Study Protocol

TITLE: A Pilot Study of Biomarker Evaluation and Safety of Pre-Incisional Ketorolac for Patients Undergoing Surgical Resection for Non-Small Cell Lung Cancer and Renal Cell Carcinoma

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REVISION HISTORY

Revision #	Version Date	Summary of Changes
1.0	26Mar2020	First version submitted to Emory IRB
2.0	27Aug2020	Second version with minor clarifications and specification of sample collection visit windows.
3.0	24Nov2020	Third version with minor dosing clarification.
4.0	19Feb2021	Fourth version with minor exclusion eGFR level changes
5.0	27Jan2022	Fifth version with increased overall enrollment goal of up to 100 patients to account for screen fails and/or withdrawals
6.0	31 Mar 2022	Sixth version with minor clarification regarding tissue collection including malignant and benign tissue.
7.0	23 FEB 2024	Ceasing enrolment for the Cardiothoracic group

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1. Study Summary

Study Title	A Pilot Study of Biomarker Evaluation and Safety of Pre-Incisional Ketorolac for Patients Undergoing Surgical Resection for Non-Small Cell Lung Cancer and Renal Cell Carcinoma
Study Design	PATIENT REGISTRATION/RANDOMIZATION Patients will be screened and recruited during the pre-operative period by the responsible medical and surgical team. Blood will be drawn pre-operatively and then at the end of the surgical procedure. Patients who are eligible to be included will be fully informed, consented for additional blood draws and will have the opportunity to ask any questions they may have. Patients will be randomized to either pre-operative Ketorolac group or a concurrent control group who will not receive pre-incisional ketorolac. The concurrent control group is to obtain untreated biologic samples for biologic correlative studies and secondary endpoints. These patients will not be compared to the investigational cohort in regards to the primary endpoint of safety. Patients will be randomized on the day of surgery to either the experimental or control arms. A total of 56 patients will be enrolled into the experimental arm (28 per disease site). About 10 patients will be allocated randomly into the concurrent control group for each disease site separately, for a total of 76 patients enrolled. The enrolment for NSCLC will cease at total of 28 patients consented with total study enrolment goal of 79 Up to 80 patients may be consented on study to account for screen fails and/or withdrawals.
Primary Objective	To test the safety of a single pre-incisional dose of 30 mg ketorolac in patients undergoing surgery for stage I/II NSCLC and stage III RCC, as these are the stages of cancer most likely to develop a recurrence while still noting a benefit from the ketorolac.
Secondary Objective(s)	To evaluate blood and tissue samples pre- and post-operatively to assess the impact of ketorolac on key

	inflammatory biomarkers using a standard cytokine panel.
Research Intervention(s)/Interactions	STUDY PROCEDURES Surgical Resection All patients will receive standard-of-care surgery. Open, video-assisted thoracic surgery, laparoscopy, or robotic surgery are allowed. Standard anesthesia will be administered. Ketorolac 30 mg ketorolac will be administered intravenously during the induction of anesthesia (pre-incision). Ketorolac administration will not be permitted during the operation. Patients randomized to the control group will not receive Ketorolac.
Study Population	See Inclusion Criteria and Exclusion Criteria.
Sample Size	See Statistical Consideration
Study Duration for individual participants	2 years
Study Specific Abbreviations/ Definitions	N/A
Funding Source (if any)	Morningside Center

2. Objectives

2.1 Primary Objective

To test the safety of a single pre-incisional dose of 30 mg ketorolac in patients undergoing surgery for stage I/II NSCLC and stage III RCC, as these are the stages of cancer most likely to develop a recurrence while still noting a benefit from the ketorolac.

2.2 Secondary Objective

To evaluate blood and tissue samples pre- and post-operatively to assess the impact of ketorolac on key inflammatory biomarkers using a standard cytokine panel.

3. Introduction and Background

Surgical resection is a cornerstone of standard-of-care treatment for early-stage non-small cell lung carcinoma (NSCLC) and renal cell carcinoma (RCC). Yet despite optimal treatment, many of these patients will develop cancer recurrence within the first few years. For example, the 5-year

survival rate for patients with stage I/II NSCLC is only around 55%.[1] As a result, more effective treatments that decrease cancer recurrence and increase survival are still needed.

