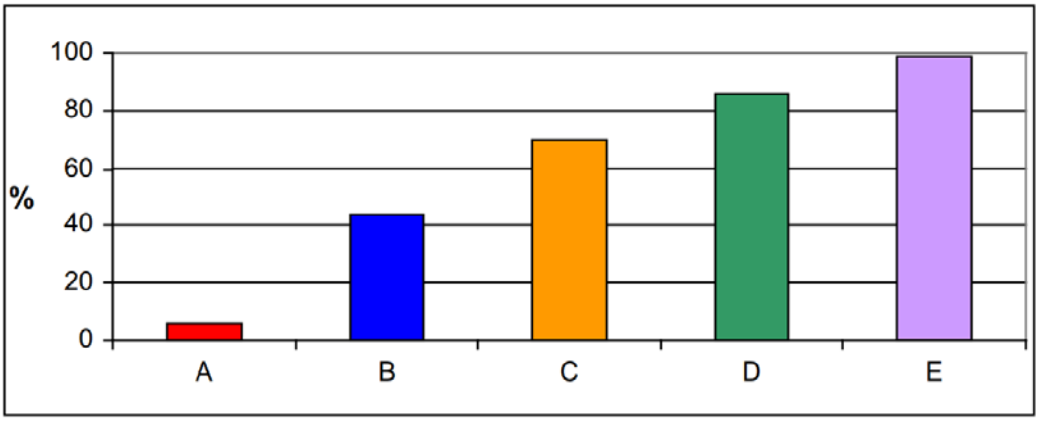
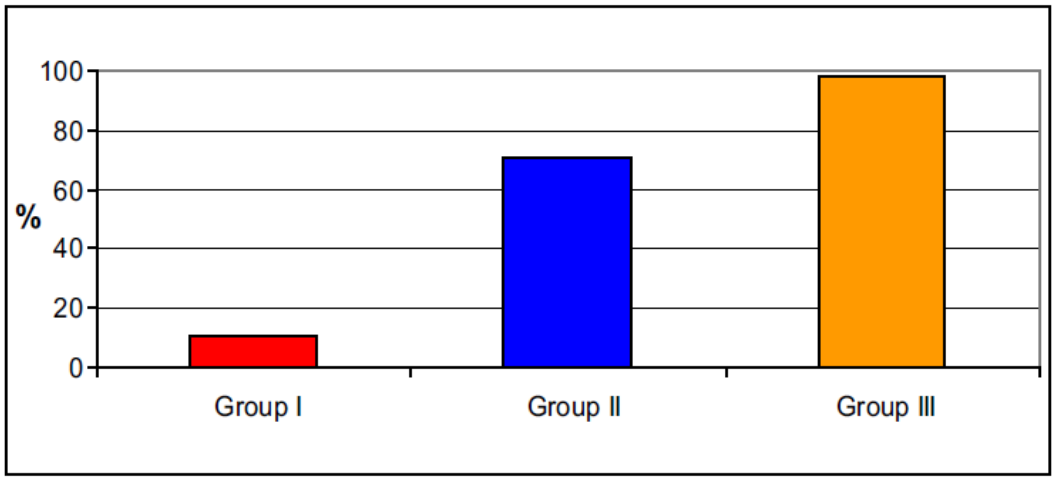


Figure 2. Simplified scoring system. Postradiotherapy ambulatory rates for patients of Group I (21–28 points), Group II (29–37 points), and Group III (38–44 points).This scoring system will be used in the trial **(12)**



1.2 *nab*-Paclitaxel (Abraxane)

nab-Paclitaxel is a novel biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. *nab*-Paclitaxel for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) is currently indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy; for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy; and for the first-line treatment of patients with metastatic

adenocarcinoma of the pancreas, in combination with gemcitabine.

Paclitaxel at the proposed dose and schedule has been studied in multiple lung cancer trials (Phase I, Phase I/II, Phase II, and Phase III) and deemed safe and effective **(13-16)**. Compared to paclitaxel, *nab*-paclitaxel causes less neutropenia, hypersensitivity reactions, diarrhea and nausea than standard paclitaxel.

1.3 Rationale for Concurrent pulsed Paclitaxel with Radiotherapy

The most radiosensitive phase of the cell cycle is G2/M. The radiosensitivity difference between G2/M and the most radioresistant phase can be an order of magnitude. Unfortunately mammalian tumor cells spend consistently around 1 hour in G2/M, while the rest of the phases in the cell cycle have high variability in length.

One strategy to exploit the radiosensitivity of G2/M is pulsed paclitaxel. This strategy was based on preclinical translational research suggesting that a low dose of paclitaxel would maximally block most tumor cells in the G2/M cell cycle phase, the most radiosensitive phase, in 24 hours. Therefore, by administering paclitaxel three times a week and using an alternating schedule of radiotherapy, the radiation treatments would be optimally radiosensitized **(17)**.

