Non-inferiority study of intra-operative indocyanine green fluorescent dye versus Technetium lymphoscintigraphy for sentinel lymph node biopsy in pediatric malignancies

PROTOCOL FACE PAGE FOR MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

OneMSK Sites
Manhattan

Participating Institutions	Site PI Name	Site Role
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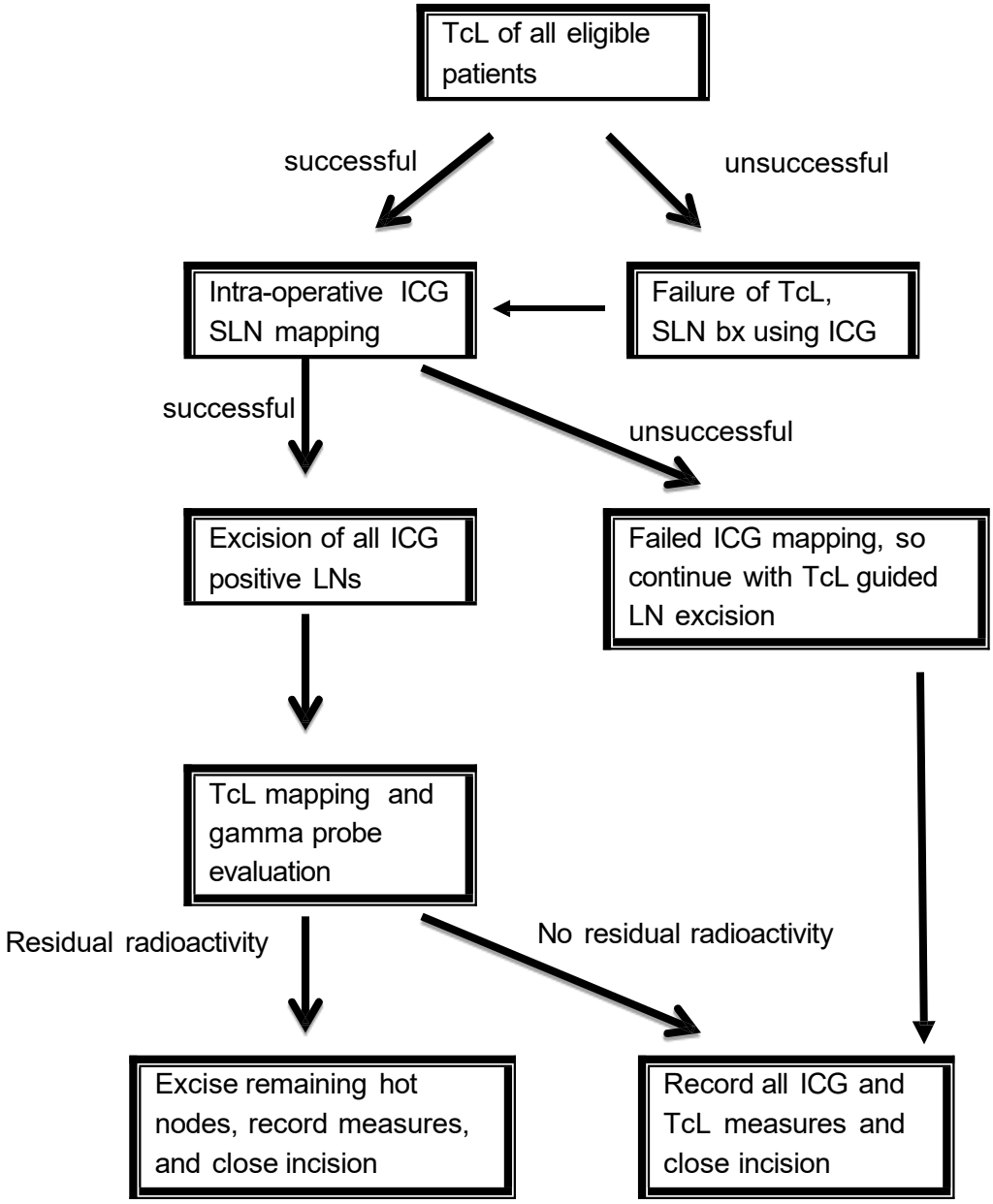
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This prospective trial will examine whether indocyanine green (ICG)-guided intraoperative transdermal lymphography is non-inferior to pre-operative technetium lymphoscintigraphy (TcL) for detecting sentinel lymph nodes (SLN) in pediatric patients with solid tumors. The primary endpoint is the detection rate for TcL-labeled and ICG-labeled SLNs. Secondary outcomes will include safety of ICG, number of positive nodes detected with each modality in each patient, and the sensitivity rate with each modality. The study population will include any patient under the age of 30 years who requires a sentinel lymph node biopsy for a solid tumor. Each patient will undergo both TcL prior to SLN biopsy and intra-operative ICG transdermal lymphography, thereby simultaneously serving as his/her own control. However, the surgeon will be blinded to the TcL results until after the ICG transdermal lymphography results have been recorded, in order to directly evaluate the detection rate of the ICG. Given the estimated sample size of 59 patients and an annual rate of SLN biopsies on patient under 30 years of age of 10 per year at MSK and 17 patients from the two collaborating institutions, this study will take approximately 4 years to complete. (Schematic provided below)