Surgery induces inflammation, immunosuppression and angiogenesis. Although these processes are important for wound healing in response to tissue injury caused by surgery, they also support the survival, growth and dissemination of any remaining cancer cells and can lead to systemic recurrence soon after surgery. Surgical trauma increases the production of prostaglandins and thromboxanes, which have tumor-promoting and immunosuppressive activities, and reduces the activity of natural killer cells, which impairs the ability of the immune system to keep cancer cells in check. However, if given just before tissue injury, non-steroidal anti-inflammatory drugs (NSAIDs) may be able to block the production of prostaglandins/thromboxanes and boost the activity of natural killer cells, and thereby decrease the risk of cancer recurrence. Indeed, NSAIDs have anticancer effects in animal models and humans.[2-5] For example, in one study, the 20-year risk of cancer-related death was significantly lower after administration of daily aspirin (HR 0.80, p<0.0001).[2]

NSAIDs such as ketorolac are already routinely given to cancer patients post-operatively for pain management and are sometimes given intra-operatively (immediately before or during surgery) to prevent post-operative pain. A retrospective clinical analysis found that intra-operative intravenous ketorolac or diclofenac (another NSAID), when added to standard of care for patients with stage I/II NSCLC, was associated with decreased risks of distant recurrence (HR = 0.50; 95% CI 0.24-1.00; *P* = 0.05) and mortality (HR = 0.64; 95% CI 0.42-0.96; *P* = 0.03) (Figure 1).[6] Similar results were seen in renal cell carcinoma (RCC).

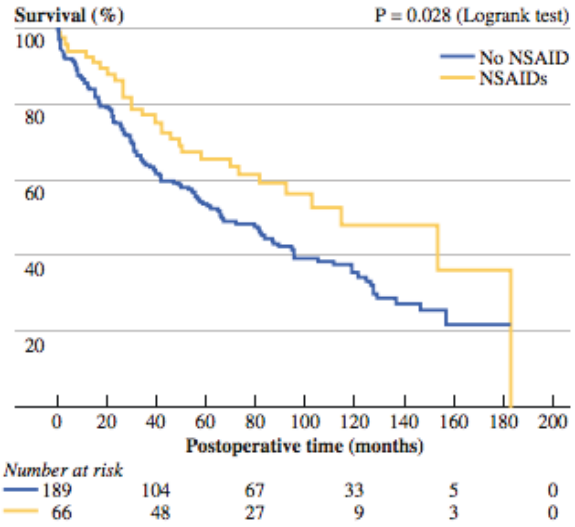

Figure 1. Kaplan–Meier curves of overall survival for 255 patients receiving or not an NSAID (ketorolac or diclofenac) intra-operatively during NSCLC surgery. Univariate analysis by log-rank test. Figure from [6].

The effect of intra-operative NSAIDs may be even more prominent in patients with pre-operative inflammation, which is associated with a greater risk of early recurrence and mortality.[6] Moreover, recent data indicates that **pre-operative**, but not post-operative, ketorolac administration can eliminate micrometastatic disease in animal lung and breast cancer resection models and create long-lasting T cell immunity.[7] Thus in addition to safety and feasibility, we will assess whether there is evidence of a tumor directed T-cell response in patients who receive pre-operative ketorolac.

We do note a recently published randomized phase III study in breast cancer failed to identify a reduction in recurrence rates in high-risk breast cancer patients[8], and did not support retrospective data which did show a benefit.[9] Though many possibilities exist for the negative results of this most recent study, one possibility is that chemotherapy was utilized in the majority of the patients, and arms were somewhat imbalanced. This may have negated the effect of the ketorolac, as noted in our preclinical animal studies.[7]

Given these overall findings, there is significant promise in the use of preoperative ketorolac to decrease the inflammatory response after surgical resection of tumors, thereby potentially reducing the risk of distant metastatic tumor spread and improving survival. These results could potentially be applied to any number of tumor sites. However, ketorolac and other NSAIDS inhibit platelet function by blocking cyclooxygenase enzymes and the formation of thromboxane A2, resulting in potentially higher risk for postoperative bleeding or result in higher rates of postoperative renal failure.[10,11] *While the risk of such complications after a single dose of ketorolac is likely low, the safety of a preoperative dose of ketorolac prior to major surgical resection needs to be assessed* prior to proceeding with a larger phase II study designed to evaluate traditional efficacy endpoints such as recurrence and overall survival. Additionally, the proposed mechanism that ketorolac effect is T-cell dependent and contributes directly to anti-tumor activity via reduction of postoperative inflammation can be further studied. Blood and tissue samples from patients enrolled in this study will be analyzed to determine if the effect of ketorolac is more prominent in patients with high pre-operative inflammation.