This strategy has been studied clinically in lung cancer at the University of Rochester, and its safety and tolerability are well documented (see **Table 2** and **Table 3**) **(13-15,18)**. Much higher doses of radiotherapy were delivered in these studies (60 to 70 Gy in 30 to 35 fractions) than the 30 Gy proposed in this trial, and with more cycles of chemotherapy. In addition, higher cumulative doses of paclitaxel were delivered (3 paclitaxel doses of 15 mg/m^2 per week, for 6 weeks), versus the proposed 4 doses of *nab*-paclitaxel of 15 mg/m^2. In the phase III trial, patients had also received 2 to 4 cycles of induction chemotherapy, including cisplatin containing doublets: vinorelbine/cisplatin, gemcitabine/cisplatin, paclitaxel/cisplatin, docetaxel/cisplatin, or pemetrexed/cisplatin **(15)**.

Another trial designed by Dr. Gay treated lung cancer patients with 55 Gy, with the last week utilizing 3 Gy fractions. The same pulsed paclitaxel strategy was used, and 4 cycles of adjuvant gemcitabine and carboplatin were delivered **(16)**. Spinal cord toxicity has not been observed in any of these clinical trials. Therefore, we anticipate that the proposed lower dose of 30 Gy in 10 fractions and only 4 doses of *nab*-paclitaxel of 15 mg/m^2 will be safe and well tolerated, even in patients who may have received previous chemotherapy.

Table 2. Arm 1 [paclitaxel at 15 mg/ m^2, three times per week (Monday, Wednesday, and Friday) for 6 weeks] and Arm 2 (weekly paclitaxel at 45 mg/m^2 for 6 weeks). **(15)**

Toxicities	Arm 1 (n = 71) vs. Arm 2 (n = 59)	Grades (no. of patients)					p-Value
		G-1	G-2	G-3	G-4	G-5	
Weight loss	1	7	1	0	0	0	0.32
	2	10	1	0	0	0	
Fatigue	1	22	2	0	0	0	0.13
	2	14	7	0	0	0	
Fever	1	23	10	0	0	0	0.97
	2	18	8	0	0	0	
Nausea	1	8	10	0	0	0	0.34
	2	3	11	1	0	0	
Vomiting	1	1	1	0	0	0	0.55
	2	3	1	0	0	0	
Cough	1	28	9	0	0	0	0.47
	2	24	5	2	0	0	
Dyspnea	1	11	5	1	0	0	0.84
	2	6	4	1	0	0	
Esophagitis	1	15	21	3	0	0	0.11
	2	4	21	5	0	0	
Pneumonitis	1	1	8	13	0	1	0.52
	2	3	7	6	0	2	

Table 3. Hematological toxicities: ≥ Grade 3. Arm 1 and 2 as in **Table 2**. **(15)**

Arms	Leucopenia		Neutropenia		Anemia		Thrombopenia	
Grades	G-3	G-4	G-3	G-4	G-3	G-4	G-3	G-4
1 (n = 71)	3	0	0	0	1	0	0	0
2 (n = 59)	14	1	8	2	2	0	2	1
p-Value	<0.001		<0.001		0.43		0.48	

A particularly useful advantage of this strategy is the rapid tumor shrinkage (average tumor volume reduction at 1 month post-therapy was 69.9 ± 22.6% [standard deviation]) **(18)**. A rapid reduction in tumor volume of a few millimeters may have a dramatic impact in a patient experiencing motor deficits, sensory deficits, and/or pain from ESCC.

2.0 OBJECTIVES

2.1 Primary Objective

To assess ambulatory status at 1 month in patients with ESCC treated with pulsed nab-paclitaxel and radiotherapy.

2.2 Secondary Objectives

1. To assess ambulatory status at 3 months, 6 months, 9 months, and 12 months in patients with ESCC treated with pulsed nab-paclitaxel and radiotherapy.
2. To assess strength of lower extremities at 1 month in patients with ESCC treated with pulsed nab-paclitaxel and radiotherapy.
3. To assess pain in the irradiated area in patients with ESCC treated with pulsed nab-paclitaxel and radiotherapy at 1 month, 3 months, 6 months, 9 months, and 12 months.

2.3 Exploratory Objectives

1. To determine the retreatment rate of patients with ESCC treated with pulsed nab-paclitaxel and radiotherapy.
2. To determine quality of life in patients with ESCC treated with pulsed nab-paclitaxel and radiotherapy at 1 month, 3 months, 6 months, 9 months, and 12 months.
3. To determine the walking index in patients with ESCC using the walking index for spinal cord injury scale (WISCI II) in patients with ESCC treated with pulsed nab-paclitaxel and radiotherapy at 1 month, 3 months, 6 months, 9 months, and 12 months.

3.0 PATIENT SELECTION

3.1 Inclusion Criteria

1. Patients with ≤ 37 points per the scoring system in the table below.

Variable	Post-RT ambulatory rate (%)	Score
Type of primary tumor		
Breast cancer	81	8
Prostate cancer	68	7
Myeloma/lymphoma	89	9
Non–small-cell lung cancer	54	5
Small-cell lung cancer	64	6
Cancer of unknown primary	45	5
Renal cell carcinoma	62	6
Colorectal cancer	64	6
Other tumors	59	6
Interval from tumor diagnosis to MSCC		
≤15 mo	58	6
>15 mo	78	8
Visceral metastases at the time of RT		
Yes	54	5
No	77	8
Motor function before RT		
Ambulatory without aid	98	10
Ambulatory with aid	89	9
Not ambulatory	28	3
Paraplegic	7	1
Time of developing motor deficits before RT		
1–7 days	37	4
8–14 days	69	7
>14 days	88	9

2. Histologically or cytologically confirmed diagnosis of cancer not of CNS or spinal column origin.

3. MRI or CT evidence of metastatic epidural spinal cord compression.

4. Patients who have started 30 Gy in 10 fractions are not excluded as long as 4 doses of chemotherapy could potentially be given. This means the latest *nab*-paclitaxel can start is the morning of the third fraction of radiotherapy. Radiotherapy should ideally be delivered at least 6 hours after the *nab*-paclitaxel infusion started.