Patient Flow Chart



- <1% of patients will fail to map with both modalities. In that rare event, the SLN biopsy will be aborted, and the patient will count as a failure of TcL and ICG in the primary objective.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

- Primary Objective
  - Show that the SLN detection rate using ICG-guided transdermal lymphography is not inferior to that of TcL in pediatric solid tumors
- Secondary Objectives
  - Safety of ICG injection
  - Compare the total number of ICG+ and TcL+ SLNs harvested in each patient
  - Compare the percent of patients who have a pathologically positive SLN identified with each technique (sensitivity rate)

3.0 BACKGROUND AND RATIONALE

Pediatric solid tumors vary greatly in their propensity to spread to regional nodes. After the development of SLN biopsy in melanoma and breast cancer in adults, pediatric surgeons adopted the technique and applied it to multiple tumors including melanoma, Spitz nevi, and soft tissue sarcomas. Technetium lymphoscintigraphy is the gold standard for mapping and identifying SLNs in pediatric patients with solid tumors. Some surgeons also inject blue dye at the site, but its use has decreased because of frequent hypersensitivity reactions (1,2).

The standard procedure for SLN biopsy includes TcL the morning of or day prior to surgery. Mapping of the SLN is accomplished with nuclear medicine scans shortly after local Tc injection; the scans identify which lymph node basin contains the SLN and how many SLNs there are (average 1-2). In the unlikely event (<3%) that mapping fails, the patient is brought back 2-3 weeks later for repeat mapping. Once mapping is confirmed, the patient is taken to the OR, where a gamma probe is used to identify the hottest point (point with the highest gamma count) on the skin overlying the lymph node basin and an incision is made. The gamma probe and blunt dissection are then used to find the hot node and it is then resected. Given the lack of specificity and resolution using the gamma probe this can result in significant time and dissection. All the hot (gamma probe positive) nodes are removed and the procedure is considered complete when the baseline gamma count of the basin is <10% of the gamma count of the hottest node.

While technetium mapping is reliable, it has several disadvantages. First, it exposes a child to a small amount of radiation. Although the radiation dose is within the range of natural background radiation, it adds to the patient's cumulative radiation exposure. Second, while the gamma probes used to identify the SLN intra-operatively are sensitive, they are not specific, have poor resolution, and do not allow for direct visualization during dissection. The inherent error in the probes and the difficulty discerning lymph tissue from the surrounding fat can make it difficult to identify small SLNs. This disadvantage led to the addition of blue dye to the SLN procedure, but its use has been limited by the high risk of hypersensitivity to the dye. Third, the TcL procedure requires several hours to complete, so most patients spend an additional day in the hospital beginning the day prior to the surgery. Last, four injections of technetium must be given around the tumor site without sedation, which can be difficult in the pediatric population.

