NCI Protocol #: 14-C-0107

Abbreviated Name: Ferumoxytol MRI in GU Cancers

TITLE: Evaluation of Ferumoxytol Enhanced MRI for the Detection of Lymph Node Metastases in Genitourinary (Prostate, Bladder and Kidney) Cancers

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Commercial Agents: Ferumoxytol

PRECIS

Background:

- Conventional imaging modalities (e.g. computed tomography [CT] and magnetic resonance imaging [MRI]) are currently used for the detection of lymph node metastases in many cancer types, including prostate, bladder and kidney cancers, however diagnosis is based on node enlargement which is neither sensitive nor specific (i.e. small nodes harbor metastases, large nodes can be hyperplastic).
- As a consequence, the standard of care is to remove numerous lymph nodes during surgery or to biopsy enlarged nodes to ascertain lymph node status.
- In 2003 Dextran coated ultra small superparamagnetic iron oxide particles (USPIO), also known as Ferumoxtran-10 (Combidex®, AMAG Pharmaceuticals, Inc. Lexington, MA, US) was shown to localize lymph node metastases with much greater accuracy than unenhanced MRI. Although a large study in prostate cancer was successful, an FDA Advisory Panel did not recommend approval and the company abandoned the agent
- In 2009 Ferumoxytol (Feraheme® AMAG Pharmaceuticals, Inc. Lexington, MA, US) a semi-synthetic carbohydrate coated, magnetic iron oxide preparation similar to ferumoxtran 10 was approved for iron replacement therapy. Like ferumoxtran 10, this compound is taken up by normal lymph nodes and excluded from malignant nodal tissue.
- Results of a recent NCI trial (11-C-0098) in 15 patients revealed that using the dose of 7.5 mg/kg Fe is safe and yields homogenous and accurate signal changes in benign lymph nodes in comparison with the 4 and 6 mg/kg Fe doses. This dose was further tested in 5 patients with known or suspected nodal involvement from prostate cancer and in four of five patients positive lymph nodes had a lower signal drop than the benign nodes. The one case in which there was uptake by positive nodes may have been on a vascular basis. This pilot study stimulated interest in a larger study involving a variety of cancer types.

Primary Objective

- To compare the difference in signal between metastatic and normal nodes in prostate, kidney and bladder cancer patients.

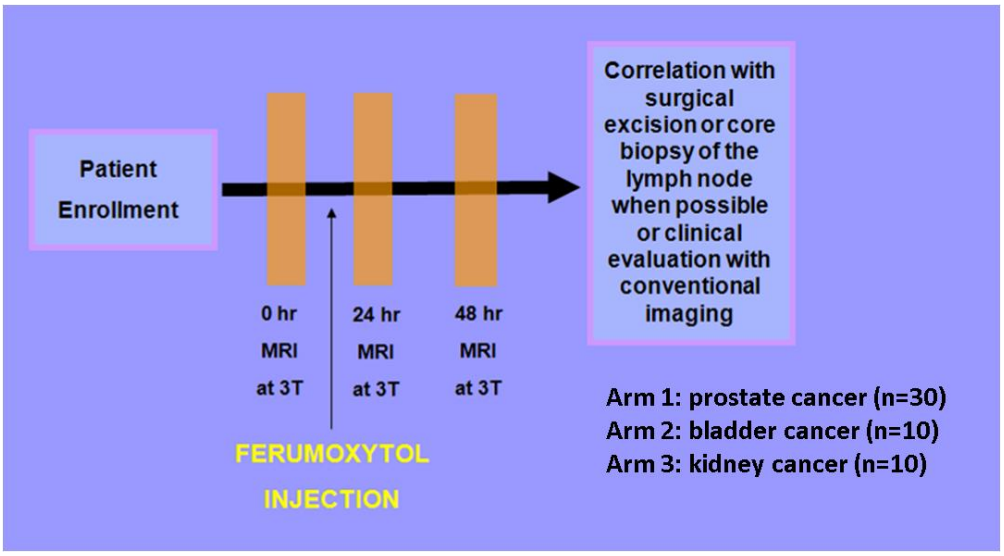
Eligibility

- Subject must be ≥18 years old.
- Eastern Cooperative Oncology Group Performance score of 0 to 2.
- There are 3 parallel arms in this study. All patients must have evidence of lymph node involvement (with a short axis diameter ≥1.5cm).
- In addition:
    - Arm 1: Subject must have a documented diagnosis of prostate cancer,
    - Arm 2: Subject must have a documented diagnosis of bladder cancer (transitional cell carcinoma)
    - Arm 3: Subject must have a documented diagnosis of kidney cancer (all renal cell cancer types)

Design:

- This is a single site 3-arm (arm 1=prostate cancer, arm 2=bladder cancer, arm 3=kidney cancer) study enrolling 50 evaluable patients (30 evaluable in arm 1, 10 evaluable in arms 2 and 3) with documented prostate, bladder or kidney cancer with evidence of lymph node involvement [with a size of ≥1.5cm measured on conventional imaging (e.g. CT, MRI)].
- All subjects will undergo pre-infusion, 24, 48 hours post-Ferumoxytol infusion (dose of 7.5mg/kg Fe) MRI consisting of T1 weighted (W), T2W and T2*W 3 Tesla MRI.
- Imaging will be correlated with histology of resected or biopsied lymph nodes when available. Occasionally, patients may not undergo biopsy or surgical excision of their lymph nodes. This may occur if their lymph nodes are overtly large and therefore highly likely to represent lymph node involvement. In such cases, patients will be evaluated with clinical follow up which typically occurs every three months in most NCI protocols. If the lesion demonstrates growth or regression based on RECIST 1.1 criteria on these follow up studies then the lesion will be considered positive for tumor. If it is stable for at least one year then it will be considered non-malignant. The MR imaging analysis will be intra-patient.
- Patients will also undergo ultrasound examination of imageable lymph nodes (e.g. inguinal nodes) at pre-infusion and 24, 48 hours post-Ferumoxytol infusion time points. The signal changes at post-infusion ultrasound will be visually evaluated to determine if the uptake of ferumoxytol alters sonographic features.

STUDY SCHEMA



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1.1.1.1 To compare the difference in signal between metastatic and normal nodes in prostate, kidney and bladder cancer patients.

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1.1.2.1 To determine the most optimal timing for imaging: 24 hours vs. 48 hours post infusion

1.1.2.2 To determine the difference in signal within metastatic nodes in prostate, kidney, bladder cancer patients at ultrasonography.

1.2 Background and Rationale

1.2.1 Ferumoxytol

Ferumoxytol (FeraHeme®, AMAG Pharmaceuticals, Inc, Lexington, MA) is a semi-synthetic carbohydrate coated magnetic iron oxide preparation indicated for iron replacement therapy specifically in patients with chronic renal disease. It is administered as a bolus and has minimal immunologic reactions. The safety profile of Ferumoxytol in Phase 1-3 clinical trials is excellent [1, 2].

Because of its magnetic properties it has been proposed as an MR imaging agent. Li et al evaluated the feasibility of first-pass contrast enhanced MR angiography using Ferumoxytol in 11 patients and reported satisfactory arterial enhancement with diluted Ferumoxytol [3]. The same group prospectively evaluated the utility of Ferumoxytol enhanced MRI for the diagnosis of deep venous thrombosis in 9 patients and compared Ferumoxytol enhanced scans with pre-contrast time-of-flight MR images and reported that Ferumoxytol enhanced MRI depicted deep venous thrombosis with higher contrast-noise-ratios than conventional non-contrast enhanced methods [4]. Neuwelt et al studied the optimum time of delayed contrast enhancement of Ferumoxytol and compared its enhancement with that of gadolinium chelates in 12 patients with malignant brain tumors. They reported a maximal Ferumoxytol enhancement at 24 to 28 hours after Ferumoxytol injection and concluded that Ferumoxytol stays intravascular in the early phase after injection, making it potentially useful to measure tumor perfusion. The injected doses were 1mg/kg Fe and 1.5mg/kg Fe, no adverse effects were reported in this trial [5]. Ultrasmall particles of iron oxide (USPIOs) such as Ferumoxytol are known to be taken up by macrophages within lymph nodes, thus providing an impetus to study them as lymph node imaging agents. There is limited clinical experience with Ferumoxytol enhanced MR imaging for metastatic lymph node mapping. Harisinghani et al. reported using Ferumoxytol in determining the magnitude of nodal MRI signal changes in 10 prostate cancer patients, who had 26 nodes of which 20 were benign. Ferumoxytol was injected at a dose of 4mg Fe/kg at a rate of 2ml/seconds. MR imaging was performed before, and 5, 18 and 24 hours following the Ferumoxytol injection. A significant drop in the signal-to-noise ratio (SNR) was shown in benign nodes, whereas little change in SNR was noted within malignant nodes. Maximum contrast was detected at scans obtained 24 hours after injection but trend curves suggested better results might be seen at later time points. No adverse effects were observed in enrolled patients [6].