4. Study Endpoints

4.1 Primary Safety Endpoints

Incidence of clinically significant pre-discharge (both intra- and post-operative) blood transfusion, clinically significant hematoma development, or return to the operating room for bleeding; post-operative renal failure; and post-operative morbidity rates.

4.2 Secondary Endpoints

A number of exploratory biological correlative studies including transcriptome analysis, flow cytometry, TCR sequencing and single cell RNA Seq to evaluate the effects of ketorolac on immune response pathways.

5. Study Intervention/Investigational Agent

5.1 Surgical Resection

All patients will receive standard-of-care surgery. Open, video-assisted thoracic surgery, laparoscopy, or robotic surgery are allowed. Standard anesthesia will be administered.

5.2 Ketorolac

30 mg ketorolac will be administered intravenously during the induction of anesthesia (pre-incision). Ketorolac administration will not be permitted during the operation.

6. Procedures Involved

6.1 Study Calendar

Tests and Observations	Within 60 days prior to reg.	Before surgery at preoperative visit	Day of surgery (Day 0)	3 days	7 days (+/- 2 days)	28 days (+/- 7 days)	1 and 2 years (+/- 3 months)
History, physical, creatinine test, ECOG/Zubrod PS	X						
PET/CT, CT, or MRI scan head, neck, chest, or abdomen per standard of care	X						
Charlson comorbidity index		X					
Blood samples for biomarker analyses*		X	X	X	X	X	
Fresh tissue collection			X				
Adverse event assessment		X		X	X	X	

Chart review or patient contact for survival assessment							X

*See section 7.1 Biological Correlative Studies

6.2 Procedures

6.2.1 Surgical Resection

All patients will receive standard-of-care surgery. Open, video-assisted thoracic surgery, laparoscopy, or robotic surgery are allowed. Standard anesthesia will be administered.

6.2.2 Ketorolac

30 mg ketorolac will be administered intravenously during the induction of anesthesia (pre-incision). Ketorolac administration will not be permitted during the operation.

6.3 Follow-up

After completion of protocol therapy, patients will be monitored for peri-operative adverse events for up to 90 days after surgery, per routine standard of care for the respective surgical procedure. Patients with benign disease on pathology will still be followed for adverse events for 90 days after surgery, however will not be counted towards the patients analyzed for the study.

Patient charts, institutional renal cell and thoracic surgical databases (Society of Thoracic Surgeons Database), and the Georgia Cancer Registry through the Winship Cancer Institute will be queried to determine patient vital status, status of tumor recurrence if any, and if applicable, cause of death, at 1- and 2-years post-surgery. Only RCC patients will be followed up at 1- and 2-years post-surgery. All study follow-up will cease for NSCLC patients.

7. Data and Specimen Banking

7.1 Biological Correlative Studies

The specific effects of ketorolac on the host immune system are not known. It is hypothesized that pre-operative ketorolac will enhance anti-tumor immunity and result in activation of tumor-specific T cell responses, as has been noted in our preclinical studies[7]. To verify this, we will collect tissue samples, including surrounding benign and malignant tissue as part of the standard surgical procedure, and peripheral blood at pre-specified time-points. The following samples will be collected from all patients on this trial:

1. Tumor tissue at the time of surgery - Tissue will be collected from patients at the time of surgery by clinical research coordinators from the Clinical Research Unit and taken to Dr. Haydn Kissick's lab if adequate tissue is available after all necessary clinical samples are obtained as determined by the pathologist. Tissue analysis will be performed on malignant and benign tissue.
2. Serum and PBMCs before and at time points after surgery - Blood will be collected in CPT from patients at the time of surgery and postoperatively, as delineated in the timeline, by clinical research coordinators.