Recently, fluorescent lymphatic mapping with indocyanine green has been shown to be equivalent to technetium in cervical, uterine, and breast SLN mapping (3-6). One of the first groups of investigators to exploit these attributes of ICG was Memorial Sloan Kettering's Gynecologic Oncology Service. Jewell et al. published an analysis of a patient series in 2014 showing a 95% detection rate for ICG in uterine and cervical cancer SLN biopsy (3). In 2015, Imboden et al. published results of their study comparing ICG to blue dye, which demonstrated bilateral SLN detection rates of 95.5 and 61%, respectively (4). Xiong et al. performed a meta-analysis of ICG SLN data in 2014 and found a pooled detection rate of 96% (5). ICG also allows for direct transcutaneous visualization and transdermal lymphography using near-infrared cameras. Wishart et al. showed a 100% detection rate for ICG transdermal lymphography in early breast cancer SLN biopsy (6). If ICG is shown to be non-inferior to TCL for the mapping and identification of SLNs in pediatric solid tumors, then the pain, radiation exposure, and time expenditure required for TcL could be eliminated.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a prospective, multi-institutional clinical trial to evaluate non-inferiority of ICG-guided SLN biopsy compared with the gold standard TcL-guided SLN biopsy in pediatric patients with solid tumors. Each patient will undergo TcL, consistent with the standard of care, but the surgeon will be blinded to the results preoperatively. Intraoperatively, ICG injection and transdermal lymphography will be used to identify the draining nodal basin and the position of the sentinel nodes. ICG transdermal lymphography will be considered successful if SLNs can be visualized on near-infrared imaging. After the transdermal lymphography results have been recorded, the surgeon will be unblinded to the TcL mapping. All ICG-positive and TcL-positive nodes will be removed and complete excision will be confirmed by intra-operative near-infrared imaging and gamma probe evaluation. Thus, in this trial each patient will serve as his/her own control. If TcL fails, no repeat TcL will be perfomed, the SLN biopsy will be done with ICG alone, and the patient will be recorded as a failure of TcL (i.e. decreasing the detection rate for TcL). If ICG mapping fails, the TcL results will be used to perform SLN biopsy and the patient will be considered a failure of ICG (i.e. decreasing the detection rate for ICG). In the <1% of patients that fail both TcL and ICG, no SLN biopsy will be performed and the patient will be recorded as a failure of both TcL and ICG . These patients will still contribute data to the primary endpoint (i.e. decreasing the detection rate for both modalities) and safety data, but will not contribute to the other secondary aims. Approximately 59 patients will be enrolled over a period of approximately 4 years.

The primary outcome, SLN detection rate, will be compared between ICG-guided transdermal lymphography and TcL to determine non-inferiority of ICG in this clinical application. Secondary outcomes include the safety of ICG in this clinical scenario, comparisons of the total number of excised nodes identified with each detection method in each patients, and the sensitivity rate (percent of patients with a pathologically positive SLN) for each technique.