See **APPENDIX A**: EXCERPT FROM FERUMOXYTOL PACKAGE INSERT [4]

2 APPENDICES

APPENDIX A for pharmaceutical details.

2.1.1.1 Pharmacology and Toxicology

Ferumoxytol is a non-stoichiometric magnetite (superparamagnetic iron oxide) coated with polyglucose sorbitol carboxymethylether. The overall colloidal particle size is 17-31 nm in diameter. The chemical formula of Ferumoxytol is $Fe_{5874}O_{8752}$-$C_{11719}H_{18682}O_{9933}Na_{414}$ with an apparent molecular weight of 750 kDa.

Ferumoxytol injection is an aqueous colloidal product that is formulated with mannitol. It is a black to reddish brown liquid, and is provided in single use vials containing 510 mg of elemental iron. Each mL of the sterile colloidal solution of Ferumoxytol injection contains 30 mg of elemental iron and 44 mg of mannitol, and has low bleomycin-detectable iron. The formulation is isotonic with an osmolality of 270-330 mOsm/kg. The product contains no preservatives, and has a pH of 6 to 8 [7].

Ferumoxytol consists of a superparamagnetic iron oxide core that is coated with a carbohydrate shell, which helps to isolate the bioactive iron from plasma components until the iron-carbohydrate complex enters the reticuloendothelial system macrophages of the liver, spleen and bone marrow. The iron is released from the iron-carbohydrate complex within vesicles in the macrophages. Iron then either enters the intracellular storage iron pool (e.g., ferritin) or is transferred to plasma transferrin for transport to erythroid precursor cells for incorporation into hemoglobin.

The pharmacokinetic (PK) behavior of Ferumoxytol has been examined in healthy subjects and in patients with chronic kidney disease on hemodialysis. Ferumoxytol exhibited dose-dependent, capacity-limited elimination from plasma with a half life of approximately 15 hours in humans. The clearance was decreased by increasing the dose of Ferumoxytol. Volume of distribution was consistent with plasma volume, and the mean maximum observed plasma concentration (Cmax) and terminal half-life (t1/2) values increased with dose. The estimated values of CL and Vd following two 510 mg doses of Ferumoxytol administered intravenously within 24 hours were 69.1 mL/hr and 3.16 L, respectively. The Cmax and time of maximum concentration (tmax) were 206 mcg/mL and 0.32 hr, respectively. Rate of infusion had no influence on Ferumoxytol PK parameters. No gender differences in Ferumoxytol PK parameters were observed. Ferumoxytol is not removed by hemodialysis [7].

The safety profile of Ferumoxytol has been assessed in clinical trials including both MR imaging and iron replacement therapy [1-4, 6]. In a randomized double-blind, ascending dose pharmacokinetic study of 61 subjects (41 healthy volunteers and 20 hemodialysis patients), 6 healthy subjects received placebo, 24 subjects received 1 (n=8), 2 (n=8) or 4 (n=8) mg/kg Fe dose injected at 60mg Fe/min, whereas the remainder 11 subjects received 4mg Fe/kg at injection rates of 90 (n=3), 180 (n=3) or 1800 (n=5) mg Fe/min. Twenty hemodialysis subjects received 125 (mean dose of 1.5+/-0.2/kg) (n=10) or 250 (mean dose of 3.2+/-0.6/kg) (n=10) mg Fe over 5 minutes. The blood half life of Ferumoxytol was 9.3 hours and it was increased to 14.5 hours in normal subjects with increasing dose, moreover the half life was similar for the hemodialysis patient group. Among normal subjects, no consistent, clinically relevant or unexpected changes were observed; only one adverse effect, which was metallic taste, was encountered in one subject. For the hemodialysis patient group, no serious adverse events, no

episodes of hypersensitivity or anaphylaxis and no episodes of hypotension were observed after Ferumoxytol injection. Reported minor adverse events included nausea and vomiting in 1 patient after injection [1].

In a randomized clinical trial including 21 adult anemic chronic kidney disease patients, 10 patients received 4 intravenous doses Ferumoxytol at 255 mg Fe given every 2-3 days, 11 patients received 2 intravenous doses of Ferumoxytol at 510 mg Fe given 1 week apart. A total of 7 non-serious adverse effects were recorded in 5 patients, the adverse events included solitary instances of mild constipation a day after injection, mild chills an hour after dosing, mild tingling a day after dosing, moderate gastrointestinal upset of presumed viral etiology a day after dosing, mild delayed pruritic, erythematous rash 3 days after dosing, and mild pain at the injection site that resolved after reinsertion of the intravenous line in a different site [2].

In imaging clinical trials [3, 4, 6], all of which were done with lower doses administered than done in iron replacement trials, no serious adverse effects were observed except in one patient, who had urgent diarrhea 1.5 hours after injection [3].

FDA has also announced a drug safety communication for ferumoxytol with strengthened warnings and changed prescribing instructions and among one of the recommendations stated that ferumoxytol should be administrated diluted as an IV infusion over a minimum of 15 minutes but not as an undiluted IV injection. (http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm440479.htm).

2.1.1.2 Ferumoxytol Enhanced MR imaging for Lymph node mapping

There is limited clinical experience with Ferumoxytol enhanced MR imaging for metastatic lymph node mapping. Harisinghani et al. reported using Ferumoxytol in determining the magnitude of nodal MRI signal changes in 10 prostate cancer patients, who had 26 nodes of which 20 were benign with a mean short axis diameter of 6mm and 6 were malignant with a mean short axis diameter of 7mm. Ferumoxytol was injected at a dose of 4mg Fe/kg at a rate of 2ml/seconds. MR imaging was performed before, at 5, 18 and 24 hours following the Ferumoxytol injection. A significant drop in the signal-to-noise ratio (SNR) was shown in benign nodes, whereas little change in SNR was noted within malignant nodes. Maximum contrast was detected at scans obtained 24 hours after injection but trend curves suggested better results might be seen at later time points. No adverse effects were observed in enrolled patients [6].

2.1.2 Study Diseases

2.1.2.1 Metastatic Lymph Node involvement in Prostate Cancer

Prostate cancer is the second most common cause of cancer death in men in the United States. The American Cancer Society estimates that there were 238,590 new cases of prostate cancer and 29,720 deaths due to prostate cancer in the United States in 2013 [8]. Approximately 17% of American men will receive the diagnosis of prostate cancer during their lifetime and 20% of these men will die of the disease [9]. Accurate lymph node staging is important for treatment planning in prostate cancer, and its implication on prognosis is well established [10-12]. However, extended pelvic node dissection represents a technically more challenging surgery and may be associated with higher complication rates (i.e. lymphocele, deep venous thrombosis, pelvic hematoma, fever, urinary retention etc.) that may result in longer hospital stays [13].

Therefore, a reliable pre-operative imaging method demonstrating metastatic involvement of lymph nodes can potentially render unnecessary, a formal lymph node dissection.

2.1.2.2 Metastatic Lymph Node Involvement in Bladder Cancer

Bladder cancer is the most common malignancy of the urinary system and is four times more common in women than in men [14]. The American Cancer Society estimates that there were 72,570 new cases of bladder cancer and 15,210 deaths due to bladder cancer in the United States in 2013 [8]. Radical cystectomy, which involves removal of the bladder and regional lymph nodes, is the mainstay of treatment for muscle-invasive bladder cancer. In patients who undergo radical cystectomy, the extent of pelvic lymph node dissection is an important predictor of survival in those with both positive and negative lymph nodes [15-18]. Lymph node dissection guides further treatment recommendations by improving regional disease control and pathologic nodal staging while also detecting and removing metastatic lymph nodes, thus offering a direct therapeutic benefit. However, the lack of standardized lymphadenectomy procedures among institutions prevents consensus on what determines an adequate lymph node dissection at the time of radical cystectomy. There is a significant need for better imaging methods to detect lymph node metastases in bladder cancer patients to improve the completeness of lymph node removal. By identifying metastatic lymph nodes before surgery, the use of pre-operative imaging may help establish standards for the anatomic extent of lymphadenectomy and improve oncologic outcomes.

2.1.2.3 Metastatic Involvement in Kidney Cancer

The role of lymph node dissection (LND) in conjunction with nephrectomy for locally advanced renal cell carcinoma (RCC) is controversial. While there is no evidence of a benefit in low stage and organ confined, the available data for locally advanced and metastatic disease is conflicting.

Lymph node involvement in RCC has been shown to be associated with larger tumors, higher grade tumors and locally advanced tumors [19]. Furthermore, most patients with positive lymph nodes also had distant metastases, although patients with both distant metastatic sites in conjunction with positive lymph nodes had markedly worse survival than those with either distant metastasis or regional lymph node metastasis [19]. Locoregional lymphadenectomy does not result in additional morbidity [19, 20]. Patients without lymph node metastasis demonstrate no benefit from LND [19, 20]. Conversely, others have demonstrated that long term durable survival can be achieved with retroperitoneal LND in patients with positive lymph nodes [19, 21]. In addition, our group and others have shown previously that degree of lymph node involvement affects survival, with a greater percentage of patients with lower volume lymph node metastases surviving 5 years [22, 23].

