Title	A Phase 2a, single-dose, open-label study to evaluate diagnostic performance, safety, and timing of postdose imaging of ONM-100, an intraoperative fluorescence imaging agent for the detection of cancer, in patients with solid tumors undergoing routine surgery
Study Drug	ONM-100
Protocol Amendment 6.0	03DEC2020
Protocol Amendment 5.0	11JUN2020
Protocol Amendment 4.0	18DEC2019
Protocol Amendment 3.1	18SEP2019
Protocol Amendment 3.0	07AUG2019
Protocol Amendment 2.0	08MAY2019
Original Protocol	25OCT2018
Sponsor	OncoNano Medicine, Inc. [redacted]
Study Medical Monitor	[redacted]

Confidentiality Statement:

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1.0 PROTOCOL SYNOPSIS

Sponsor: OncoNano Medicine, Inc.

Product Name: ONM-100

Active Ingredients: poly(ethyleneoxide)-b-poly(dibutylaminoethyl methacrylate) copolymer-indocyanine green conjugate

Protocol Title: A Phase 2a, single-dose, open-label study to evaluate diagnostic performance, safety, and timing of postdose imaging of ONM-100, an intraoperative fluorescence imaging agent for the detection of cancer, in patients with solid tumors undergoing routine surgery

Planned Study Centers: 2 to 5 centers in the United States

Phase of Development: 2a

Background:

ONM-100 is an intraoperative fluorescence imaging agent that was evaluated in the completed Study ON-1001, a first in human Phase 1 study in the Netherlands of patients with solid cancers needing surgical excision of their tumors. The dose escalation part of the study (Phase 1a with up to 15 patients and up to 5 dose levels) evaluated the safety, pharmacokinetics (PK), imaging feasibility, and diagnostic performance of a single dose of ONM-100 administered 24 ±8 hours prior to surgery in breast cancer and head and neck cancer patients up to a dose of 1.2 mg/kg.

ONM-100 was well tolerated and showed no dose-limiting toxicity (DLT) or study drug related serious adverse events (SAEs).

ONM-100 exhibited dose-proportionality with respect to initial plasma concentration.

Histology confirmed tumor and normal tissue specimens [redacted]

Objectives of the Study

The main purpose of this study is to investigate whether ONM-100 can be used to image primary tumors and metastatic lymph nodes at an imaging schedule earlier than [redacted] hours postdose in patients undergoing routine surgery of their solid cancers and whether the diagnostic performance to detect metastatic lymph nodes can be improved by optimizing the dose and the imaging schedule.

Part 1 Primary Objectives:

- Evaluate the dose(s) at which ONM-100 fluorescence imaging is feasible at 3 ±2 hours postdose, and if needed at an alternate imaging schedule postdose, for the detection of metastatic lymph nodes and primary tumors after a single intravenous (IV) dose of ONM-100 in patients with head and neck squamous cell cancer (HNSCC) or breast cancer undergoing routine surgery
- Evaluate safety at the dose(s) used to assess imaging feasibility and select the dose(s) and imaging schedule(s) postdose that are safe and provide optimal imaging of solid tumors and metastatic lymph nodes; the dose and time postdose chosen for the detection of primary tumors and metastatic lymph nodes may be the same or different

Part 2 Primary Objective:

- Verify the safety and diagnostic performance of ONM-100 compared to standard pathology at the dose(s) and imaging schedule(s) postdose selected from Part 1 for the detection of the primary tumors and the metastatic lymph nodes in a variety of solid cancers (which may include [redacted]

Part 1 and Part 2 Secondary Objective

- Evaluate the PK profile of ONM-100 at the dose(s) and imaging schedule(s) postdose used to assess optimal imaging in Part 1 and Part 2

Part 3 Objective:

- To assess the safety and efficacy (sensitivity and positive predictive value [PPV]) of ONM-100 at a dose of 1 mg/kg for intraoperative imaging during head and neck squamous cell carcinoma (HNSCC) surgery, administered at 24 ±8 hours prior to surgery.