The following studies are planned in the bio-specimens collected: 1. Flow cytometry (at least to assess proliferating and activated T-cells in blood); 2. TCR sequencing to assess diversity of the T cell repertoire intra tumorally and in blood; and 3. Single cell RNA Seq in blood. Samples will be suitably prepared to allow for this at a future date. Collectively these assays will provide evidence for whether pre-op ketorolac can unleash post-operative anti-tumor T cell response in humans, thus extending the mouse data above. In addition, we will measure NLR, CRP, and IL-6 – all of which have been correlated to prognosis in a number of tumor types at baseline and some of which have been correlated to recurrence outcomes. Additional exploratory studies may also be conducted based on the results of these studies. Peripheral blood mononuclear cells (PBMCs) and plasma will be isolated from CPTs and cryopreserved. The correlative work will be conducted in the lab of Rafi Ahmed, Manoj Bhasin and Haydin Kissick.

Tissue analysis: In this proposal, we will measure how organization of immune cells in the tumor change after treatment. The tumor architecture and immune organization will be examined via IF and this imaging data will be quantitatively analyzed. We will determine the relative infiltration of stem-like T-cells, effector-like T-cells, and DCs, lymphatic and blood vessels. We will measure the distance between cells, and quantify their aggregation. We will specifically quantitate regions of sufficient antigen presenting density (5 APCs/100um^2) that are generated following implantation of the niche, and how these regions are located relative to the implant. A specific focus of this work will be how lymphatic and vasculature is altered before and after treatment and how this correlates with response to therapy.

Serum analysis: We will measure NLR, CRP, and IL-6 – all of which have been correlated to prognosis in a number of tumor types at baseline and some of which have been correlated to recurrence outcomes.

PBMC analysis: In ongoing work we have collected blood and tissue from patients receiving checkpoint blockade therapies at Emory and studied the immune response of these patients. We have found that in the blood of patients that have a clinical response to checkpoint therapy, there is a proliferative burst of newly generated effector CD8 T-cells in the blood. In comparison, patients that do not have clinical response to the treatment fail to generate this population of cells. This marker has significant predictive power to identify which patients will respond after the first treatment cycle with PD-1

blockade. In this proposal we will determine if measuring this marker after surgery and treatment with Ketorolac is associated with improved response to treatment.

7.2 Blood Sample Collection

Blood samples will be obtained before surgery in the preoperative holding area at the time of routine IV placement and at day 3 after surgical resection. Additional samples will be collected at Day 7 (+/- 2) and Day 28 (+/- 7) post-surgery. Lung resection and nephrectomy patients are typically admitted after surgery. Therefore day 3 blood samples will be obtained while patients are admitted to the hospital. However, if patients are discharged prior to day 3 samples will be collected via mobile blood draw services at patient's home. In addition, study team may use mobile blood draw services to collect some postoperative samples at patients' homes. Tumor samples will be collected from pathology at the time of resection.

CPT tubes should be at stored at room temperature following blood collection. CPT tubes should be inverted approximately 10 times after blood collection and kept rocking until processing. CPT tubes should be processed the same day.

Blood specimens taken from	Collected when	Submitted as
PBMCs and plasma: 3 CPTs (8 mL each) of whole blood for collection of plasma and PBMCs	**Pre-surgery:** at preoperative anesthesia visit and the day of surgery **Post-surgery:** Post-operative day 2-3 while in the hospital Between post-operative day 5-20, either prior to discharge or at postoperative clinic visit	Frozen plasma samples containing 2 mL per aliquot in 2 mL cryovials: Cryopreserved PBMCs containing 10^7 PBMCs per aliquot in 2 mL cryovials

8. Sharing of Results with Participants

There are no plans to share results with the participants.

9. Study Timelines

The study will be closed to enrollment for all patients. Only RCC participants are expected to participate in the study for 2 years. All study related assessments and activities to cease for NSCLC participants. The estimated date for investigators to complete this study is March 1, 2025.

10. Inclusion and Exclusion Criteria

SUBJECT ELIGIBILITY

Eligibility waivers are not permitted. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

10.1 Inclusion Criteria

10.1.1 Age ≥ 18 years and ≤ 80 years.

10.1.2 Pathology-proven or suspected stage 1 or 2 NSCLC and Stage 3 T3N0 RCC, that require surgical resection as the treatment of choice

10.1.3 ECOG performance status (PS) 0, 1, or 2.

10.1.4 Ability to understand and the willingness to sign an informed written consent.

10.2 Exclusion Criteria

10.2.1 Individuals with pure lung ground-glass opacity (GGO) lesions or mixed GGO with <50% solid component.

10.2.2 Patients undergoing pneumonectomy

10.2.3 History of cancer in the 3 years prior to surgery (except for basal-cell carcinoma of the skin or cervical neoplasia).