5. At least 18 years of age.

6. Normal bone marrow and organ function as defined below:
   a. Absolute neutrophil count ≥ 1,500 cells/mm^3
   b. Platelets ≥ 100,000 cells/mm^3 (transfusion independent, defined as not receiving platelet transfusions within 7 days prior to blood draw)
   c. Hemoglobin > 9.0 g/dL
   d. Total bilirubin ≤ 1.5 mg/dL
   e. AST(SGOT)/ALT(SGPT) ≤ 2.5 x IULN
   f. Alkaline phosphatase ≤ 2.5 x IULN (unless bone metastasis is present (< 5 x IULN) in the absence of liver metastasis)
   g. Creatinine ≤ 1.5 mg/dL

7. Women of childbearing potential (defined as a sexually mature woman who (1) has not undergone hysterectomy or bilateral oophorectomy or (2) has not been naturally postmenopausal for at least 24 consecutive months) must:
   a. Either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting treatment with nab-paclitaxel and while on study; and
   b. Have a negative serum pregnancy test result at screening and agree to ongoing pregnancy testing during the course of the study and after the end of study therapy. This applies even if the subject practices true abstinence from heterosexual contact.

8. Male subjects must practice true abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions, and for 6 months following nab-paclitaxel discontinuation, even if he has undergone a successful vasectomy.

9. Ability to understand and willingness to sign an IRB approved written informed consent document (or that of legally authorized representative, if applicable).

3.2 Exclusion Criteria

1. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, or cardiac arrhythmia.

2. Pregnant and/or breastfeeding. Women of childbearing potential must have a negative serum pregnancy test prior to study entry.

3. Known HIV-positivity on combination antiretroviral therapy because of the potential for pharmacokinetic interactions with nab-paclitaxel. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

4. Previous spinal cord radiotherapy that would overlap with the proposed treatment field.

5. Spinal instability or bony retropulsion causing the cord compression. That is, mechanical, not tumor, cord compression. In these cases surgery may be indicated.

6. Patients eligible for surgical decompression like laminectomy.

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 by 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.

5.0 TREATMENT PLAN

5.1 Chemoradiotherapy

A total of 10 fractions of 3 Gy each are delivered. A total of four chemoradiation blocks as described in the table below should be delivered ideally in consecutive days (Day 1 and 2 ideally not separated by a weekend). On Day 1 of the chemoradiation block, *nab*-paclitaxel (15 mg/m^2) is delivered in the morning followed by radiotherapy the latest possible and ideally at least 6 hours later (no earlier than 4 hours after the start of *nab*-paclitaxel). On Day 2, radiotherapy is delivered in the morning, ideally within 24 hours from the start of the *nab*-Paclitaxel infusion the previous day. There is flexibility in how these blocks are arranged. There will be 2 radiation fractions that won't be part of any chemoradiation block and can be placed anywhere before, after, or between blocks.

Chemoradiation block x 4

	Day 1***	Day 2***
AM	*nab*-Paclitaxel 15 mg/m^2	3 Gy**
PM	3 Gy*	

*latest possible, ideally at least 6 hours later after the start of the *nab*-Paclitaxel infusion
**earliest possible, ideally within 24 hours from the start of the *nab*-Paclitaxel infusion the previous day
***Avoid splitting Day 1 and Day 2 over a weekend.

5.2 *nab*-Paclitaxel Premedication Administration

Patients do not require premedication prior to *nab*-paclitaxel administration, as hypersensitivity reactions are rare. In the unlikely event of a mild hypersensitivity reaction, premedication may be administered using the premedication regimen the institution typically uses for solvent based paclitaxel. In the rare event of a severe hypersensitivity reaction, discontinue *nab*-paclitaxel (but continue RT). However, it is recommended that patients receive granisetron 1mg prior to receiving *nab*-paclitaxel.

5.3 *nab*-Paclitaxel Agent Administration

Albumin-bound paclitaxel should be administered by IV over 30 minutes. The drug can be administered either inpatient or outpatient depending on the condition of the patient.

NOTE: It is not a requirement to use filter needles in the preparation of, or in-line filters during the administration of *nab*-paclitaxel. In any event, filters of pore-size less than 15 micrometers must not be used.

5.4 Dexamethasone

At the discretion of the physician, patients without neurologic deficits or with only

radiculopathy and no massive invasion of the spine do not need to receive dexamethasone. **(20)** The rest of the patients with cord compression should receive a loading IV dose of dexamethasone (suggested dose 10 mg IV), followed by dexamethasone 4 to 6 mg every 6 to 8 hours unless the physician thinks the potential for harm outweighs the benefits (i.e. diabetes, peptic ulcer disease, etc.).