Crispen et al showed that nearly 40% of patients with high risk features will have lymph node metastases [24]. However, even with enlarged lymph nodes on standard preoperative imaging, fewer than half of patients with high risk tumors will be found to have pathological evidence of lymph node metastasis [25, 26]. More worrisome, a small percentage of patients with no evidence of lymph node involvement on preoperative imaging will be found with pathologic evidence of nodal disease at the time of surgery [20, 25]. Therefore it is clear that preoperative staging is inadequate to accurately detect lymph node involvement. Based upon the preponderance of data available, lymph node dissection in the presence of small volume lymph node metastasis appears to be beneficial in terms of overall and cancer specific survival.

Consequently, improvement in identification of lymph node involvement preoperatively is a clinical imperative.

2.1.3 Rationale

2.1.3.1 Conventional Methods for Imaging of Metastatic Lymph Node Involvement

Currently available imaging modalities for detection of metastatic lymph node include computed tomography (CT) and magnetic resonance imaging (MRI), both of which rely primarily on size criteria for distinction of benign nodes from malignant ones. Using the size criteria for differentiating involved nodes from non-involved nodes can result in failure to detect metastases in small unenlarged nodes, whereas enlargement of a lymph node may be secondary to other pathologies such as hyperplasia, infection and inflammation [27, 28]. Thus, both false negative and false positive results are frequent. Reported sensitivity for CT and MRI for detection of lymph node metastases in prostate cancer varies between 24-78% and 27-69%, respectively depending on the mixture of advanced patients in the study group [29-33]. Hence, a method incorporating both anatomical and functional information for accurate imaging of metastatic lymph nodes is needed at the pretreatment stage of prostate cancer.

2.1.3.2 Metastatic Lymph Node Imaging with Lymphotrophic nanoparticle MRI (LNMRI) Technique

LNMRI is a recent technique for mapping metastatic lymph nodes which employs ultrasmall superparamagnetic iron oxide particles (USPIO) as contrast agents. Originally, USPIO particles [Ferumoxtran-10, Combidex® (Advanced Magnetics, Lexington, MA, USA), Sinerem® (Laboratorie Guerbet, Aulnay-sous-Bois, France)) were used in these studies. Ferumoxtran-10 particles range from 30 and 50nm in diameter and are composed of an iron oxide crystalline core measuring 4.3-6 nm and a covering material made up of low-molecular-weight dextran, which can pass through capillaries whereupon they are taken up by the reticuloendothelial system [34]. For instance, a USPIO agent can localize within the normal lymph node either by direct transcapillary passage from the venules to the medullary sinuses or by extravasation across permeable capillary beds by a non-selective endothelial transcytosis allowing particles to drain into lymph nodes [35]. Regardless of how it arrives, within the normal lymph nodes, USPIO is internalized by macrophages thus causing accumulation within the node, which results in signal loss on MRI within normal areas of lymph nodes [36]. This accumulation of USPIO agents in benign lymph nodes causes a signal drop (negative contrast enhancement) in the T2* MR images, whereas lymph nodes completely or partially involved with metastatic cells retain their baseline signal characteristics [37].

LNMRI with a variety of USPIO agents has been reported to be useful in various cancer types including prostate, bladder, testicular, renal and rectum cancer. Harisinghani et al. reported the utility of USPIO enhanced MRI in detection of small and undetectable lymph node metastases in 33 prostate cancer patients using ferumoxtran 10 [38]. Heeskkers et al. examined the feasibility of USPIO (ferumoxtran-10) enhanced MRI and compared image quality of 1.5T and 3T systems in 48 patients with prostate cancer and concluded that 3T systems provide improved image quality and node border delineation [39]. Recently, the same group reported the utility of USPIO enhanced MRI for detection of lymph node metastases outside the area of routine pelvic lymph node dissection area in 41% of 58 prostate cancer patients [40].

Deserno et al. examined the role of USPIO enhanced MRI in the detection of lymph node metastases in 58 patients with bladder cancer and reported a sensitivity of 95% for USPIO

enhanced MRI, whereas the sensitivity for conventional MRI was 76% [41]. Harisinghani et al. evaluated feasibility of USPIO enhanced MRI for detecting metastatic disease within retroperitoneal nodes in 18 testicular cancer patients and reported sensitivity, specificity and accuracy as 88.2%, 92% and 90.4%, respectively [42]. Guimares et al. assessed USPIO enhanced MRI in identifying malignant nodal involvement in 9 renal cancer patients and reported sensitivity and specificity values of 100% and 95.7%, respectively [43]. Lahaye et al. determined diagnostic performance of predictive criteria for nodal staging with USPIO enhanced MRI in 28 rectal cancer patients and concluded that the estimated percentage of white region on USPIO enhanced T2* MRI, that corresponds to the portion of the lymph node involved with metastatic cells, can be used as an index of lymph node involvement [44]. Recently, Birkhauser et al. evaluated the diagnostic accuracy of combined USPIO (ferumoxtran-10) enhanced MRI and diffusion-weighted (DW MRI) in staging of normal-sized pelvic LNs in bladder and/or prostate cancer patients with 3-Tesla MRI. They imaged 75 patients 24–36 h after administration of ferumoxtran-10. All patients were staged previously as N0 by conventional cross-sectional imaging. Combined USPIO-DW-MRI findings were analyzed by three independent readers and correlated with histopathologic LN findings after extended pelvic LN dissection and resection of primary tumors. Sensitivity and specificity for LN status of combined USPIO-DW-MRI versus histopathologic findings were evaluated on a per patient basis (primary end point) and per pelvic side (secondary end point). At histopathologic analysis, 2993 LNs (median: 39 LNs; range: 17–68 LNs per patient) with 54 LN metastases (1.8%) were found in 20 of 75 (27%) patients. Per-patient sensitivity and specificity for detection of LN metastases by the three readers ranged from 65% to 75% and 93% to 96%, respectively; sensitivity and specificity per pelvic side ranged from 58% to 67% and 94% to 97%, respectively. A potential limitation was the absence of a node-to-node correlation of combined USPIO-DW-MRI and histopathologic analysis. They concluded that combined USPIO-DW-MRI improved detection of metastases in normal-sized pelvic LNs of bladder and/or prostate cancer patients [45].

USPIO enhanced MRI technique has practical difficulties and challenges, first is the need for performing pre and 24-36 hours post-contrast injection due to slow accumulation of the contrast within lymph nodes, which may diminish cost-effectiveness of this method. Second is the intravenous infusion of ferumoxtran-10, which should be administered slowly through a filtered needle over a period of 15-30 minutes to minimize hypersensitivity-related side effects. Finally, ferumoxtran-10 is currently not FDA approved and is unavailable both in the US and Europe. Therefore, although it was highly promising, Ferumoxtran-10 is simply unavailable.

However, a similar agent, ferumoxytol (trade name FeraHeme), developed by the same company (AMAG Pharmaceuticals) was approved by the FDA in 2009 for iron replacement therapy. In this study, our primary objective will be to compare the difference in signal between metastatic and normal nodes in prostate, kidney and bladder cancer patients using intravenous ferumoxytol.

2.1.4 Protocol 11-C-0098 Results

Protocol 11-C-0098 was a dose ranging study in which the following doses of ferumoxytol were evaluated: 4mg/kg, 6mg/kg, 7.5mg/kg. The results revealed that the dose of 7.5 mg/kg Fe was safe and yielded the best imaging results with more homogenous and reliable signal changes in benign lymph nodes in comparison with the 4 and 6 mg/kg Fe doses (**Figure 1**, **Figure 2**, **Figure 3, Figure 4**). One patient out of 21 developed an allergic reaction after receiving approximately 2.5mg/kg dose. Patient had sneezing, redness in the face and the neck, he felt dizziness and hot. His mouth and throat became swollen. He had hives in his lips, left shoulder and nasal

congestion as well. He was assessed to have Grade 2 allergic reaction. He was discharged after a 5 hour observation following resolving his symptoms. At 24 hour follow up, he reported no complaints.

This study was conducted in patients undergoing surgery at NIH for localized prostate cancer where the incidence of prostate cancer lymph node metastases is realtively low. Thus, the utility of the agent in depiction of signal change differences between benign and malignant lymph nodes could not be assessed. Therefore, an additional five subjects with known or suspected lymph node metastases were added to validate the signal change differences between benign and malignant lymph nodes invaded with prostate cancer.