10.2.4 Contraindication for NSAIDs (peptic ulcer disease, pre-operative chronic kidney disease with eGFR <45 measured with the MDRD equation used widely, including at Emory), allergies or intolerance to NSAIDs, coagulation disorder, or age > 80 years).

10.2.5 Having taken an NSAID within 5 days prior to surgery.

10.2.6 Immunocompromised status

10.2.7 Refusal or inability to understand the protocol and consent form or to receive follow-up in line with the recommendations.

10.2.8 Preoperative hemoglobin < 9.0

11. Local Number of Participants

Up to 80 patients will be enrolled locally.

12. Recruitment Methods

Participants may be identified by review of medical records or physician referral. After an investigator introduces the study to the participant, the consent form may be given in person, mailed, emailed, or sent to the participant through EPIC or the Emory Patient Portal. The study team will follow up with the participant through the methods of communication listed above, by phone, and/or in person to communicate with the participant about the study. The participant will be given time to read the consent form and ask questions. A member of the study team will reach out to the participant to make sure the participant understands all aspects of the study and the participant is ready to sign the consent documentation. The participant may sign the consent forms in a private setting at Emory. Also, the participant has the option to consent by mail. Subjects with LEP may be enrolled and study team members will use Emory IRB approved shortforms to conduct the consent process. Participants will not receive any payment or reimbursement for this study. Study enrolment will cease for NSCLC participates.

13. Withdrawal of Participants

Participation in this study is completely voluntary and participants can withdraw at any time without any consequences. Participants can also be withdrawn from the study without their consent if their safety is at risk. This is unanticipated for this study. The revocation form specifies the procedures for participants withdrawing from the study.

14. Risks to Participants

Expected Adverse Events - Ketorolac

The expected incidence of postoperative adverse events attributable to a single preoperative ketorolac dose is expected to be very low. Known gastrointestinal side effects of ketorolac include (gastritis, gastroduodenal ulcer), pulmonary side effects (bronchospasm) and renal side effects (kidney failure) and typically arise with long-term use.11, 12 Ketorolac has been routinely used for postoperative analgesia in each of disease sites being studies. For example, Freedland, et al., in a retrospective review of 198 patients undergoing donor nephrectomy, found no increased risk of complications or worsening of long-term renal function with postoperative ketorolac use.13 Similar results have been seen after lung and other cancer resections with postoperative use.14-16 Non-selective NSAIDs, such as ketorolac, are known to have the potential to affect platelet function. This does not prevent them from being routinely used after numerous surgical procedures including trauma surgery. However, pre-/intra-operative use of ketorolac has not been studied in lung and kidney surgical patients. Therefore, intra- and post-operative and transfusion rates will be monitored as the primary endpoint for this study. Operative blood loss will also be monitored. Subjects will also be monitored for change in decline in eGFR greater than expected for the procedure. For example, for kidney removal, we expect eGFR to decline 50%, and consider this

expected. However, it if declines by more than 75%, we would consider this unexpected, possibly due to ketorolac.

15. Potential Benefits to Participants

There is significant promise in the use of preoperative ketorolac to decrease the inflammatory response after surgical resection of tumors, thereby potentially reducing the risk of distant metastatic tumor spread and improving survival.

16. Data Management and Confidentiality

16.1 Data and Safety Monitoring

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when

applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

There is no dose escalation planned for this study. The procedures to assure data integrity and protocol adherence are standard of care procedures for this study. Regular data verification and protocol adherence will take place in real time. The standard of care labs will be collected and the PI will review and analyze the results in real time. All data will be recorded and all adverse events will be graded and reported in real time using the CTCAE criteria for evaluation. The oversight of the study team be carried out by the PI reviewing data in real time and results being discussed at the GU working group meetings as necessary. The evaluation of kidney function and labs is standard of care. The study team will not need to be trained on study procedures because there are no new procedures being done that are not part of the standard of care.