5.5 Radiotherapy

A total dose of 30 Gy in 10 consecutive daily fractions (Monday to Friday) will be delivered to the vertebral body(ies) causing the cord compression. Treatments can start during the weekend if necessary. An additional 1-2 vertebral bodies above and below the target lesion may be treated at the discretion of the radiation oncologist. Other vertebral bodies with radiologic evidence of metastatic disease may be treated if the patient is experiencing pain, neurologic symptoms, or if the radiation oncologist anticipates tumor progression may result in future symptoms that may require palliation. Treatment technique could be 2D, 3D conformal, or IMRT at the discretion of the radiation oncologist as long as treatment starts within 36 hours of the cord compression referral**. Choose a beam arrangement to avoid or minimize radiation to the esophagus, head and neck mucosal surfaces and salivary glands, and small bowel. AP-PA beams may be preferred ONLY in the thorax if there is tumor in the lung, sternum, or mediastinum anterior to the vertebral bodies to be treated since this approach has been used to treat lung tumors and is well understood. Avoid AP-PA arrangements encompassing the gastrointestinal tract and to a lesser degree the head and neck as feasible to minimize unnecessary toxicity.**

5.5.1 CT Simulation

As per routine practice, computed tomography (CT) will be the primary image platform for targeting and treatment planning.

5.5.2 Virtual Simulation and Contouring

The CT scan will be exported to a commercially available virtual simulation software package.

5.6 Evaluability

All patients who receive any study treatment are evaluable for toxicity. Patients are evaluated from first receiving study treatment until a 28-day follow up after the conclusion of treatment or death.

Response will be evaluated at 1 month and every 3 months for one year. A positive response to treatment will be scored for patients who were nonambulatory or paraplegic and then became ambulatory without an aid or ambulatory with an aid. A positive response to treatment will be scored for patients who were ambulatory with an aid and then became ambulatory without an aid. **(11)**

5.7 Women of Childbearing Potential

Women of childbearing potential (defined as a sexually mature woman who (1) has not undergone hysterectomy or bilateral oophorectomy or (2) has not been naturally postmenopausal for at least 24 consecutive months) must either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis) or agree to use, and be able to comply with, effective contraception without interruption, 28 days prior to starting treatment with nab-paclitaxel and while on study; and have a negative serum pregnancy test result at screening and agree to ongoing pregnancy testing during the course of the study and after the end of study therapy. This applies even if the subject practices true abstinence from heterosexual contact.

Male subjects must practice true abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions, and for 6 months following nab-paclitaxel discontinuation, even if he has undergone a successful vasectomy.

If a patient is suspected to be pregnant, 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 or within 28 days after the last dose of nab-paclitaxel, the investigator must be notified in order to facilitate outcome follow-up.

5.8 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 10 fractions of RT (including 4 blocks of chemoradiation) 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 unable to receive 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.

5.9 Duration of Follow-up

Patients will be followed for one year after the completion of treatment. A phone evaluation, review of medical record, or physical follow-up visit ensues every 3 months for a year or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6.0 DOSE DELAYS/DOSE MODIFICATIONS

6.1 nab-Paclitaxel

Dose reductions or discontinuation may be needed based on severe hematologic, neurologic, cutaneous, or gastrointestinal toxicities. Use the table below as a guideline for dose modifications.

Dose Level	*nab*-Paclitaxel (mg/m^2)
Starting Dose	15
-1	10
-2	omit

Sensory Neuropathy
If ≥ Grade 3 sensory neuropathy develops, withhold nab-paclitaxel until resolution to Grade 1 or 2 followed by a dose reduction for all subsequent courses of nab-paclitaxel.

Hypersensitivity Reactions
Hypersensitivity reactions rarely occur, but severe and sometimes fatal hypersensitivity reactions, including anaphylactic reactions, have been reported.

If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Patients who experience a severe hypersensitivity reactions to nab-paclitaxel should not be re-challenged. The use of nab-paclitaxel in patients previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Administration of Study Drug to Patients with Abnormal Hematologic Function
nab-Paclitaxel dosing should not be administered unless the patient's ANC > 0.5×10^9 cells/L and platelets > 50×10^9 cells/L. If the ANC or platelets are not adequate on the day of administration, the dose for that day will be omitted.

Hepatic Impairment
For patients with mild hepatic impairment (total bilirubin > ULN and ≤ 1.5 x ULN and AST ≤ 10 x ULN), no dose adjustments are required regardless of indication. For patients with moderate hepatic impairment (total bilirubin between 1.5 x ULN and 5 x ULN), reduce nab-paclitaxel by one dose level. Do not administer nab-paclitaxel to patients with total bilirubin > 5 x ULN or AST > 10 x ULN regardless of indication as these patients have not been studied.

Other Toxicities
If toxicities are > grade 3, except for anemia and lymphopenia, treatment should be withheld until resolution to < grade 1 or baseline if baseline was greater than grade 1, then

reinstituted, if medically appropriate, at the next lower dose level.

6.2 Radiotherapy

No dose adjustments are permitted for radiotherapy.

7.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outline below.

The Washington University Human Research Protection Office (HRPO) requires that all events meeting the definition of unanticipated problem or serious noncompliance be reported as outlined in Section 7.2.