Part 3 Primary Endpoints:

- Sensitivity: True Positive Biopsies / (True Positive + False Negative Biopsies)
- PPV: True Positive Biopsies / Tumor Positive Biopsies + False Positive Biopsies

Part 3 Secondary Endpoints:

- Proportion of patients with at least one clinically significant event identified during surgery (occult disease detected, positive margin)
- Number of margins identified by ONM-100 and NIR imaging that could not be observed with white light and palpation alone
- Detection rate of HNSCC between ONM-100 fluorescence at time of surgery versus frozen sections determined by final pathology report
- Detection of positive margins at time of surgery that triggers subsequent biopsy
- Re-resection rate

Part 3 Exploratory Endpoints:

- [redacted]

Study Design:

This is a non-randomized, open-label, multi-center, safety, PK, and imaging feasibility study of ONM-100, an intraoperative fluorescence imaging agent. The study consists of 3 parts (Parts 1, 2 and 3).

- Part 1 will be performed in a dose-escalation design (maximum of 5 cohorts of 3 patients each) to determine the dose(s) at which ONM-100 fluorescence can be used to image metastatic lymph nodes and primary tumors in patients with HNSCC and breast cancer undergoing routine surgery at 3 ±2 hours, and if needed at an alternate imaging schedule postdose.

- Part 2 will be a verification of the dose(s) and imaging schedule(s) from Part 1. Approximately 10 to 20 patients will be enrolled in Part 2. Eligible patients will have a confirmed diagnosis (or high clinical suspicion in the opinion of the Investigator) from among the following list of solid tumor types [redacted] Initial enrollment will begin with prostate and ovarian cancer patients only. Eligible tumor types will be opened and/or closed to enrollment based on continuous review of imaging results. The Sponsor will inform Investigators which tumor types are open to enrollment during the conduct of Part 2.
- In Part 3, the dose and tumor type selection is based on information available from the results of all previous doses and tumor types, including information from the Phase 1 study. HNSCC has been selected for investigation in Part 3. Approximately 20 to 30 patients will be enrolled in Part 3.

All included patients will satisfy the inclusion and exclusion criteria of Part 1, Part 2 or Part 3.

[redacted]
species) Good Laboratory Practices (GLP) toxicology study. The planned dose range ([redacted]) is within the maximum allowable human equivalent dose based on all available nonclinical PK and toxicology data. Dose escalation steps of [redacted] are chosen to minimize the number of cohorts likely needed to meet the objectives. If needed, a smaller step change or an intermediate dose level may be selected as the next dose. Dose levels [redacted] will be evaluated only as needed.

The dose escalation phase (Part 1) is anticipated to be completed with up to [redacted] a single dose of ONM-100 at [redacted] and will undergo surgery and fluorescence imaging at [redacted] postdose. After the completion of surgery and imaging of Cohort A, 3 patients in Cohort B will receive a single dose of ONM-100 ([redacted] for safety evaluation and surgery and imaging at [redacted]. If safety and the imaging feasibility for detecting primary and metastatic lymph nodes is acceptable in Cohort A and/or Cohort B, further dose escalation in Part 1 may not be necessary. Cohort C ([redacted] at [redacted] hours postdose) and Cohort D ([redacted] and imaging at [redacted] hours postdose) may be included either to establish the safety margin or if the imaging results at the preceding lower dose level are sub-optimal. Smaller dose changes may be selected for doses [redacted] (ie, Cohort C or Cohort D). Cohort E and Cohort F (3 patients each) may be included at 1 of the ONM-100 dose levels between [redacted] to evaluate whether alternate imaging schedules postdose (ie, other than [redacted] hours postdose) provide acceptable imaging results at doses ≤[redacted]. Any cohort in which safety at that dose level is already established in a prior cohort in this study, or in Study ON-1001, may be enrolled for the purposes of evaluating an alternate imaging schedule postdose, in parallel to another cohort being evaluated. All dosing decisions will be made after discussing all available data between the Sponsor and Principal Investigators (PIs) and documenting the decision.

Table 1: ONM-100 Doses and Surgery/Imaging Schedules Evaluated in Part 1

Study Part	Cohort	ONM-100 Single Dose [a], mg/kg	Surgery / Imaging Time [a], hours	Number of Patients	Tumor Types[b]
Part 1	A	[redacted]			[redacted]
	B	[redacted]			[redacted]
	C (if needed)	[redacted]			[redacted]
	D (if needed)	[redacted]			[redacted]
	E (if needed)	[redacted]			[redacted]
	F (if needed)	[redacted]			[redacted]

a. [redacted] TBD = to be determined. Based on review of safety and fluorescence data from previously treated cohorts, actual doses selected may be smaller increases from the dose studied in the previous cohort or may be an intermediate dose between previously studied doses.

b. Attempts should be made to have at least 1 patient with [redacted] in each cohort

In Part 2, up to 3 ONM-100 doses and imaging schedules will be evaluated to verify the diagnostic performance of ONM-100 fluorescence imaging for detecting primary tumors and metastatic lymph nodes (Table **2**).