16.2 Statistical Consideration

16.2.1 Sample size determination

It is a pilot study that aims to monitor the hemorrhage side effects who received Ketorolac pre-operatively with the primary safety endpoint being pre-discharge blood transfusion. According to the historical data, among 3280 nephrectomy cases during 2015-2020 in Emory, 20% need a blood transfusion before the discharge, and the mean number of units transfused is 0.286 (standard deviation = 0.12). Among 1212 thoracotomy cases during 2014 -2020 in Emory, 3.4% need a blood transfusion before the discharge, and the mean number of units transfused is 0.098 (standard deviation = 0.075). We anticipate a similar safety profile among the patients who received the pre-operative Ketorolac in this study. A sample size of 50 (25 patients in each disease site) produces a one-sided 90% confidence interval with an upper limit of 0.12 (the distance from the mean number of units transfused to the upper limit = 0.02) for thoracotomy. For nephrectomy, the upper limit of a one-sided 90% confidence interval would be 0.318 (the distance from the mean number of units transfused to the upper limit = 0.032). To account for a possible 10%, drop off, we will plan to enroll 28 patients in each disease type.

16.2.2 Stopping Rule

The PIs will monitor the blood transfusion ordered and the units transfused before patients' discharge. In any case, blood transfusion with more than 2 units (BT2U) happens, the trial will pause to examine the cause and decide whether to continue or terminate the trial due to the safety concern. The trial will be terminated if the accumulative relevant BT2U number reaches to six for nephrectomy (24%) or two for thoracotomy (8%). The stopping rule is to stop the trial early due to any high chance of toxicity.

16.2.3 Analysis of safety data

All subjects who receive Ketorolac will be included in the summaries and listings of safety data. Overall safety profile will be characterized by type, frequency, severity, timing, during, and relationship of Ketorolac. The rate of pre-discharge blood transfusion and the mean blood unit transfused will be summarize by frequency and proportion with 95% confidence interval for the rate of AEs, and mean (range) and 95% Wald confidence interval.

16.2.4 Analysis of the secondary endpoints

For all biomarkers, descriptive statistics (means, medians, standard deviations, interquartile range) and graphical displays will be used to characterize central tendency and variability over time. Values will be log transformed as appropriate to reflect biologic plausibility.

16.3 EVALUATION OF OUTCOMES

All patients will be followed for adverse events including surgical morbidity and mortality for 90 days after surgery. Toxicity will be graded according to the NCI CTC version 4.4. The rates of all Grade 3-5 adverse events during or within 90 days of surgery will be tested for equality using a two-sided chi-square test or Fisher's exact test with a 0.05 significance level.

16.3.1 Overall safety assessment

The primary objective is to assess the safety data by using ketorolac pre-operatively, and we plan to longitudinally collect safety data from each patient. The study team will meet on a regular basis to review safety events and make decision about trial stopping based on the safety concerns.

16.3.2 Bleeding

Post-operative bleeding will be assessed as follows:

16.3.2.1 Need for return to the operating room for bleeding as determined by the treating surgeon

16.3.2.2 Need for transfusion, > 2units of blood, which are not related to vascular injury due to technical considerations or complications, as determined by the operating surgeon.

16.3.2.3 Hemoglobin < 7.0 postoperatively, regardless of whether transfusion has occurred.

17. Provisions to Protect the Privacy Interests of Participants

All actions described in HIPAA section of consent form will be taken to protect the privacy of participants. The study will be explained to participants and they will have the opportunity to ask as many questions as necessary to feel comfortable consenting to participate in the study.

18. Economic Burden to Participants

There are no additional costs that participants will be responsible for if they participate in this research study.

19. Consent Process

Participants may be identified by review of medical records or physician referral. After an investigator introduces the study to the participant, the consent form may be given in person, mailed, emailed, or sent to the participant through PowerChart or the Emory Patient Portal. The study information, such as the consent form, may be sent to the patient using an encrypted email. The study team will follow up with the participant through the methods of communication listed above, by phone, Emory licensed Zoom, and/or in person to communicate with the participant about the study. The study team member will confirm with the participant that they received all pages of the consent form. The participant will be given time to read the consent form and ask questions. A member of the study team will reach out to the participant to make sure the participant understands all aspects of the study and the participant is ready to sign the consent documentation. Identity of each participant will be confirmed prior to consent. The informed consent discussion can take place in person or via phone or Emory licensed Zoom. The consent process may take place in the ways described below.