4.3 Intervention

On the day of or the day before the scheduled OR procedure, the patient will undergo TcL, but the surgeon will be blinded to the results preoperatively. On the day of surgery, 4 cc of 1.25 mg/mL ICG will be injected at 4 points directly surrounding the tumor site (1cc per point, depth will vary with position of the tumor) after the patient is under anesthesia. Transdermal lymphography and analysis of all possible draining nodal basins will then be performed using a near-infrared camera in real time. ICG mapping to the SLN takes approximately 5min. If the SLN cannot be identified 20min after ICG injection, it will be considered a failure of ICG, and the TcL results will be used to perform the SLN biopsy. If the ICG does map and a SLN is identified, the transdermal lymphography results will be recorded and the surgeon will be unblinded to the TCL results. All fluorescent lymph nodes will then be resected using the near-infrared camera. After all ICG-positive nodes have been resected, but before closure, gamma probes will be used intraoperatively to ensure all TcL-positive SLNs have been removed. As is standard with TcL SLN biopsy any activity in the nodal bed <10% of the "hottest" node removed will be considered background. This will act as the threshold for all TcL positive nodes being removed. The detection rates for each tracer, ICG and TcL positivity for every node removed, and number of ICG and TcL positive nodes per patient will be recorded. If TcL fails, no repeat TcL will be perfomed, the SLN biopsy will be done with ICG alone, and the patient will be recorded as a failure of TcL (i.e. decreasing the detection rate for TcL). If ICG mapping fails, the TcL results will be used to perform SLN biopsy and the patient will be considered a failure of ICG (i.e. decreasing the detection rate for ICG). In the <1% of patients that fail both TcL and ICG, no SLN biopsy will be performed and the patient will be recorded as a failure of both TcL and ICG with respect to detection rate. These patients will still contribute data to the primary endpoint (i.e. decreasing the detection rate for both modalities) and safety data, but will not contribute to the other secondary aims.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

ICG is an FDA-approved drug for IV, subcutaneous, and topical use. Safety and effectiveness of this agent in pediatric patients have been established (8-10). ICG is currently used at MSK for viability and perfusion analysis in colorectal and plastic surgery as well as SLN identification in gynecologic cancer. It is supplied in a kit with sterile covers for the near-infrared camera and the agent is easily diluted to the goal concentration of 1.25mg/mL prior to injection.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

Describe the characteristics of the patient/subject population.

6.2 6.1 Subject Inclusion Criteria

- Patients <30 years old with an extracoelomic solid tumor, diagnosis confirmed at the enrolling institution, requiring SLN biopsy
- Women of childbearing potential must have a negative pregnancy test (urine or blood) pre-operatively as per the standard hospital policy. A woman of childbearing potential is defined as one who is biologically capable of becoming pregnant.

- Patients who are cleared for surgery as noted in Section 8.0

6.3 Subject Exclusion Criteria

- History of reaction to ICG, iodides, or technetium radiocolloid
- Intracoelomic primary tumors or tumors expected to drain to an intracoelomic SLN
- Patients with extensive prior surgery at the primary site or nodal basin expected to affect the lymphatic drainage
- Patients unwilling or unable to sign informed consent
- Women who are pregnant or breast-feeding.

7.0 RECRUITMENT PLAN

Any patient meeting the above criteria who is referred to a surgery clinic at a participating institution will be recruited for the study. The consenting professional will be responsible for explaining the study to the patient and obtaining written informed consent. The clinical research coordinator will be responsible for registering the patient on study. Recruitment of 59 patients is expected to be completed in approximately 4 years.

8.0 PRETREATMENT EVALUATION

All standard pre-operative tests including CBC, coagulation studies, electrolytes, and imaging (determined by the location and attributes of the tumor) will be obtained within the time limits set forth in the participating institution's pre-operative work-up guidelines. No additional tests will be required prior to our intervention.

9.0 TREATMENT/INTERVENTION PLAN

Pre-operative studies as detailed above will be performed in the days leading up to the intervention. The injection of ICG at 4 points directly surrounding the tumor site will take place at the time of operation after the patient is under anesthesia. Transdermal lymphography and analysis all possible draining nodal basins will then be performed for 20min using near-infrared cameras in real time in the operating room. Immediate ICG mapping and detection results will be compared with the pre-operatively obtained TcL and the standard post-operative pathology results. Patients will be monitored intra-operatively for any adverse reaction to ICG and will be specifically asked about adverse events at the time of follow up 1-4 weeks after surgery.

Day w/ respect to operation	Intervention
-45 to -1 (Baseline)	Pre-operative labs and imaging
-1 to 0 (Visit 1)	TcL
0 (Visit 2)	ICG mapping and SLN biopsy
7-28 (Visit 3)	Post-op evaluation and interview for adverse events

10.1 EVALUATION DURING TREATMENT/INTERVENTION

No additional tests or follow-up over the standard intra-operative and post-operative monitoring will be required in this trial.