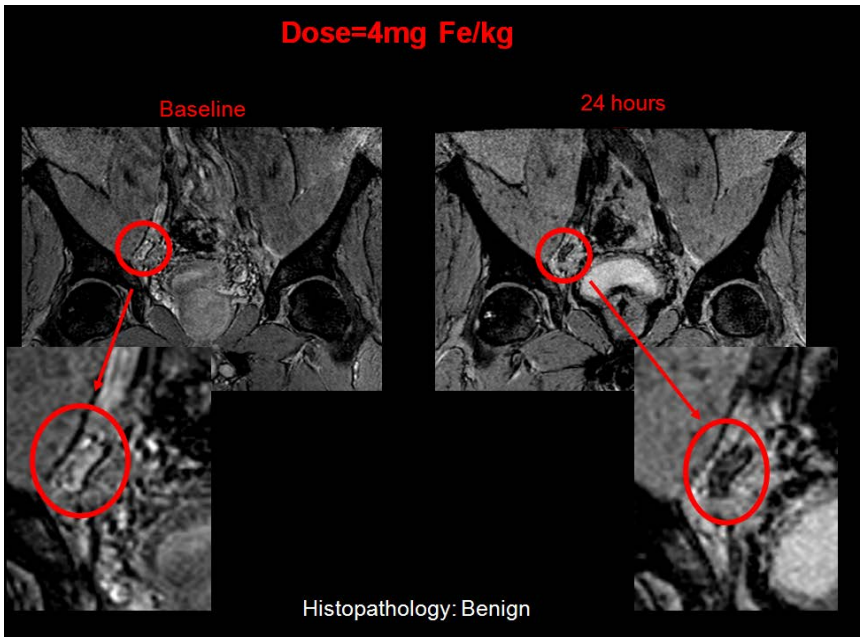

Figure 1: Coronal T2* weighted MRI at the baseline scan demonstrates a right iliac chain lymph node, 24hr follow up scans after 4mg Fe/kg Ferumoxytol injection demonstrate a heterogeneous signal drop within the lymph node.

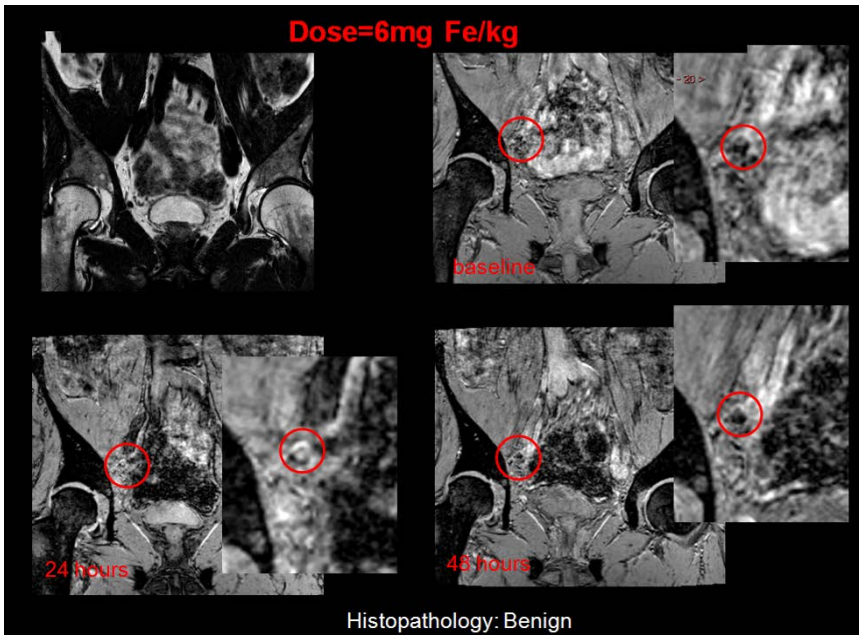

Figure 2: Coronal T2* weighted MRI at the baseline scan demonstrates a right iliac chain lymph node, 24 and 48 hours follow up scans after 6mg Fe/kg Ferumoxytol injection demonstrate a heterogeneous signal drop within the lymph node.

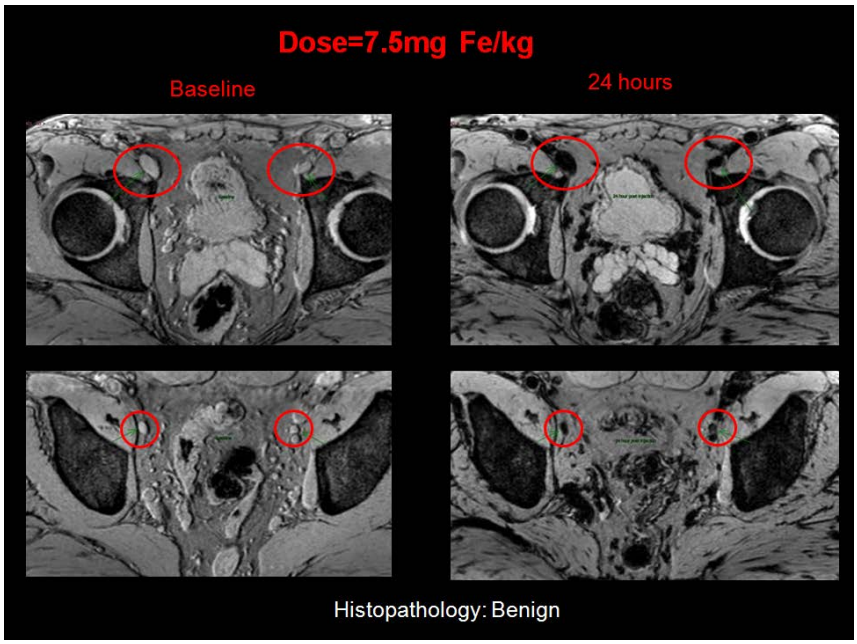

Figure 3: Axial T2* weighted MRI at the baseline scan demonstrates a bilateral iliac chain lymph nodes, 24hr follow up scan after 7.5mg Fe/kg Ferumoxytol injection demonstrate a homogeneous signal drop within the lymph node.

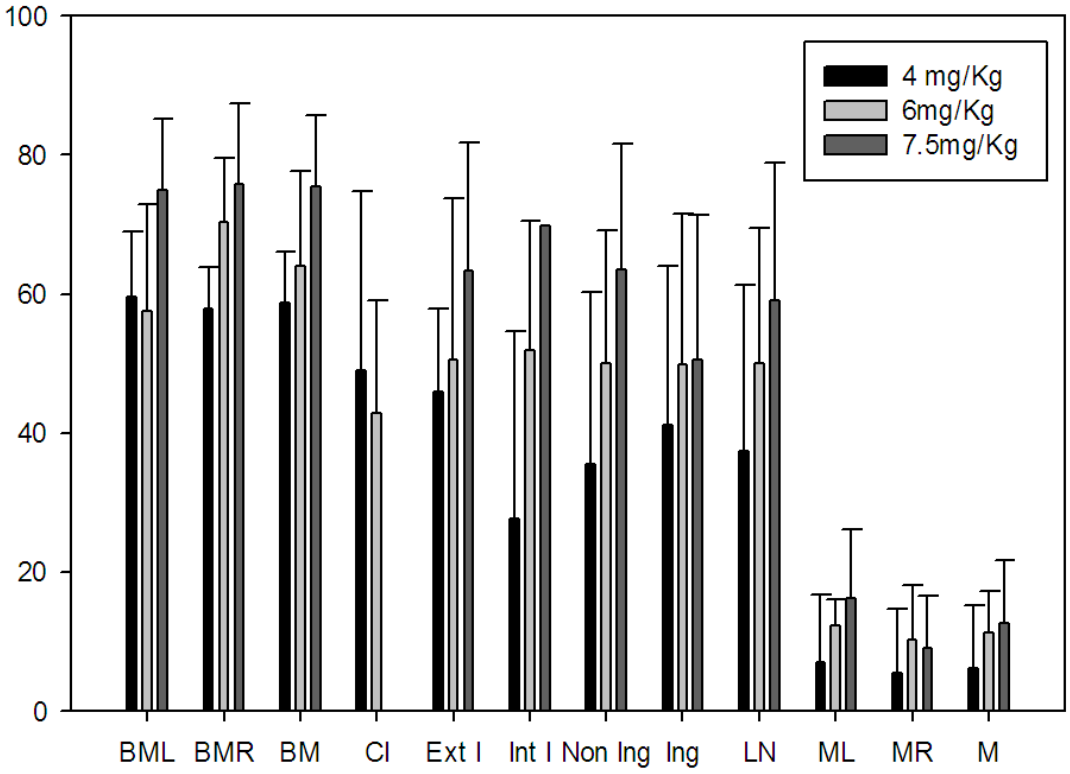

Figure 4: Bar graphs show that the greatest signal drop was observed at 7.5mg Fe/kg dose in lymph nodes (LN), bone marrow right, left (BMR, BML).