Within each actively enrolling tumor type, treatment will be divided into up to 3 activated dose and schedule groups (Groups). The number of Groups and the ONM-100 dose and imaging schedule for each of the Groups in Part 2 will be determined after reviewing the available safety, PK, and imaging feasibility results to date from Part 1 and Part 2. Any dose selected for Part 2 will have a complete safety evaluation completed in Part 1 at the same dose or at a higher dose. Note that the dose(s) selected for Part 2 may be an intermediate dose level within the ranges of doses evaluated in Part 1.

In Part 2, enrollment will begin with [redacted] cancers based on ongoing review of imaging data obtained, the Sponsor may open enrollment in additional tumor types and/or selectively close enrollment in one or more tumor types. All the available data to date will be used to decide the additional tumor type(s), number of patients per tumor type, and number of Group(s) to be enrolled. Approximately 10 to 20 patients will be enrolled in Part 2, depending on the number of tumor types and Groups that are activated for enrollment.

The Sponsor will inform Investigators when each Group has been opened to enrollment and provide the dose and, as applicable, dose schedule to be used in each Group, and when any tumor type is activated or deactivated for enrollment. Any Group in Part 2 may begin dosing at any time during Part 1 if the safety and observed detection of metastatic lymph nodes or the primary tumors at the same or higher dose level has been demonstrated in Part 1.

Table 2: Doses and Surgery/Imaging Schedules Evaluated in Part 2

Study Part	Group	ONM-100 Single Dose, mg/kg	Surgery / imaging time, hours	Tumor Types[a]
Part 2	1	[redacted][b]		[redacted]
		[redacted]		

	3	TBD [b] (between 0.5 to 7)	16 - 70	

[redacted]; TBD = to be determined.

a. Part 2 enrollment will begin with prostate cancer and ovarian cancer patients. For prostate cancer, the number of Stage 2 patients is not to exceed 2 patients in each Group. Based on interim safety and/or imaging data, enrollment may stop early in either of these 2 tumor types. All the available data to date will be used to decide the additional tumor type(s), number of patients per tumor type, and number of Group(s) to be enrolled. Approximately 10 to 20 patients will be enrolled in Part 2, depending on the number of tumor types and Groups that are activated for enrollment.
b. All Groups in Part 2 will be demonstrated to be safe based on results from Part 1; no patient accrual will be allowed at any dose in Part 2 until the same or higher dose level has been demonstrated to be safe in Part 1.

In Part 3, ONM-100 at a dose of [redacted] mg/kg will be evaluated in HNSCC to assess the safety, sensitivity and PPV. ONM-100 will be administered at [redacted] hours prior to surgery. Approximately [redacted] patients will be enrolled in Part 3.

Schematics of the study designs for Part 1 and Part 2 are presented in Figure 1. The Schedule of Assessments and Procedures for Part 1 (all cohorts) (

Table **3**), Part 2 for Groups dosing on Day of surgery (

Table **4**), Part 2 for Groups dosing ≥1 day ([redacted]s) before surgery (Table 4A), and Part 3 (Table 5) are presented. Note that the timing provided for postdose assessments and procedures begins after infusion of study drug has been completed (ie, time = 0 begins at the end of study drug infusion).

On Day 0, each patient will receive a single IV dose of ONM-100. The ONM-100 dose level, surgery time, and imaging schedule will be based on the Cohort in Part 1, Group in Part 2 or Part 3 in which each patient is enrolled. The patient will undergo anesthesia in accordance with standard surgical practice. The surgery with tissue excision will occur as per routine surgical standards and the surgical specimens will be collected for pathologic evaluations.

ONM-100 fluorescence imaging of the lymph nodes and the primary tumors (including any other planned [redacted] intraoperative near infrared (NIR) camera. If [redacted] are planned as part of standard surgery, the surgeon will mark the orientation of each of these planned tissue specimens before ONM-100 imaging.

<u>In Part 1 and Part 2:</u>

Any ONM-100 fluorescence areas in the wound bed will be identified and regions of interest will be biopsied ([redacted]t none of the ONM-100 florescence imaging results will be used for any therapeutic or patient management decisions intraoperatively or post operatively.