The FDA requires that all serious and unexpected adverse events be reported as outlined in Section 7.5. In addition, any fatal or life-threatening adverse experiences where there is a reasonable possibility of relationship to study intervention must be reported.

Celgene Corporation requires that all events being reported to the FDA be reported as outlined in Section 7.4.

7.1 Definitions

7.1.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

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

7.1.2 Serious Adverse Event (SAE)

Definition: any adverse drug experience occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention

to prevent one of the outcomes listed above

All unexpected SAEs must be reported to the FDA.

7.1.3 Unexpected Adverse Experience

Definition: any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

Events that are both serious AND unexpected must be reported to the FDA.

7.1.4 Life-Threatening Adverse Experience

Definition: any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Life-threatening adverse experiences must be reported to the FDA.

7.1.5 Unanticipated Problems

Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.1.6 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

7.1.7 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

7.1.8 Protocol Exceptions

Definition: A planned deviation from the approved protocol that are under the research team's control. Exceptions apply only to a single participant or a singular situation.

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

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

The PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at WU, any BJH or SLCH institution, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within **10 working days** of the occurrence of the event or notification to the PI of the event. The death of a research participant that qualifies as a reportable event should be reported within **1 working day** of the occurrence of the event or notification to the PI of the event.

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

The PI is required to notify the QASMC of any unanticipated problem occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO as reportable. (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 a QASMC auditor.

7.4 Reporting to Celgene Corporation

All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's

knowledge of the event by facsimile or other appropriate method using the SAE report form or approved equivalent form.

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to nab-paclitaxel based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (AX-CL-OTHER-PI-13261) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

7.4.1 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 28 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

IF THE OUTCOME OF THE PREGNANCY WAS ABNORMAL (E.G., SPONTANEOUS OR THERAPEUTIC ABORTION), THE INVESTIGATOR SHOULD REPORT THE ABNORMAL OUTCOME AS AN AE. IF THE ABNORMAL OUTCOME MEETS ANY OF THE SERIOUS CRITERIA, IT MUST BE REPORTED AS AN SAE TO CELGENE DRUG SAFETY IMMEDIATELY BY FACSIMILE, OR OTHERAPPROPRIATE METHOD, WITHIN 24 HOURS OF THE INVESTIGATOR'S KNOWLEDGE OF THE EVENT USING THE SAE REPORT FORM, OR APPROVED EQUIVALENT

FORM.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

7.4.2 Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. Male patients treated with nab-paclitaxel are advised not to father a child during and up to 6 months after treatment.

7.4.3 Overdose

Overdose, as defined for this protocol, refers to nab-paclitaxel dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of nab-paclitaxel assigned to a given patient, regardless of any associated adverse events or sequelae.

PO	any amount over the protocol-specified dose
IV	10% over the protocol-specified dose
SC	10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. For nab-paclitaxel, an infusion completed in less than 25 minutes may increase Cmax by approximately 20%, therefore a nab-paclitaxel infusion completed in less than 25 minutes will meet the infusion rate criterion for an overdose.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

7.4.4 Drug Safety Contact Information

Celgene Corporation
Global Drug Safety and Risk Management
86 Morris Avenue

Summit, New Jersey 07901
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com
Telephone: 1-908-673-9667
Toll Free: 1-800-640-7854

7.5 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR HRPO/QASMC.** It is the responsibility of the investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences (Section 7.1.4) associated with use of the drug (i.e., there is a reasonable possibility that the experience may have been caused by the drug) by telephone or fax no later than **7 calendar days** after initial receipt of the information.
- Report any serious, unexpected adverse experiences (Section 7.1.2), as well as results from animal studies that suggest significant clinical risk within **15 calendar days** after initial receipt of this information.

All MedWatch forms will be sent by the investigator or investigator's team to the FDA at the following address or by fax:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products
5901-B Ammendale Rd.
Beltsville, MD 20705-1266
FAX: 1-800-FDA-0178

7.6 Timeframe for Reporting Required Events

Adverse events will be tracked for 28 days after the last dose of nab-paclitaxel. Late toxicities for RT will be collected for 1 year after the end of RT.

8.0 PHARMACEUTICAL INFORMATION

8.1 *nab*-Paclitaxel Description

8.1.1 *nab*-Paclitaxel Description

nab-Paclitaxel is a novel biologically interactive albumin-bound paclitaxel combining a protein with a chemotherapeutic agent in the particle form. *nab*-Paclitaxel for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) is currently indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.

Molecular formula: C47H51N014
Chemical name: 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13
Molecular weight: 853.91.

8.1.2 Clinical Pharmacology

nab-Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. Paclitaxel induces abnormal arrays or "bundles" of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

8.1.3 Pharmacokinetics and Drug Metabolism

Absorption
The pharmacokinetics of total paclitaxel following 30 and 180-minute infusions of *nab*-Paclitaxel at dose levels of 80 to 375 mg/m2 were determined in clinical studies. Dose levels of mg/m2 refer to mg of paclitaxel in *nab*-Paclitaxel. Following intravenous administration of *nab*-Paclitaxel, paclitaxel plasma concentrations declined in a biphasic manner, the initial rapid decline representing distribution to the peripheral compartment and the slower second phase representing drug elimination. The drug exposure (AUCs) was dose proportional over 80 to 300 mg/m2 and the pharmacokinetics of paclitaxel for *nab*-Paclitaxel were independent of the duration of intravenous administration. The pharmacokinetic data of 260 mg/m2 *nab*-Paclitaxel administered over a 30-minute infusion was compared to the pharmacokinetics of 175 mg/m2 paclitaxel injection over a 3-hour infusion. Clearance was larger (43%) and the volume of distribution was higher (53%) for *nab*-Paclitaxel than for paclitaxel injection. There were no differences in terminal half-lives.