In the 5 patients with suspected lymph node involvement (with a size of ≥1.5cm) ferumoxytol was injected (7.5mg Fe/kg) prior to imaging. Among 5 patients 4 patients had positive findings in their lymph nodes and the amount of signal drop was less in those suspicious lymph nodes than it was in the benign ones (**Figure 5**). However, there were some controversial findings in a small number of suspicious lymph nodes as a result of variable and heterogeneous signal changes after Ferumoxytol injection (**Figure 6**). For instance, in one patient with obvious retroperitoneal lymphadenopathy there was uptake into the lymph nodes. We believe this is on a vascular basis in which permeable angiogenic vessels in the nodes leaked ferumoxytol into the lymph node. At histopathology, no normal lymphatic tissue was seen indicating the uptake was not due to macrophages but rather to leakage.

MIP has two other MRI trials for prostate cancer, Protocols"13-C-0018" and "13-C-0145". Protocol 13-C-0018, aims to evaluate feasibility of determining MR contrast enhancement differences in prostate cancers after Eovist injection. Protocol 13-C-0145, will not compete with this trial since patients previously enrolled on the 13-C-0145 study can still be eligible for the ferumoxytol trial. However, if a patient completes the current ferumoxytol protocol, he will not be eligible for the 13-C-0145 study since possibly retained iron particles will affect the accuracy of the Eovist enhanced MRI.

Figure 5: Axial T2* weighted MRI at the baseline scan demonstrates a right internal iliac chain lymph node, 24hr follow up scan after 7.5mg Fe/kg Ferumoxytol injection demonstrate a homogeneous hyperintense signal within the lymph node, which is suspicious for malignant involvement.

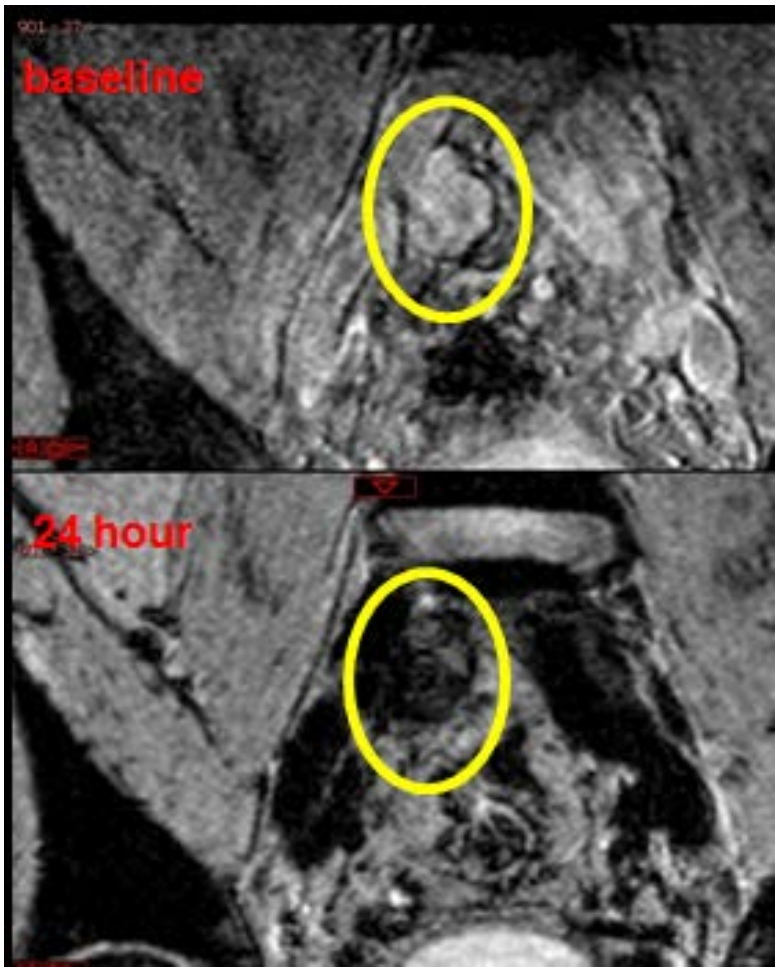

Figure 6: Coronal T2* weighted MRI at the baseline scan demonstrates an enlarged right common iliac chain lymph node, 24hr follow up scan after 7.5mg Fe/kg Ferumoxytol injection demonstrate a heterogenous signal pattern with partial hyperintense focus within the lymph node, which is suspicious for partial malignant involvement.

3 ELIGIBILITY ASSESSMENT AND ENROLLMENT

3.1 Eligibility Criteria

3.1.1 Inclusion Criteria

3.1.1.1 Subject must be ≥18 years old.

3.1.1.2 Diagnosis

- Arm 1: Subject must have a documented diagnosis of prostate cancer with evidence of lymph node involvement (with a short axis diameter of ≥1.5cm on a conventional CT or MRI obtained within 8 weeks of the Ferumoxytol imaging procedure)
- Arm 2: Subject must have a documented diagnosis of bladder cancer (transitional cell carcinoma) with evidence of lymph node involvement (with a short axis diameter of ≥1.5cm on a conventional CT or MRI obtained within 8 weeks of the Ferumoxytol imaging procedure)

- Arm 3: Subject must have a documented diagnosis of kidney cancer (all renal cell cancer types) with evidence of lymph node involvement (with a short axis diameter of ≥1.5cm on a conventional CT or MRI obtained within 8 weeks of the Ferumoxytol imaging procedure)

3.1.1.3 Subject must have Eastern Cooperative Oncology Group Performance score ≤ 2.

3.1.1.4 Ability to provide informed consent. All subjects must sign an informed consent form indicating their understanding of the investigational nature and risks of the study before any protocol-related studies are performed.

3.1.2 Exclusion Criteria

3.1.2.1 Subjects with known hypersensitivity and allergy to iron

3.1.2.2 Subjects with evidence of iron overload with a pre-study ferritin level greater than 370 ng/ml and percent saturation of transferrin level greater than 40%. Patients with lab values above these limits may be included in the study if documented hematology consultation rules out hemochromatosis, idiopathic or iatrogenic iron overload.

3.1.2.3 Subjects with any coexisting medical or psychiatric condition that is likely to interfere with study procedures and/or results

3.1.2.4 Subjects with severe claustrophobia unresponsive to oral anxiolytics

3.1.2.5 Subjects with contraindications to MRI

3.1.2.6 Subjects weighing >136 kg (weight limit for scanner table)

3.1.2.7 Subjects with any type of pacemaker, cerebral aneurysm clips, shrapnel injury, or other implanted electronic devices or metal not compatible with MRI.

3.1.2.8 Subjects with abnormal liver function tests suggesting liver dysfunction (AST and ALT ≥3 x of the upper limits of normal; total bilirubin ≥2 x the upper limits of normal or >3.0 mg/dl in patients with Gilbert's syndrome).

3.1.2.9 Subjects with other medical conditions deemed by the principal investigator (or associates) to make the subject ineligible for protocol procedures.

3.1.2.10 Women who are pregnant or breast-feeding. The effects of ferumoxytol on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for 1 day after study related imaging is completed. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.3 Inclusion of Women and Minorities

Members of all races and ethnic groups are eligible for this trial. Women are excluded from arm 1 of this trial as prostate cancer does not occur in females.

3.2 Screening Evaluation

Subjects will be seen in the UOB, GMB or ROB clinics by members of each respective team. Conventional imaging (e.g. CT, MRI) confirming presence of prostate or bladder (transitional cell carcinoma) or kidney cancer (all types of renal cell cancer) with evidence of lymph node involvement [with a short axis diameter of ≥1.5cm measured on conventional CT or MRI] will be reviewed by Molecular Imaging Program Staff.

3.2.1 Screening Test

3.2.1.1 Evaluations:

- History
- Weight
- vital signs (BP, HR, RR, & Temperature)
- clinical laboratory assessments (CBC w/diff, Acute Care Panel, Hepatic Panel, Mineral Panel, serum Iron, ferritin, % saturation transferrin and TIBC).
- Serum or Urine Pregnancy Test in women of reproductive potential

3.3 Registration Procedures

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) <ncicentralregistration-l@mail.nih.gov>. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

4 STUDY IMPLEMENTATION

4.1 Study Design

This is an open label single site. The study will enroll 10 evaluable patients in each of the 3 study arms for a total of evaluable 30 patients. The 3 arms are:

- Arm 1: Prostate Cancer,
- Arm 2: Bladder Cancer (transitional cell carcinoma),
- Arm 3: Kidney Cancer (all types of renal cell cancer).

All subjects will undergo pre-infusion, 24, 48 hours post-Ferumoxytol infusion (dose of 7.5mg/kg Fe) MRI consisting of T1 weighted (W), T2W and T2*W MRI in a 3 Tesla magnet. Additionally, all subjects will undergo pre-infusion, 24 hours, 48 hours post-Ferumoxytol infusion (dose of 7.5mg/kg Fe) ultrasound. Imaging will be correlated with histology of resected or biopsied lymph nodes when available or patient will be evaluated with clinical assessment and conventional imaging findings. Occasionally, patients may not undergo biopsy or surgical excision of their lymph nodes. This may occur if their lymph nodes are overtly large and therefore highly likely to represent lymph node involvement. In such cases, patients will be evaluated with clinical follow up which typically occurs every three months in most NCI protocols.