ONM-100 imaging will be performed on the whole excised specimen [redacted] intraoperative camera. [redacted]

[redacted]

Imaging procedures will be similar in Part 1 and Part 2 and will be performed as per the ON-1002 Imaging Manual. The intraoperative in vivo and ex vivo imaging of ONM-100 will be performed using the [redacted] or similar NIR cameras approved for the intraoperative detection of indocyanine green (ICG). When feasible, more than one intraoperative camera may be used within the same imaging session. [redacted]

[redacted]

Medical history, prior medication use, hemoglobin, and Karnofsky performance status will be evaluated at Screening and pretreatment on Day 0. Pregnancy tests will be performed at Screening and at Day 28 (±48 hours) in Part 1 and at Day 28 (±5 days) in Part 2. Electrocardiograms (ECGs) will be performed pretreatment and at 30 ±10 minutes postdose on Day 0.

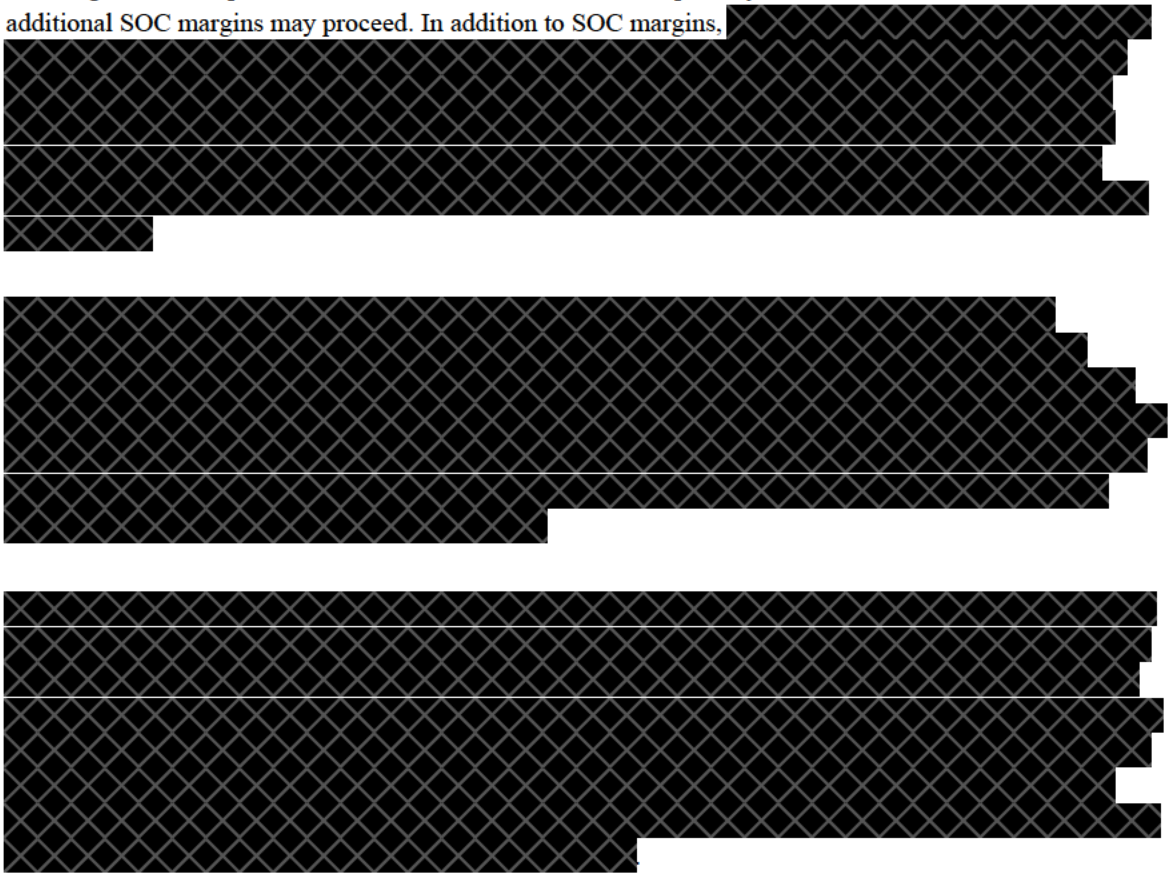
Patient safety will be assessed for 28 days (±48 hours) postdose in Part 1 and 28 days (±5 days) in Part 2. All patients will be monitored for vital signs and physical examination pretreatment and at various time points up to Day 6 (±24 hours) in Part 1 and up to Day 10 (±5 days) in Part 2. All patients will be monitored for comprehensive metabolic panel (CMP) and complete blood count (CBC) with differentials pretreatment and at various time points up to Day 28 (±48 hours) in Part 1 and up to Day 28 (±5 days) in Part 2. [redacted]