1. The participant may sign the consent form in a private setting at Emory.
2. The participant may print the consent form at home and sign with a wet ink signature. The participant can send the consent form back to the study team using the following methods:
    a. The participant will scan and send the signature pages of the consent form back to the study team via email
    b. The participant may take pictures of the signature pages of the consent form and send it back to the study team via email

c. The participant can mail the wet ink signed pages of the consent form to the study team.

Participants will be given a copy of the consent form. Participants with LEP may be enrolled and study team members will use Emory IRB approved short forms to conduct the consent process. There will be a translator present when the study team enrolls a participant with LEP.

20. Setting

Subjects will be identified prior to surgery. They may be consented in a clinic or hospital setting.

21. Resources Available

There are hundreds of resections for Non-Small Cell Lung Cancer and Renal Cell Carcinoma each year. Within 5 years of recruiting, the goal of 76 patients enrolled is feasible. 50% of one full time research coordinator's effort will be devoted to this trial annually. Medical and psychological resources that participants might need as a result of an anticipated consequences of the human research are available at Emory.

A dedicated clinical research team will be available to assist in proper conduct of this research study. There will be extensive documentation of training for study personnel. This will be documented on training forms, delegation of authority forms, the 1572, and other documents. Training is ongoing and will be updated as needed.

22. References

1. Asamura H, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the N Descriptors in the Forthcoming 8th Edition of the TNM Classification for Lung Cancer. *J Thorac Oncol.* 2015;10(12):1675-1684.
2. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet.* 2011;378(9809):2081-2087.
3. Rothwell PM, Fowkes FG, Belch JF, Ogawa H, Warlow CP, Meade TW. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet.* 2011;377(9759):31-41.
4. Rothwell PM, Price JF, Fowkes FG, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomised controlled trials. *Lancet.* 2012;379(9826):1602-1612.

5. Rothwell PM, Wilson M, Price JF, Belch JF, Meade TW, Mehta Z. Effect of daily aspirin on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. *Lancet.* 2012;379(9826):1591-1601.
6. Forget P, Machiels JP, Coulie PG, et al. Neutrophil:lymphocyte ratio and intraoperative use of ketorolac or diclofenac are prognostic factors in different cohorts of patients undergoing breast, lung, and kidney cancer surgery. *Ann Surg Oncol.* 2013;20 Suppl 3:S650-660.
7. Panigrahy D, Gartung A, Yang J, et al. Preoperative stimulation of resolution and inflammation blockade eradicates micrometastases. *J Clin Invest.* 2019;129(7):2964-2979.
8. Forget P, Bouche G, Duhoux FP, et al. Intraoperative ketorolac in high-risk breast cancer patients. A prospective, randomized, placebo-controlled clinical trial. *PLoS One.* 2019;14(12):e0225748.
9. Forget P, Vandenhende J, Berliere M, et al. Do intraoperative analgesics influence breast cancer recurrence after mastectomy? A retrospective analysis. *Anesth Analg.* 2010;110(6):1630-1635.
10. Schafer AI. Effects of nonsteroidal antiinflammatory drugs on platelet function and systemic hemostasis. *J Clin Pharmacol.* 1995;35(3):209-219.
11. Ungprasert P, Cheungpasitporn W, Crowson CS, Matteson EL. Individual non-steroidal anti-inflammatory drugs and risk of acute kidney injury: A systematic review and meta-analysis of observational studies. *Eur J Intern Med.* 2015;26(4):285-291.
12. Patrono C, Baigent C, Hirsh J, Roth G. Antiplatelet drugs: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133(6 Suppl):199S-233S.
13. Freedland SJ, Blanco-Yarosh M, Sun JC, et al. Ketorolac-based analgesia improves outcomes for living kidney donors. *Transplantation.* 2002;73(5):741-745.
14. Kelley BP, Chung KC, Chung TT, et al. Postoperative Ketorolac in Breast and Body Contouring Procedures: A Nationwide Claims Analysis. *Plast Reconstr Surg.* 2018;142(4):472e-480e.
15. Forrest JB, Camu F, Greer IA, et al. Ketorolac, diclofenac, and ketoprofen are equally safe for pain relief after major surgery. *Br J Anaesth.* 2002;88(2):227-233.
16. Schleiffarth JR, Bayon R, Chang KE, Van Daele DJ, Pagedar NA. Ketorolac after free tissue transfer: a comparative effectiveness study. *Ann Otol Rhinol Laryngol.* 2014;123(6):446-449.