An evaluable patient is defined as a patient who receives a dose of Ferumoxytol and receives the pre-infusion, 24 hour post-infusion and 48 hour post-infusion MRI and Ultrasound scans.

Patients who do not undergo surgical excision or biopsy of the lymph nodes will be followed (per treatment protocol) for a minimum of 12 months. During this follow up, conventional images (e.g. CT, MRI) will be evaluated and RECIST 1.1 criteria will be used for assessment of metastatic involvement for correlation of Ferumoxytol enhanced MRI findings. According to

RECIST 1.1 criteria a lymph node is accepted as "pathologically enlarged" if its short axis diameter is ≥1.5cm on CT scan. During follow-up, lymph nodes identified as target lesions should always have the actual short axis measurement recorded. During follow up, at least a 30% decrease in size compared to the baseline, or a 20% increase in the short axis diameter compared to the baseline measurement will be considered as evidence of malignancy in the node. If the target lymph node demonstrates a decrease in size ≤ 30% or an increase in size ≤20% it will be determined to be stable and therefore likely to be non-malignant over a period of at least one year (**Figure 7**) [46].

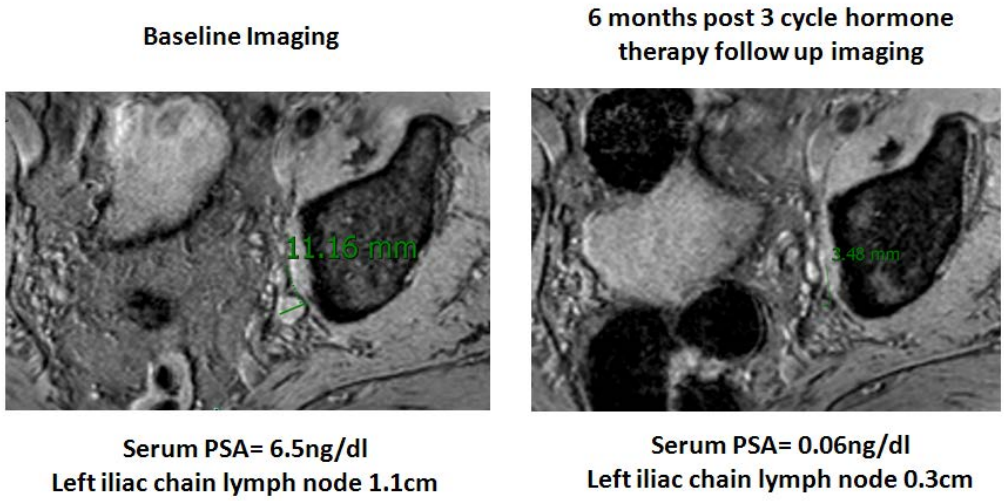

Figure 7: Example of the use of follow up studies. Baseline imaging demonstrates a lymph node with a short axis size of 1.1cm in presence of a serum PSA of 6.5ng/dl in a 72-year old S/P radical prostatectomy patient. 6 months follow up MRI after 3 cycles of hormone therapy demonstrates decrease of the lymph node size to 0.3cm accompanied with a PSA of 0.06ng/dl. The original lymph node would be considered malignant based on its shrinkage on appropriate therapy

4.2 Ferumoxytol Administration

For all subjects in all three arms, ferumoxytol will be administered at a dose of 7.5mg/kg Fe. Each arm will include 10 evaluable patients.

Ferumoxytol will be administered as an intravenous infusion in 50-200 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP over at least 15 minutes..

4.3 MRI scan

Prior to entering the scanner the patient will answer the standard MRI safety checklist administered to all patients undergoing MRI in the Clinical Center to insure that it is safe to perform an MRI. The patient will be placed into the magnet in supine position and an intravenous line will be placed. A 32 channel cardiac coil will be used for MR imaging.

The following scans will be obtained:

- Scout view of the target lesion area to check positioning of the phased array cardiac coil.
- Axial T1 weighted MRI of pelvis.
- Axial T2 weighted MRI of pelvis.
- Axial T2* weighted MRI of pelvis.

- Axial diffusion weighted MRI of the pelvis
- Total nominal time: 40 minutes +/- 5 minutes for setup and clean-up +/- 10 minutes in case any sequence needs to be repeated due to unforeseen events such as patient motion during imaging acquisition. At any given time the patient will be required to lie still for 5-7 minutes.

After completion of the pre-infusion MRI scan, the patient will be taken into observation room and Ferumoxytol infusion will be performed as detailed above. The patient will be released after determining vital signs are stable and requested to return for MR imaging at approximately 24 and 48 hours later.

24 hours following the Ferumoxytol infusion, the same MR imaging protocol specified above will be performed with the same MRI set up.

48 hours following the Ferumoxytol infusion, the MR imaging protocol will again be performed with the same MRI set up.

Following imaging acquisition, the data will be transferred to the clinical PACS system for storage.

4.4 Ultrasound

Ultrasound images of the target lymph nodes will be obtained in accessible lymph nodes with 2 different probes (9MHz and 6-15MHz probes) in the same session. Total nominal time for ultrasound imaging is expected to be 10-15 minutes. The same machine (GE LOGIQ E9) will be used for each scan and ultrasound will be performed by the same sonography technician to keep the imaging consistent.

4.5 Procedure Monitoring

The Principal Investigator or other Licensed Independent Practitioner (individual who is licensed to practice independently, i.e. MD, NP, or PA) will be in attendance during infusion. In the event of an emergency such as allergic reaction, emergent treatment will be initiated using emergency medication kits available in Molecular Imaging Clinic. The attending from UOB, ROB, or GMB will be paged (301-496-1211) if needed to treat patient symptoms or for follow up care. In the event the attending is unavailable, Dr. Turkbey should be called (240-760-6112).

Vital signs: Blood pressure, heart rate, respiratory rate, will be taken prior to infusion and every 15 minutes after infusion for 1 hour or until stable. Once stable, patient will be released from Molecular Imaging Clinic.

4.6 Duration of Follow Up

Patients removed from study for unacceptable adverse events will be followed until the resolution or stabilization of the adverse event.

Patients who will undergo biopsy or surgical intervention will remain on study until completion of their surgical procedure or biopsy (core needle biopsy or fine needle aspiration) and analysis of lymph node dissection, at which time they will be removed from study.

Patients who do not undergo biopsy or surgical intervention will have their disease monitored per the protocol they are enrolled in. If the target node is determined to be malignant based on >30% decreases or >20% increases in size then the patient will be removed from the study. In cases when the target node does not change (≤30% decrease, ≤20% increase) then they will be

followed for at least one year. The patient's medical history and imaging studies will be acquired from the patient's medical record, PACs, or their primary care MD. Thus, the patients will remain on study until such time as the nature of their target lymph node can be determined by follow up testing.

In the event that a patient experiences an allergic reaction or toxicity greater than grade 2 during the Ferumoxytol infusion, the infusion will be stopped immediately and standard supportive measures instituted. No further Ferumoxytol will be administered.

4.7 Study Calendar

All efficacy and safety measurements obtained during the course of the study are summarized in the Study Calendar.

Table 1: Study Calendar

	Pre-study	**[a,b]Ultrasound and MR imaging**				**[c, d]Surgical procedure/ Core Needle/fine needle aspiration Biopsy**	**[c]Follow up of medical history and conventional imaging studies**
		Just prior to MRI	Pre-infusion MRI scan	24 hour post infusion MRI scan	48 hour post infusion MRI scan	Within 12 weeks following Ferumoxytol enhanced MR imaging	at least 1 year after Ferumoxytol infusion MRI
Pathology report confirming prostate, bladder or kidney cancer	X					X	
Informed consent	X						
Demographics	X						
Medical history	X						
CBC w/diff, plts	X						
Serum chemistry	X						
Serum Iron, ferritin, % saturation transferrin and TIBC	X			X			
Serum or Urine Pregnancy Test	X	X[e]					
Intravenous line started		X	X				
Ferumoxytol infusion			X				

	Pre-study	[a,b]Ultrasound and MR imaging				[c, d]Surgical procedure/ Core Needle/fine needle aspiration Biopsy	[c]Follow up of medical history and conventional imaging studies
		Just prior to MRI	Pre-infusion MRI scan	24 hour post infusion MRI scan	48 hour post infusion MRI scan	Within 12 weeks following Ferumoxytol enhanced MR imaging	at least 1 year after Ferumoxytol infusion MRI
Vital sign monitoring		X	X	X	X		

a: Ultrasound and MRI will be done on the same day. For the baseline (pre-infusion) time point, ultrasound will be done before the MRI and for post-infusion 24hr and 48hr time points the sequencing of these studies can change.

b: Intravenous line starting, vital sign monitoring will be done after the MRI scans only, but not after the ultrasound scans.

c: Imaging will be correlated with histology of resected or biopsied lymph nodes when available or patient will be evaluated with clinical assessment and conventional imaging findings (using RECIST criteria), which may be extended up to a period of at least 12 months in cases of stable nodes.

d: Surgical excision or biopsy of the target lymph node will be performed within 12 weeks following the ferumoxytol enhanced MRI.

e: Performed ≤ 48 hours prior to infusion of Ferumoxytol for all women of reproductive potential. The test need not be performed if screening test was done within appropriate time frame.