In Part 1, safety results for each cohort will be reviewed by the Internal Safety Review Committee. Escalation to doses higher than those previously tested will not occur until the safety of lower doses has been confirmed following review by the Internal Safety Review Committee.

Plasma samples for PK analyses will be collected from all patients pretreatment and at various time points up to Day 6 [redacted] in Part 1 and up to Day 1 [redacted] in Part 2.

In Part 3:

ONM-100 imaging will be performed on the whole tumor specimen and excised specimen margins using the designated intraoperative camera. After the removal of the primary tumor, identification and resection of additional SOC margins may proceed. In addition to SOC margins,



Surgical specimens obtained during the routine surgery and any ONM-100 fluorescence guided biopsies will be prepared using standard specimen processing methods and timelines. Specimens will be sampled and analyzed according to routine pathologic evaluation.

After surgery, the patient will be strictly observed following the standard, respective, postoperative protocol. Patients will be monitored for safety assessments and sample procurement.

Medical history, prior medication use, hemoglobin, and Karnofsky performance status will be evaluated at Screening and pretreatment on Day 0. Pregnancy tests will be performed at Screening and at Day 28 (±5 days). Electrocardiograms (ECGs) will be performed pretreatment, at 30 ±10 minutes postdose on Day 0 and Day 10 (±5 days).

Patient safety will be assessed for 28 days (±5 days). All patients will be monitored for vital signs and physical examination pretreatment and at various time points up to Day 10 (±5 days). All patients will be monitored for comprehensive metabolic panel (CMP) and complete blood count (CBC) with differentials pretreatment and at various time points up to Day 28 (±5 days). All patients will be monitored for treatment-emergent adverse events (TEAEs) and concomitant medication use from the start of dosing up to Day 28 (±5 days). TEAEs will be followed closely during the study to identify any potential DLTs.

Number of Patients

Up to 60 patients will be enrolled in this study (with planned allocation of up to 15 patients in up to 5 cohorts in Part 1, approximately 10 to 20 patients in Part 2, and approximately 20 to 30 patients in Part 3). The actual number of patients in Part 1 and Part 2 may vary, depending on the number of Part 1 cohorts and Part 2 Groups/tumor types that are activated for enrollment.

All patients will receive a single dose of ONM-100 followed by routine surgery and pathology of the respective solid cancer. Based on the ON-1001 study experience, we estimate that 3 patients for each dose is sufficient for safety and imaging feasibility evaluations in Part 1. Each patient's tumors will be imaged intraoperatively and at planned sites post operatively. For those patients with fluorescence in the surgical wound bed after standard procedures, tissue biopsy may be taken at surgeon's or pathologist's discretion. Up to 3 additional patients may be enrolled in the event of a DLT.

Inclusion Criteria

Patients must meet the following inclusion criteria:

1. Adults ≥18 years of age
2. Biopsy-confirmed diagnosis, for primary or recurrent disease (or high clinical suspicion in the opinion of the Investigator)
   a. Part 1: Stage 0 to 4 [redacted]
   b. Part 2:
      - Stage 0 to 4 [redacted]
      - Stage 2 to 4 [redacted]
   c. Part 3:
      - Stage 2 to 4 [redacted] Including [redacted]
3. Acceptable hematologic status (as standard surgery protocol requires, as determined by the Investigator), kidney function and liver function. Elevations of creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, or total bilirubin >1.5× the upper limit of normal [ULN] must be determined to be not clinically significant by the Investigator and approved by the Medical Monitor.
4. Documented negative serum pregnancy test for women of childbearing potential (ie, premenopausal women with intact reproductive organs and women <2 years after menopause)
5. Male patients and female patients of child-bearing potential (ie, premenopausal women with intact reproductive organs and women <2 years after menopause) must agree to and comply with using medically acceptable contraception including surgical sterilization (eg, hysterectomy, bilateral oophorectomy, bilateral tubal ligation), intrauterine device, oral contraceptive, contraceptive patch,

long acting injectable contraceptive, partner's vasectomy, double-barrier method (condom or diaphragm plus spermicide or condom plus diaphragm), or abstinence during the trial and for 6 months thereafter