Distribution
Following *nab*-Paclitaxel administration to patients with solid tumors, paclitaxel is evenly distributed into blood cells and plasma and is highly bound to plasma proteins (94%). In a within-patient comparison study, the fraction of unbound paclitaxel in plasma was significantly higher with *nab*-Paclitaxel (6.2%) than with solvent-based paclitaxel (2.3%). This contributes to significantly higher exposure to unbound paclitaxel with *nab*-Paclitaxel compared with solvent-based paclitaxel, when the total exposure is comparable. In vitro studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0.1 to 50 μg/mL, indicated that the presence of cimetidine, ranitidine, dexamethasone, or diphenhydramine did not affect protein binding of paclitaxel. The total volume of distribution is approximately 1741 L; the large volume of distribution indicates extensive extravascular distribution and/or tissue binding of paclitaxel.

Metabolism
In vitro studies with human liver microsomes and tissue slices showed that paclitaxel was metabolized primarily to 6α- hydroxypaclitaxel by CYP2C8; and to two minor metabolites, 3'-p-hydroxypaclitaxel and 6α, 3'-p-dihydroxypaclitaxel, by CYP3A4. In vitro, the metabolism of paclitaxel to 6α-hydroxypaclitaxel was inhibited by a number of agents (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporin, teniposide, etoposide, and vincristine), but the concentrations used exceeded those found in vivo following normal therapeutic doses. Testosterone, 17α-ethinyl estradiol, retinoic acid, and quercetin, a specific inhibitor of CYP2C8, also inhibited the formation of 6α-hydroxypaclitaxel in vitro. The pharmacokinetics of paclitaxel may also be altered in vivo as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4.

Elimination
At the clinical dose range of 80 to 300 mg/m2 , the mean total clearance of paclitaxel ranges from 13 to 30 L/h/m2 , and the mean terminal half-life ranges from 13 to 27 hours. After a 30-minute infusion of 260 mg/m2 doses of ABRAXANE, the mean values for cumulative urinary recovery of unchanged drug (4%) indicated extensive non-renal clearance. Less than 1% of the total administered dose was excreted in urine as the metabolites 6α-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel. Fecal excretion was approximately 20% of the total dose administered.

Pharmacokinetics in Hepatic Impairment
The effect of hepatic impairment on the pharmacokinetics of paclitaxel following ABRAXANE administration was studied in patients with advanced solid tumors. The results showed that mild hepatic impairment (total bilirubin >1 to ≤1.5 x ULN, AST ≤10 x ULN, n=8) had no clinically important effect on pharmacokinetics of paclitaxel. Patients with moderate (total bilirubin >1.5 to ≤ 3 x ULN, AST ≤10 x ULN, n=7) or severe (total bilirubin >3 to ≤5 x ULN, n=5) hepatic impairment had a 22% to 26% decrease in the maximum elimination rate of paclitaxel and

approximately 20% increase in mean paclitaxel AUC compared with patients with normal hepatic function (total bilirubin ≤ULN, AST ≤ULN, n=130).

Elimination of paclitaxel shows an inverse correlation with total bilirubin and a positive correlation with serum albumin. Pharmacokinetic/pharmacodynamic modeling indicates that there is no correlation between hepatic function (as indicated by the baseline albumin or total bilirubin level) and neutropenia after adjusting for ABRAXANE exposure. Pharmacokinetic data are not available for patients with total bilirubin >5 x ULN or for patients with metastatic adenocarcinoma of the pancreas.

Pharmacokinetics in Renal Impairment
The effect of pre-existing mild (creatinine clearance ≥60 to <90 mL/min, n=61) or moderate (creatinine clearance ≥30 to <60 mL/min, n=23) renal impairment on the pharmacokinetics of paclitaxel following ABRAXANE administration was studied in patients with advanced solid tumors. Mild to moderate renal impairment had no clinically important effect on the maximum elimination rate and systemic exposure (AUC and Cmax) of paclitaxel.

Other Intrinsic Factors
Population pharmacokinetic analyses for ABRAXANE show that body weight (40 to 143 kg), body surface area (1.3 to 2.4 m2), gender, race (Asian vs. White), age (24 to 85 years) and type of solid tumors do not have a clinically important effect on the maximum elimination rate and systemic exposure (AUC and Cmax) of paclitaxel.

The effect of pre-existing mild (creatinine clearance ≥60 to The metabolism of paclitaxel is catalyzed by CYP2C8 and CYP3A4. Caution should be exercised when administering ABRAXANE concomitantly with medicines known to inhibit (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) or induce (e.g., rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) either CYP2C8 or CYP3A4.