4.8 Surgical Guidelines

As part of their standard of care for their cancer (prostate, bladder or kidney), subjects in each arm may have surgery or a biopsy of the lymph node within 12 weeks following Ferumoxytol enhanced MR imaging. Pathologic specimens will be obtained for histological assessments.

4.9 Criteria for Removal from Study

- If a patient is found to be pregnant after study enrollment but prior to Ferumoxytol infusion
- Patients will be removed from study following prostatectomy or biopsy or after their 1 year clinical assessment. If the patient experiences an AE that prohibits them from completing the Ferumoxytol enhanced MR imaging session they will be taken off-study upon resolution of toxicity. In cases where Ferumoxytol enhanced MR imaging findings indicate possible loco-regional and/or distant metastases, the information will be discussed with the referring physician. Further evaluation with standard of care diagnostic imaging and/or biopsy will be performed at the discretion of the referring physician. The surgical excision or biopsy will be performed only if it is clinically

indicated (standard of care). As the significance of a Ferumoxytol enhanced MR imaging-depicted lesion is uncertain, the decision to pursue pathological confirmation and the methods of doing so will be left to the referring clinician and is not dictated by this imaging protocol.

- A patient may withdraw from the study at any time.

4.9.1 Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) <ncicentralregistration-l@mail.nih.gov>.

4.10 Supportive Care Guidelines

In the event that a subject has a reaction (allergic) to Ferumoxytol, all appropriate medical measures will be taken immediately. In rare instances, this may entail admission to the hospital on according to the directions from the referring team.

5 DATA COLLECTION AND EVALUATION

5.1 Data Collection

Data will be collected by the Molecular Imaging Program staff and stored in a password-protected file in NCI C3D. The data will be entered at least on a weekly basis.

Data collection will include demographics, the primary tumor diagnosis date, biopsy date, and pathological diagnosis including tumor grade. Monitoring for AEs will be performed from the start of Ferumoxytol infusion until 48 hours post infusion. AEs related to the standard of care prostatectomy or needle biopsy will NOT be collected or reported under this protocol. Raw image data will be stored on a secure external drive. Reconstructed imaging data will include storage of anonymized images from each time point and other extracted image parameters. This will be stored in a secure, password protected imaging database. Post-operative histology data and subsequent correlative analysis will be stored in the password-protected database.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

5.2 Toxicity Criteria

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

5.3 Imaging Interpretation

The location of lymph nodes will be indicated on T1W, T2W and T2*W unenhanced MR images and the size of each node will be measured from the T1 images. Each visualized node will be assigned a number and a site (e.g. right, left, internal, external iliac, right left retroperitoneal). The location of the nodes will be transcribed to a map of the targeted region (chest, abdomen or pelvis). The map, nodal characterizations, and the MR images will be made available to the referring physician for reference. Signal intensity of visualized target lymph node will be recorded on unenhanced and 24 and 48 hours post Ferumoxytol infusion T2*W MR images by placing operator defined region-of-interest. Signal intensity changes will be measured between pre-infusion, 24 and 48 hours post Ferumoxytol infusion MR scans.

For the ultrasound imaging interpretation, the baseline and 24hour, 48hour post-infusion ultrasound images will be visually compared to monitor the signal changes.

5.4 Pathology and Imaging Correlation

As part of standard care, lymph nodes mapped on MR imaging may be resected during at the time of surgery or may be biopsied via core needle technique or fine needle aspiration. Resected nodes will be named and numbered based on their location in diagrammatic maps obtained from MR images. Multiple sections of resected or biopsied lymph nodes will be stained with hemotoxylin and eosin and the slides will be reviewed by NCI pathologists. The histopathology results will be compared with signal intensity change amounts between unenhanced, 24 and 48 hours post Ferumoxytol infusion T2*W MR images. No samples will be obtained or stored on this protocol other than in the Pathology Department, NCI, NIH.

Patients who do not undergo surgical excision or biopsy of the lymph nodes will be followed (per treatment protocol) for a minimum of 12 months. During this follow up, conventional images (e.g. CT, MRI) will be evaluated and RECIST 1.1 criteria will be used for assessment of metastatic involvement for correlation of Ferumoxytol enhanced MRI findings.

6 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

6.1 Definitions

6.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section **5.1**.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed for 48 hours after dose infusion. AEs should be reported up to 30 days following the last dose of study drug.

6.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

6.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

6.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

6.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

6.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, 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.

6.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

6.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

6.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

(a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

(b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.2 NCI-IRB and NCI Clinical Director (CD) Reporting

6.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

6.2.2 NCI-IRB Requirements for PI Reporting of Adverse Events at Continuing Review

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
    - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
    - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
    - All Grade 5 events regardless of attribution;
    - All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

6.3 Data and Safety Monitoring Plan

6.3.1 Principal Investigator/Research Team

This study will not have a formal data safety monitoring plan (DSMP), however, the Principal Investigator and Lead Associate Investigator will re-evaluate the protocol after each patient.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7 STATISTICAL CONSIDERATIONS

7.1 Study Design/Endpoints

- This is an open-label, single-center study. Fifty evaluable subjects in three different arms (30 in arm 1 and 10 in arms 2 and 3) will be enrolled into the study.
- The primary objective is to compare the difference in signal between metastatic and normal nodes in prostate, kidney and bladder cancer patients.
- For determining the difference in signal between metastatic and normal nodes patients will be infused 7.5mg/kg Fe dose of Ferumoxytol.
- Subjects with documented prostate or bladder or kidney cancer will undergo pre-infusion and 24, 48 hours post-Ferumoxytol infusion MRI consisting of T1 weighted (W), T2W and T2*W MRI at 3 Tesla (T) magnet.
- The difference in signal between metastatic and normal nodes will be determined by measuring the difference in signal between tumor and normal node, and determining the maximum difference per each imaging time point.
- Patients will also undergo ultrasound examination pre-infusion and 24, 48 hours post-Ferumoxytol infusion time points. The signal changes at post-infusion ultrasound will be visually evaluated in an exploratory manner.

7.2 Sample Size/Accrual Rate

Thirty evaluable patients in 3 different arms (arm1=prostate cancer, arm 2=bladder cancer, arm 3=kidney cancer) will be included in this trial with an accrual rate of 1-2 patients a month. A patient will be evaluable if he/she completes pre and 24 hours, 48 hours post ferumoxytol infusion MRI scans and may undergo surgical excision of the lymph node dissection or needle biopsy of the lymph node or completes the clinical assessment including conventional imaging evaluation. In order to allow for the possibility of a small number of inevaluable patients, the accrual ceiling will be set least 56. Therefore, it is expected that this study will be completed within 2 years.

7.3 Stratification Factors

- Arm 1

    - Subject must have a documented diagnosis of prostate cancer with evidence of lymph node involvement (with a short axis diameter of ≥1.5cm)
- Arm 2
    - Subject must have a documented diagnosis of bladder cancer (transitional cell carcinoma) with evidence of lymph node involvement (with a short axis diameter of ≥1.5cm)
- Arm 3
    - Subject must have a documented diagnosis of kidney cancer (all types of renal cell cancer) with evidence of lymph node involvement (with a short axis diameter of ≥1.5cm)

All patients will receive a dose of 7.5mg/kg Fe Ferumoxytol.

7.4 Analysis of Primary Endpoint

The primary objective of the ferumoxytol study is to compare the difference in pre-post ferumoxytol infusion signal change between metastatic and normal nodes in prostate, kidney and bladder cancer patients. Based on the previous study (Neoplasia, 2007), the mean signal drop of benign lymph nodes was 6.3. In comparison, most of the malignant nodes showed little change in signal with mean signal drop equal to 0.63. The standard deviation of signal change was similar for benign and malignant nodes and equaled 1.7 approximately.

Each patient is expected to have at least 1-2 benign lymph nodes and 1-2 metastatic nodes. For the purpose of sample size calculation, we use the conservative assumption that each patient has only one benign and one metastatic node and there is no correlation between benign lymph and metastatic node in pre-post ferumoxytol infusion signal change. With 10 patients for each cancer, the study has 93% power to detect a minimal mean signal change of three with the two-sided paired t-test at the 5% significance level. The power will increase if each patient has signals observed in multiple benign lymph nodes and metastatic nodes, as well as if the signal changes in benign and metastatic node are positively correlated. Thus, a total of 30 patients, 10 for each cancer are sufficient to achieve adequate power for the primary objective of the study. In order to allow for the possibility of a small number of unevaluable patients, the accrual ceiling will be set at 36 patients.