6. [redacted]
7. Adequate potential for follow up
8. Willing and able to provide written informed consent

Exclusion Criteria

Patients must NOT meet any of the following exclusion criteria:

1. Histologically diagnosed by an excisional biopsy procedure
2. [redacted]
3. Life expectancy <12 weeks
4. Karnofsky Performance Status <70%
5. Hepatic impairment (Child-Pugh score >5) or significant liver disease including active hepatitis or cirrhosis
6. Lab values or any sign, symptom, or medical condition that in the opinion of the PI would prevent surgical resection
7. Medical or psychiatric conditions that compromise the patient's ability to give informed consent.
8. Pregnant or lactating women
9. [redacted]
10. [redacted]
11. [redacted]
12. Receiving or planned to receive, during the duration of the study, concomitant medication with a high chance of h[redacted]y, as judged by the PI based on standard protocols within the study center
13. [redacted]
14. Received an investigational agent within the shorter of 5 half-lives or 30 days before ONM-100 dosing
15. Inability to adhere to the schedule of assessments or any circumstance that would interfere with the validity of assessments performed in the study
16. The PI considers that the patient should not participate in the study

Test Product, Dose and Mode of Administration

[redacted]

Comparator

There is no comparator imaging agent used in this study.

Expected Duration of Patient Participation

In Part 1, study participation will require 28 days (±48 hours), not counting the prestudy screening visit from Day -30 to Day -1. Following a single dose of ONM-100 administered by IV infusion on Day 0, [redacted] are considered clinically significant by the Investigator, will be repeated on Day 28 (±48 days). All TEAEs and abnormal laboratory findings that are considered at least possibly related to ONM-100 will be followed until resolved or stabilized.

In Part 2, study participation will require 28 days (±5 days), not counting the prestudy screening visit from Day -30 to Day -1. Imaging is performed during surgery. Surgery could be on the same day as ONM-100 dosing [redacted]. All TEAEs and abnormal laboratory findings that are considered at least possibly related to ONM-100 will be followed until resolved or stabilized.

In Part 3, study participation will require 28 days (±5 days), not counting the prestudy screening visit from Day -30 to Day -1. [redacted] All TEAEs and abnormal laboratory findings that are considered at least possibly related to ONM-100 will be followed until resolved or stabilized.

Criteria for Evaluation

Efficacy Analyses

In Part 1 and Part 2, ONM-100 fluorescence from in vivo and excised tissues will be imaged using intraoperative and post-operative NIR cameras and will be correlated with the histopathological confirmation of tumor and normal tissues to determine ONM-100's diagnostic performance.

In Part 3, the intraoperative fluorescence status of collected primary tumor, SOC and ONM-100 guided biopsies, as well as lymph nodes will be compared to histological analyses of the collected specimens.

Safety Analyses

Safety assessments will include the following safety related parameters:

- TEAE incidence, severity, and relationship to study drug
- Physical examination
- Vital signs
- ECGs
- Clinical laboratory (CMP, hemoglobin, and CBC with differentials)

Pharmacokinetic Analyses

Characterization of the ONM-100 PK profile will include the following major PK parameters:

- Maximum plasma concentration (C_{max})
- Time to C_{max} (T_{max})
- Area under the time-concentration curve (AUC)
- Total body clearance (CL)
- Volume of distribution (Vz)
- Volume of distribution at steady state (Vss)
- Elimination rate constant (λz)
- Terminal elimination half-life ($t_{1/2}$)

Statistical Methods

This is a pilot study with the intention of gathering data to assess feasibility and imaging metrics for the efficacy analysis. Therefore, no formal statistical hypothesis testing will be performed for making development decisions.

Analysis populations

- Safety Population: all patients who receive any dose of ONM-100
- Efficacy Population: all patients who received any dose of ONM-100 and who have sufficient imaging and pathology analysis data to calculate fluorescence intensity and pathology correlation for ≥1 tumor sample
- Pharmacokinetic Population: all patients who receive ONM-100 and who have sufficient ONM-100 plasma concentration data to calculate ≥1 PK parameter.