The tests included under standard of care are:

- CBC
- Coagulation tests
- Pre-operative technetium lymphoscintigraphy (TcL)

11.0 TOXICITIES/SIDE EFFECTS

COMMON, SOME MAY BE SERIOUS **In 100 people receiving ICG dye, more than 20 and up to 100 may have:**
• **Mild burning at the injection site lasting up to a few hours** • **Green or yellowish discoloration at the injection site lasting up to several hours**
OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving ICG dye from 4 to 20 may have:**
• **General yellowish skin discoloration lasting up to 24 hours** • **Orange urine discoloration lasting up to 24 hours**
RARE, AND SERIOUS **In 100 people receiving ICG dye 3 or fewer may have:**
• **Allergic reaction – most are mild with pruritus and hives, but some can be serious with wheezing/bronchospasm and facial edema**

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Please refer to sections 4.0 and 9.0 for the overview of the study design, intervention, and treatment plan.

13.0 CRITERIA FOR REMOVAL FROM STUDY

- Patient refuses to continue with study
- Immediate adverse reaction to ICG injection precluding complete dosing

14.0 BIOSTATISTICS

Primary objective

Non-inferiority studies concentrate on proving that the tested method is not clinically inferior to the standard of care by a particular margin decided upon using prior knowledge of the external (to the trial) advantages of the new method. They are extremely useful in rare conditions and when comparing a new test to a standard of care with a very high success rate. Both TcL and ICG have a success rate of 95% and pediatric solid tumors requiring SLN biopsy are rare. In order to perform a standard superiority study comparing ICG to TcL, thousands of patients would be necessary, which is not clinically feasible. As described above, from the clinical standpoint, ICG is superior to TcL for patient care because it provides much more accurate visualization of SLNs during biopsy, does not expose the patient to radiation, does not require painful injections without sedation, and does not require additional time commitments from the patient and family. The non-inferiority margin was, therefore, set at 10% using this clinical knowledge. Using an alpha level of 0.05 and a beta level of 0.2, and knowing TcL and ICG detect a SLN in 95% of cases, the calculated N per group for paired values is 59. Because each patient serves as his/her own control, these tests are considered “paired” values. Adjustment to the non-inferiority study statistics has been described by Liu et al (7). Given that each of our patients will be evaluated with both TcL and ICG, each case counts towards both groups and our total N = 59. Given the rate of 15-20 pediatric SLN biopsies per year at our institution, patient accrual should be completed within approximately 4 years.

The primary outcome of this study is the detection rate (% of patients in whom a SLN is identified) for ICG and TcL. These percentages will be compared using a non-inferiority comparison for matched pair data as described above. In the unlikely event that SLNs are not found with either modality, these patients will still contribute data to the primary endpoint (i.e. decreasing the detection rate for both modalities) and safety data, but will not contribute to the other secondary aims.

Secondary objectives

Safety will be analyzed with descriptive statistics of the number and type of adverse reactions encountered (per CTCAE guidelines).

The number of nodes identified by each technique will be compared using a paired Wilcoxon signed-rank test.

To evaluate sensitivity, the percent of patients in whom a SLN is found to contain tumor on pathology using each technique will be compared with McNemar’s test for matched pair data.

Finally, to determine whether the intensity of each node is associated with pathologic positivity, a logistic regression model will be fit with pathologic positivity as the outcome and intensity as the predictor, and robust standard errors will account for correlation among multiple nodes per patient. This will be done separately for ICG and TcL intensity.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in the section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

The individual signing the Eligibility Checklist is confirming that the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.2.1 Registration for Participating Sites:

Central registration for this study will take place through MSK's Clinical Trials Management System (CTMS).

To complete registration and enroll a participant from another institution, the site must first contact the MSK study coordinator to notify him/her of the participant registration.

Once the MSK study coordinator is notified, the site will document the participant's consent by associating the participant to the protocol in CTMS. This will generate a study ID number that is unique and must be written on all data and correspondence for the participant.