8.1.4 Supplier(s)

nab-Paclitaxel will be distributed by Celgene Corporation and labeled appropriately as investigational material for this study. Labels will bear Celgene's name and address, the protocol number, product name, dosage form and strength, medication identification/kit number, lot number, expiry date, dosing instructions, storage conditions, the quantity of IP contained, and require education statements and/or regulatory statements as applicable. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with *nab*-Paclitaxel upon identification and screening of a potential trial subject.

Upon identification of a potential subject, sites must fax a completed Drug Request

Form to Celgene Corporation. Allow at least 5 working days for drug shipment. There are no shipments on Fridays or holidays. For re-supply of drug, please complete and fax the Drug Request Form to Celgene Corporation at 908-673-2779.

8.1.5 Dosage Form and Preparation

Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel.

Please see local prescribing information for *nab*-paclitaxel for detailed instructions on the reconstitution and administration.

8.1.6 Storage and Stability

Please see local prescribing information for *nab*-paclitaxel for detailed instructions on the reconstitution, storage conditions, and IV administration of *nab*-paclitaxel.

8.1.7 Administration

nab-Paclitaxel is injected into a vein [intravenous (I.V.) infusion] over 30 minutes. The use of an in-line filter is not recommended. Following administration, the intravenous line should be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure complete administration of the complete dose, according to local practice.

8.1.8 Special Handling Instructions

nab-Paclitaxel is a cytotoxic drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling *nab*-Paclitaxel. The use of gloves is recommended. If *nab*-Paclitaxel (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If *nab*-Paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water.

9.0 STUDY CALENDAR

Scans and x-rays must be done no more than 8 weeks prior to SIM date.

	Screening[e]	**Baseline**	**Treatment**	**1 month +/- 1 week**	**Every 3 months for 1 year**
Informed consent	X				
Physical exam, weight	X				
CBC	X		X[d]	X	
CMP	X		X[d]	X	
Pregnancy test[c]	X				
MRI or CT of cervical, thoracic, and/or lumbar spine	X				
ECOG	X			X*	X*
Radiation			X[a]		
nab-Paclitaxel			X[b]		
Lower extremity strength		X		X	X
Ambulatory Status		X		X*	X*
Pain		X		X*	X*
WISCI II scale		X		X	X
SF-12		X		X*	X*
Adverse event assessment		X ---------- X			

a. 10 daily fractions of 3 Gy
b. 4 doses; refer to Section 5.1 for schedule
c. Women of childbearing potential only
d. Prior to the 3rd dose of nab-paclitaxel only
e. +/- 2 days after start of RT

*Office visit preferred. Phone call allowed if patient is unable to come to clinic.

10.0 DATA SUBMISSION SCHEDULE

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

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form	Prior to starting treatment
Treatment Summary Form	End of treatment
Toxicity Form	Continuous
Follow Up Form	1 month, 3 months, 6 months, 9 months, 12 months
Ambulatory Status Form Lower Extremity Strength Form Pain Form QOL Form	Baseline, 1 month, 3 months, 6 months, 9 months, 12 months
MedWatch Form	See Section 7.0 for reporting requirements

11.0 DATA AND SAFETY 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 five patients have been enrolled) or one year after accrual has opened (if fewer than five patients have been enrolled at the six-month mark).

The Principal Investigator will review all patient data at least every six 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
- 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.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study design

This is a single arm phase II study. All enrolled patients will receive both radiation therapy and chemotherapy when the trial starts. A score using a scoring system in the table below will be calculated for every patient at the beginning of the trial. The patients with ≤ 37 points per the scoring system are included in this study. Groups I and II include the patients with scores of 21-28 and 29-37, respectively.

Variable	Post-RT ambulatory rate (%)	Score
Type of primary tumor		
Breast cancer	81	8
Prostate cancer	68	7
Myeloma/lymphoma	89	9
Non–small-cell lung cancer	54	5
Small-cell lung cancer	64	6
Cancer of unknown primary	45	5
Renal cell carcinoma	62	6
Colorectal cancer	64	6
Other tumors	59	6
Interval from tumor diagnosis to MSCC		
≤15 mo	58	6
>15 mo	78	8
Visceral metastases at the time of RT		
Yes	54	5
No	77	8
Motor function before RT		
Ambulatory without aid	98	10
Ambulatory with aid	89	9
Not ambulatory	28	3
Paraplegic	7	1
Time of developing motor deficits before RT		
1–7 days	37	4
8–14 days	69	7
>14 days	88	9

12.2 Study Endpoints

12.2.1 Primary Endpoint

The primary endpoint includes ambulatory status at 1 month. Ambulatory status is categorized as paraplegic, not ambulatory, ambulatory with aid (for example, with assistive device like walker or crutches), and ambulatory without aid. Ambulatory rate is defined as the proportion of number of patients who are either ambulatory

with aid or ambulatory without aid among the enrolled patients.

12.2.2 Secondary Endpoints

The secondary endpoints include ambulatory status and pain in irradiated area every 3 months until 1 year, strength assessment of lower extremities at 1 month. Ambulatory status at 3 months and every 3 months for 1 year, may be though phone interview. Strength assessment is categorized as follows

Strength assessment of lower extremities

0/5	no contraction
1/5	muscle flicker, but no movement
2/5	movement possible, but not against gravity (test the joint in its horizontal plane)
3/5	movement possible against gravity, but not against resistance by the examiner
4/5	movement possible against some resistance by the examiner
5/5	normal strength.