If each patient has multiple and unequal number of benign lymph nodes and metastatic nodes, the linear mixed effects model will be used to model and test the difference of signal changes between benign lymph and metastatic nodes, where the random intercept is used to account for the within-patient correlation of signal changes of multiple nodes.

7.5 Analysis of Secondary Endpoints

The secondary endpoint of this study is to determine the most optimal timing for imaging: 24 hours vs. 48 hours post infusion.

One secondary objective of the study is to determine the most optimal timing for imaging: 24 hours vs. 48 hours post infusion. All the enrolled patients will be imaged at both time points post infusion, and signal change at both time points will be calculated. The time point with larger separation between metastatic and normal nodes with respect to post-infusion signal change will be considered the optimal timing for imaging.

Another second objective of the study is to use an ultrasound scan to evaluate visually (qualitatively) if there is agent uptake. The ultrasound scan will be done before infusion and 24 hours, 48 hours after infusions. This second objective is exploratory, and as such summary statistics such as the proportion of agent take at each time point and the corresponding standard error will be reported. In order to account for the intra-patient correlation of agent uptake of multiple nodes, the linear mixed effects model with the random intercept will be used to estimate the proportion of agent uptake at each time point.

8 PHARMACEUTICAL INFORMATION

8.1 Ferumoxytol

8.1.1 Source

Ferumoxytol is a commercial drug. It will be purchased by the NIH Clinical Center Pharmacy, and billed to the Molecular Imaging Program.

8.1.2 Route of Administration:

Intravenous

8.1.3 Method of Administration:

Ferumoxytol will be administered as an intravenous infusion in 50-200 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP over at least 15 minutes.

8.1.4 Formulation and preparation

Feraheme (30 mg/mL) is available for intravenous injection in single use vials. Each vial contains 510 mg of elemental iron in 17 mL.

8.1.5 Stability and Storage

Store at controlled room temperature (20° to 25°C [68° to 77°F]). Excursions permitted to 15° – 30°C (59° – 86°F).

8.1.6 Agent Ordering

Ferumoxytol is a commercial drug. It will be purchased by the NIH Clinical Center pharmacy, and billed to the Cancer Imaging Program.

8.1.7 Agent Administration

Ferumoxytol will be administered as an intravenous infusion in 50-200 mL 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP over at least 15 minutes..

8.1.8 Toxicity

- Hypersensitivity reactions (anaphylaxis and/or anaphylactoid reactions)
- Hypotension
- Iron overload
- Diarrhea
- Nausea
- Dizziness

- Constipation
- Peripheral edema

9 HUMAN SUBJECTS PROTECTIONS

9.1 Rationale For Subject Selection

Subject must be ≥18 years old, with a documented diagnosis of prostate, bladder or kidney cancer (for arm 1, which includes prostate cancer only patients, subjects will be male).

Subjects may be scheduled for clinically indicated surgical resection or needle biopsy of the lymph node due to strong suspicion of harboring metastatic lymph nodes.

9.2 Participation of Children

Prostate, bladder and kidney cancers are not seen in children. Thus, we will not include children in this study.

9.3 Participation of Subjects Unable to Give Consent

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is minor increase over minimal risk from research participation (section **9.4**), all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

9.4 Evaluation of Benefits and Risks/Discomforts

There is no possibility of direct benefit to participants in this study. The results of this trial could generate generalizable information that may benefit future patients with prostate cancer and therefore, subjects may benefit by knowing they have contributed to scientific knowledge.

The risks for participating are also small. Because the risks of Ferumoxytol infusion and MR are uncommon, we anticipate a low rate of adverse events at any 3 arm in this study.

Specific risks and potential complications will be clearly outlined in a separate consent form at the time of each procedure. Most complications are expected to be minor and require no treatment. Risks and discomforts associated with Ferumoxytol infusion and imaging are discomfort of an IV placement and the theoretical effects allergic reaction. The subject will be required to lay still on their back for back for 5-7 minutes for the MRI scan.

A licensed clinical practitioner will be immediately available during the infusion and imaging period and they will be backed by the Clinical Center's Code team. If hospitalization is required the participant will be admitted. However, this is unlikely to occur based on what is known of this agent. There is an added inconvenience of having to return for follow-up scan (at 24 and 48 hours) that the subjects will be made aware of.

Adverse events will be reviewed after every case and a decision will be made about moving forward to the next participant so that each participant will have the benefit of the prior participant's experience.

As this is a new imaging agent, the alternative is to choose not to participate.

9.5 Consent and Assent Process and Documentation

The participant will be informed of the study by a member of the Urological Oncology Branch, Radiation Oncology Branch, or Genitourinary Malignancies Branch research team and the subject will be contacted by the study research nurse who will explain the study in detail and provide a copy of the consent form and protocol (if requested) to the participant. If the participant has any questions they will be answered by telephone. A signed consent will be obtained by the principal investigator or an associate investigator on the day of the initial MR. The original signed consent goes to Medical Records; a copy is placed in the research record.

9.5.1 Telephone consent

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

9.5.2 Informed consent of non-English speaking subjects

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OSHRP SOP 12, and 45 CFR 46.117 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using either the long translated form or the short form). Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

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11 APPENDICES

11.1 APPENDIX A: EXCERPT FROM FERUMOXYTOL PACKAGE INSERT [4]

Ferumoxytol

(NSC 729745)

Other Names:

Code 7228

CAS Registry Number:

1309-38-2

Molecular Formula:

$FeO_{1.49}$ (approximately);$C_{398}H_{646}O_{337}$ (coating)

Description:

Ferumoxytol is a non-stoichiometric magnetite (superparamagnetic iron oxide) coated with polyglucose sorbitol carboxymethylether. The overall colloidal particle size is 17-31 nm in diameter. The chemical formula of Ferumoxytol is $Fe_{5874}O_{8752}$-$C_{11719}H_{18682}O_{9933}Na_{414}$ with an apparent molecular weight of 750 kDa.

How Supplied:

Ferumoxytol is supplied as a sterile, single-use, vial. Each 510 mg vial contains 17 mL of a black to reddish brown liquid of 30 mg Fe/mL and 44 mg/mL of mannitol. The formulation is isotonic with an osmolality of 270-330 mOsm/kg. The product contains no preservatives, and has a pH of 6 to 8.

Preparation:

No additional preparation is necessary unless otherwise directed in the protocol.

Storage:

The intact vials should be stored at controlled room temperature 20-25ºC (68-77ºF). Excursions permitted to 15º-30ºC (59º-86ºF)

Stability:

The intact vials remain clinically acceptable until the expiration date indicated on the vial.

CAUTION: The single-use dosage form contains no antibacterial preservatives. Therefore, it is advised that the product be discarded 6 hours after initial entry.

Route of Administration:

Intravenous

Method of Administration:

Ferumoxytol will be administered as an intravenous infusion in 50-200mL 0.9% Sodium Chloride,

USP or 5% Dextrose Injection, USP over at least 15 minutes.

ADVERSE REACTIONS: Feraheme injection may cause serious hypersensitivity reactions and hypotension.

In clinical studies, 1,726 subjects were exposed to Feraheme; 1,562 of these had CKD and 164 did not have CKD. Of these subjects 46% were male and the median age was 63 years (range of 18 to 96 years).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice.

ADVERSE REACTIONS IN CLINICAL STUDIES:

Across the three randomized clinical trials, a total of 605 patients were exposed to two injections of 510 mg of Feraheme and a total of 280 patients were exposed to 200 mg/day of oral iron for 21 days. Most patients received their second Feraheme injection 3 to 8 days after the first injection.

Adverse reactions related to Feraheme and reported by ≥ 1% of Feraheme-treated patients in the randomized clinical trials are listed in Table 1. Diarrhea (4.0%), constipation (2.1%) and hypertension (1.0%) have also been reported in Feraheme-treated patients.

Table 1: Adverse Reactions to Feraheme Reported in ≥1% of Patients with CKD Adverse Reactions	**Feraheme 2 x 510 mg (n = 605)**	**Oral Iron (n = 280)**
Nausea	3.1%	7.5%
Dizziness	2.6%	1.8%
Hypotension	2.5%	0.4%
Peripheral Edema	2.0%	3.2%
Headache	1.8%	2.1%
Edema	1.5%	1.4%
Vomiting	1.5%	5.0%
Abdominal Pain	1.3%	1.4%
Chest Pain	1.3%	0.7%
Cough	1.3%	1.4%
Pruritus	1.2%	0.4%
Pyrexia	1.0%	0.7%
Back Pain	1.0%	0%
Muscle Spasms	1.0%	1.4%
Dyspnea	1.0%	1.1%
Rash	1.0%	0.4%

11.2 APPENDIX B: Performance Status Criteria

ECOG Performance Status Scale	
Grade	Descriptions
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.