After associating the participant to the protocol, the site will enter the consent status in real-time, but no later than 2 business days, from when the informed consent was signed.

The following documents must be saved to CTMS within 2 business days of documenting consent status:

- The completed or partially completed MSK eligibility checklist
- The signed informed consent and HIPAA Authorization form

Supporting source documentation for eligibility questions (e.g. laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report) will be sent to the MSK study coordinator within 30 days of consent so eligibility can be verified. Once the MSK study coordinator verifies eligibility the site will be notified to enter eligibility and on study status in CTMS, which will complete participant registration.

15.3 Randomization

This study does not involve randomization.

16.1 DATA MANAGEMENT ISSUES

All experimental data including TcL, ICG mapping and detection, nodal ICG and TcL measurements and correlating pathology results will be stored in a REDCap database.Data from patients accrued at other institutions will also be submitted to the secure REDCap

database. External institutions will only have access to patient information submitted from their respective institution. The PI and MSK research team will be the only researchers with access to other institutions data submissions.

Data will be managed through REDCap (Research Electronic Data Capture), a data management software system supported by Clinical Research Administration at MSK. Members of the Clinical Research Administration supporting the REDCap software will have access to the data for the purpose of ensuring the proper functioning of the database and the overall software system. REDCap is a tool for the creation of customized, secure data management systems including web-based data entry forms, reporting tools, and a full array of security features including user and group based privileges with a full audit trail of data manipulation and export procedures. REDCap is maintained on MSK-owned servers that are kept in a locked server room with appropriate environmental modifications (e.g., special air conditioning), supported by an uninterrupted power supply, and backed up nightly with some backup tapes stored off-site. All connections to REDCap utilize encrypted (SSL-based) connections. Nationally, the REDCap software is developed, enhanced, and supported through a multi-institutional consortium led by the Vanderbilt University CTSA. REDCap will only be used for the housing of survey data. Use of REDCap has been approved by the department's manager of IT Systems and by MSK Information Security.

16.1.1 Data and Source Documentation for Participating Sites

Data

The participating site(s) will enter data onto a standardized data collection CRF. Data entry guidelines have been generated for this study and blank data collection CRFs will be sent to the study staff at each participating site for use. The participating site PI is responsible for ensuring these forms are completed accurately, legibly and in a timely manner.

The participating site(s) will enter data remotely into an electronic database using the internet based system, REDCap. Data entry guidelines have been generated for this study and site staff will receive database training prior to enrolling its first participant. The participating site PI is responsible for ensuring these forms are completed accurately and in a timely manner. A schedule of required forms is shown in section 16.0.3.

Source Documentation

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data recorded on CRFs and entered into the REDCap database. Relevant source documentation to be submitted throughout the study includes:

- Diagnosis
- Patient history/MD notes
- Operative reports

Source documentation should include a minimum of two identifiers to allow for data verification. MSK will maintain the confidentiality of any subject-identifiable information it may encounter.

16.1.2 Data and Source Documentation Submission for Participating Sites

Participating sites should email source documentation to MSK at the contact information provided by the MSK study coordinator. Submissions should include a cover page listing all documents enclosed per participant.

Participating sites should enter data directly into REDCap and study-specific paper CRFs. Source documentation should be sent to MSK at the contact information provided by the MSK study coordinator. Submissions should include a cover page listing relevant records enclosed per participant.

16.1.3 Data and Source Documentation Submission Timelines for Participating Sites

Data and source documentation to support data should be transmitted to MSK according to chart 2.

Chart 2: Data and Source Submission Requirements and Timelines

	Baseline	Visit 1	Visit 2	Visit 3	SAE	Off Study
Submission Schedule						
Source Documentation	Within 2 days (see section 13.1.1)	Within 14 days of visit if diagnostic or other clinical protocol			Within 3 days of event updates to be submitted as available	Within 14 days of visit if diagnostic or other clinical protocol
REDCap eCRFs	Within 7 days of visit					
Required Forms						
SAE Form					X	

16.2 Quality Assurance

Completeness of registration data will be monitored by the clinical research coordinator on a regular basis. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates, and the extent and accuracy of evaluations and follow-up, will be monitored periodically throughout the study. Potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team at a minimum of twice per year, or more frequently if indicated.