Pain in irradiated area from 0-10 at 3 months and every 3 months for 1 year, may be though phone interview, medical record review, or office visit.

12.2.3 Exploratory Endpoints

The exploratory endpoints include retreatment rate, quality of score and walking index at 1 month and every 3 months until 1 year. Retreatment rate is defined as the proportion of number of patients who are retreated during the study among the enrolled patients. Quality of life score and walking index are calculated using the 12-Item Short Form Health Survey (SF-12) questionnaire and WISCI II, respectively.

12.3 Sample size calculation

The sample size calculations are based on the primary endpoint – ambulatory status only. Patients with cord compression have a number of clinical characteristics listed in **Table 1** including type of primary tumor, interval from tumor diagnosis, visceral metastases, motor function before RT, and time of developing motor deficits. Each one is associated with a score and although these scores were simplified into groups I, II, and III (**Figure 2**) with ambulatory rates of 10.6 %, 70.9 %, and 98.5 % respectively, there is continuum of ambulatory rates seen in the clinic **(Figure 3)**. We will focus this study on the worst two groups, **group I and II**. The reason is that these two groups are the ones that will gain the most from the proposed treatment. Focusing on these two groups will also reduce the number of patients needed to show a positive trial, and will accelerate the accrual rate. In the Rades *et al.* study, 21.6 % of patients were in group I, and 48.4% and in Group II. **(12)** Therefore, approximately 70 % of the cord compression patients referred for radiotherapy may be eligible for the trial, thus accelerating the accrual rate.

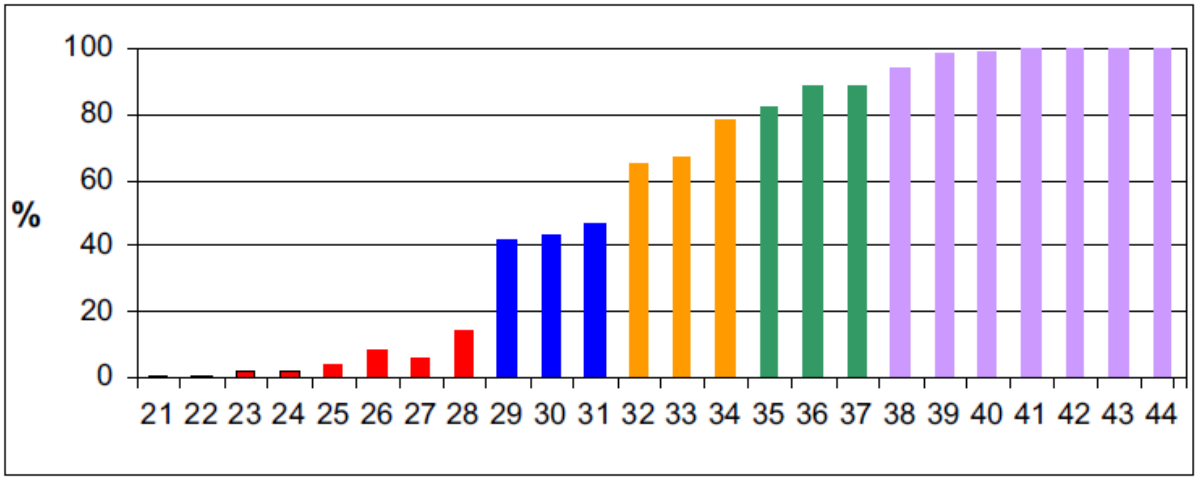


Figure 3. The total score, which ranged between 21 and 44 points in relation to the post radiotherapy ambulatory rate, given as a percentage.

Using a one-sided Exact test, with a type I error of 0.05 and 80% power, a sample size of 15 for group I is needed to detect the difference if the post-RT/Chemo ambulatory rate at one month is increased by 24% (34.6%) and a sample size of 16 for group I is needed to detect the difference if the post-RT/Chemo ambulatory rate at one month is increased by 24% (94.9%). Powers were calculated using Power Analysis and Sample Size (PASS 15) software.

12.4 Accrual

We estimate around 30 patients/year may be eligible for this trial at Washington University. We expect approximately 30% of the eligible patients for this trial to fall in Group I, and 70 % in Group II based on the Rades *et al*. study **(12)**. Approximately two years to enroll 15 patients in Group I and one year to enroll 16 patients in Group II are anticipated.

12.5 Statistical analysis

One-group proportion test using binomial distribution will be used for ambulatory rate at 1 month, strength assessment of lower extremities at 1 month, and retreatment rate per group. The proportion and 95% CI will be calculated. The descriptive statistics will be used to summarize pain in irradiated area at 1 month. The generalized estimating equation (GEE) model with logit link function will be used to analyze the longitudinal data, in which the correlation among the repeated measures from the same patient need be considered. The autoregressive of first order as working correlation structure will be used. The GEE model includes time points only. The p-value will be estimated to assess whether the percentages across all time points are different. Least square means for ambulatory status at each time point will be estimated and the standard errors will be calculated within the use of GEE sandwich method when accounting for within-patient correlation. All analyses will be conducted using SAS (SAS Institute, Cary, NC) at the two-sided 5% significance level.

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