16.2.1 Quality Assurance for Participating Sites

Each site accruing participants to this protocol will be audited by the staff of the MSK study team for protocol and regulatory compliance, data verification and source documentation.

Audits will be conducted annually during the study (or more frequently if indicated) and at the end or closeout of the trial. Ideally the first audit will occur shortly after the first patients are enrolled. The number of participants audited will be determined by auditor availability and the complexity of the protocol. Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1*. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.4 Regulatory Documentation

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document and each participating site will utilize that document.

The following documents must be provided to MSK before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved informed consent form
- Participating Site IRB's Federal Wide Assurance (FWA) number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research and Good Clinical Practice Certification for investigators, consenting professionals and key study personnel at the participating site.

For interventional studies funded by the NIH, GCP training must be renewed every 3 years.

Upon receipt of the required documents, MSK will formally contact the site and grant permission to proceed with enrollment.

16.4.1 Amendments

Each change to the protocol document must be organized and documented by MSK and approved first by the MSK IRB/PB. Protocol amendments that affect MSK only (e.g. change in MSK Co-Investigator, MSK translation, etc.) do not require IRB review at the participating site(s). All other protocol amendments will be immediately distributed to each participating site upon receipt of MSK IRB/PB approval.
Each participating site must obtain IRB approval for all amendments within 90 calendar days of MSK IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, participating sites will not be permitted to continuing enrolling new participants until site IRB approval of the revised protocol documents is granted and submitted to MSK.

Each participating site must provide all site IRB approvals for amendments/modifications and the most current approved version of the site informed consent form and HIPAA authorization at the time of approval. Documents must be submitted to MSK on a continuing basis.

16.4.2 Additional IRB Correspondence

Continuing Review Approval

The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form and HIPAA authorization must be submitted to MSK within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of new participant enrollment.

Deviations

A protocol deviation on this study is defined as any incident involving non-adherence to an IRB approved protocol. Deviations typically do not have a significant effect on the rights, safety, or welfare of research participants or on the integrity of the resultant data. Deviations that represent unanticipated problems involving risks to participants or others, or serious adverse events must be reported according to sections 17.2.1.

Deviations that do not adversely affect the rights and/or welfare of the participant or the scientific validity of the study and are related to protocol scheduling changes outside of the allowed window due to a holiday (e.g., New Year's, Thanksgiving, etc.) and/or inclement weather or other natural event do not require reporting to the MSK IRB/PB. However, they must be clearly documented in the patient's medical record.

Prospective Deviations

Deviations to the research protocol that involve patient eligibility, an informed consent procedure change, and/or treatment/pharmacy alterations that are not allowed by the protocol require prospective approval from the MSK IRB/PB prior to the change being carried out. Participating sites must contact the MSK PI who will in turn seek approval from the MSK IRB/PB.

Retrospective Deviations
Deviations that include a change or departure from the research protocol without prior approval from the MSK IRB/PB are considered retrospective deviations. Retrospective deviations must be reported to the MSK PI as soon as possible, who will in turn report the deviation to the MSK IRB/PB as per MSK guidelines.

Participating Site IRB Reporting

Participating sites must report all deviations to their institution's IRB per local guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations must be submitted to MSK upon receipt.

Other correspondence
Participating sites must submit other correspondence to their institution's IRB according to local guidelines, and submit copies of all site IRB correspondence, including approvals and acknowledgements, to MSK.

16.4.3 Document maintenance
The MSK PI and participating site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all regulatory documents and participating site IRB correspondences are maintained in an onsite regulatory binder and are sent to MSK as outlined within the protocol. A regulatory binder for each site will also be maintained at MSK; this binder may be paper or electronic.

After study closure, the participating sites will maintain all source documents, study related documents and CRFs for 3 years.

16.5 Noncompliance
If a participating site is found to be noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments may be withheld (if applicable), until the outstanding issues have been resolved.

17.1 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients or their legal guardians will be required to sign a statement of informed consent, which must conform to MSKCC IRB guidelines. The informed consent must contain a full explanation of the possible advantages, benefits, risks,

alternative treatment options, and availability of treatment in the case of injury, in accordance with Federal Regulations as detailed in 21CFR50. The investigator is responsible for obtaining written informed consent from potential patients or legal guardian before performing any trial tests or assessments required by the protocol. A copy of the signed document will be given to the patient or legal guardian , and the original will be retained by the investigator with his/her copy of the record forms.

Given the nature of these tumors, most patients will be children, adolescents, and young adults. Patients of both sexes and all racial/ethnic backgrounds are eligible for this study. Alternative treatments are available and will be discussed with the patient or legal guardian.

Benefits: This study is not expected to help treat the cancer, but it may lead to removal of extra lymph nodes for analysis. What we learn from this study may help patients in the future.

Risks: The potential risks of this therapy as described in section 11 of this protocol may outweigh the potential benefits in an individual patient. The potential risks are related to the adverse effects which could be induced by the ICG dye.

Patients or their legal guardians will be charged for the costs for all routine visits, treatment, and non-research testing related to the cancer. Patients will not be charged for the ICG dye, the preparation, or for use of the specialized camera used as part of the study.

17.2 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB). The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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.

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the IRB office per IRBSOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event.All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s) (drug, device, or intervention)
- If the AE was expected
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

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17.2.1 SAE Reporting for Participating Sites

Responsibilities of Participating Sites

- Participating sites are responsible for reporting all SAEs to their local IRB per local guidelines. Local IRB SAE approvals/acknowledgments must be sent to MSK upon receipt.
- Participating sites are responsible for submitting the SAE Report form found in Appendix A to MSK within 3 calendar days of learning of the event.
- When a life-threatening event or death is unforeseen and indicates participants or others are at increased risk of harm, participating sites should notify the MSK PI as soon as possible but within 24 hours of the time the site becomes aware of the event.

SAE contact information:

Email: cavallim@mskcc.org to the attention of 16-1003 Research Staff

AND

Email: heatont@mskcc.org

Responsibilities of MSK

- MSK Research Staff are responsible for submitting all SAEs to the MSK IRB/PB as specified in 17.2.
- The MSK PI is responsible for informing all participating sites about all unexpected SAEs that are either possibly, probably or definitely related to the study intervention within 30 days of receiving the stamped SAE from the MSK IRB/PB.
- The MSK PI is responsible for informing all participating sites within 24 hours or on the next business day about a life-threatening event or death that is unforeseen and indicates participants or others are at increased risk of harm.

17.4 Unanticipated Problems

Unanticipated problems involving risks to participants or others (UPs) are defined as any incident, experience or outcome that meets all of the following criteria:

- Unanticipated (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; and
- Related or possibly related to participating in the research (possibly related means there is a reasonable probability that the incident, experience or outcome may have been caused by procedures involved in the research); and
- Suggests that the research place participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Participating sites are responsible for reporting all UPs to MSK as soon as possible but within 3 calendar days of learning of the event. UPs that are SAEs must be reported to MSK via SAE Report form as per section 14.3. All other UPs must be reported to MSK in a memo signed by the site PI.

MSK is responsible for submitting UPs to the MSK IRB/PB according to institutional guidelines. In addition, MSK is responsible for notifying participating sites of all non-SAE UPs that may affect the sites.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain to participants the full details of the protocol and study procedures, as well as the risks involved, prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18.1 Informed Consent Procedures for Participating Sites

The investigators listed on the Consenting Professionals Lists and/or Delegation of Authority Log at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

19.1 REFERENCES

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20.0 APPENDICES

Appendix A: SAE Report Form