Sample Size Calculation

Given the exploratory nature of the study, formal sample size calculations were not performed. [redacted]

[redacted]

Efficacy Analyses

In Part 1 and Part 2, feasibility assessment of ONM-100 for intra-operative imaging of solid tumors and metastatic lymph nodes will include quantification of intraoperative fluorescence signals [redacted]

[redacted]

Diagnostic performance of ONM-100 will be assessed [redacted] In addition to the primary analyses, additional supplemental analyses will also be performed that will omit data from patients designated prospectively as run-in patients in order to assess the potential contribution of training and optimization of the imaging procedure.

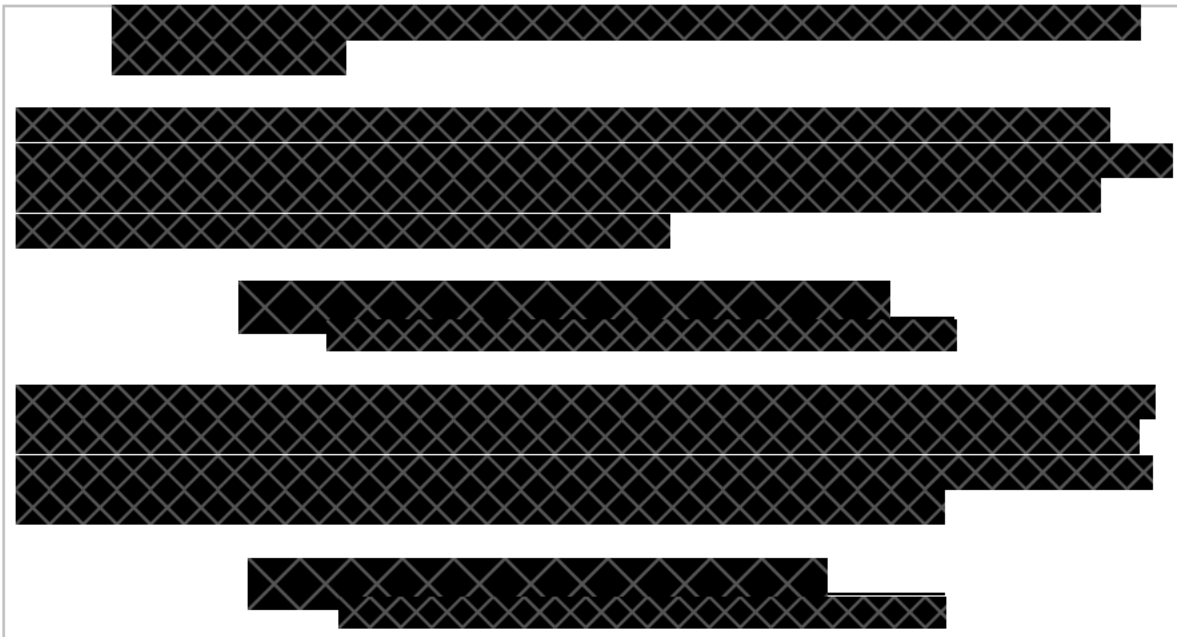
In Part 3, [redacted]

[redacted]

Additional performance metrics will include the identification of a clinically significant event (CSE) detected by ONM-100. [redacted]

[redacted]

[redacted]



Safety Analyses

The safety analyses will be in the Safety Population.

Adverse events (AEs), vital signs, ECGs, and conventional clinical laboratory data (CMP and CBC with differentials) will be summarized using descriptive statistics.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1. The incidence of TEAEs will be presented by system organ class and preferred term, by relationship to study drug, by severity, and by whether or not they resulted in alteration of administration of or discontinuation of study drug. A TEAE is defined as an AE that occurs during or after study drug administration and up through 28 days (±48 hours) in Part 1 and up through 28 days (±5 days) in Part 2 and Part 3 after administration of study drug. In addition, the incidence of serious TEAEs and TEAEs leading to discontinuation of study drug will be presented by system organ class, preferred term, and relationship to study drug.

Descriptive statistics for clinical laboratory test results and vital signs, and for changes from Baseline, will be presented by time point. Baseline is defined as the measurement closest to, but before, the administration of study drug. Incidences of potentially clinically meaningful clinical laboratory results and vital signs, determined based on normal ranges and percentage changes from Baseline, will also be summarized by time point. The number and percentage of abnormal ECGs will be provided by time point.

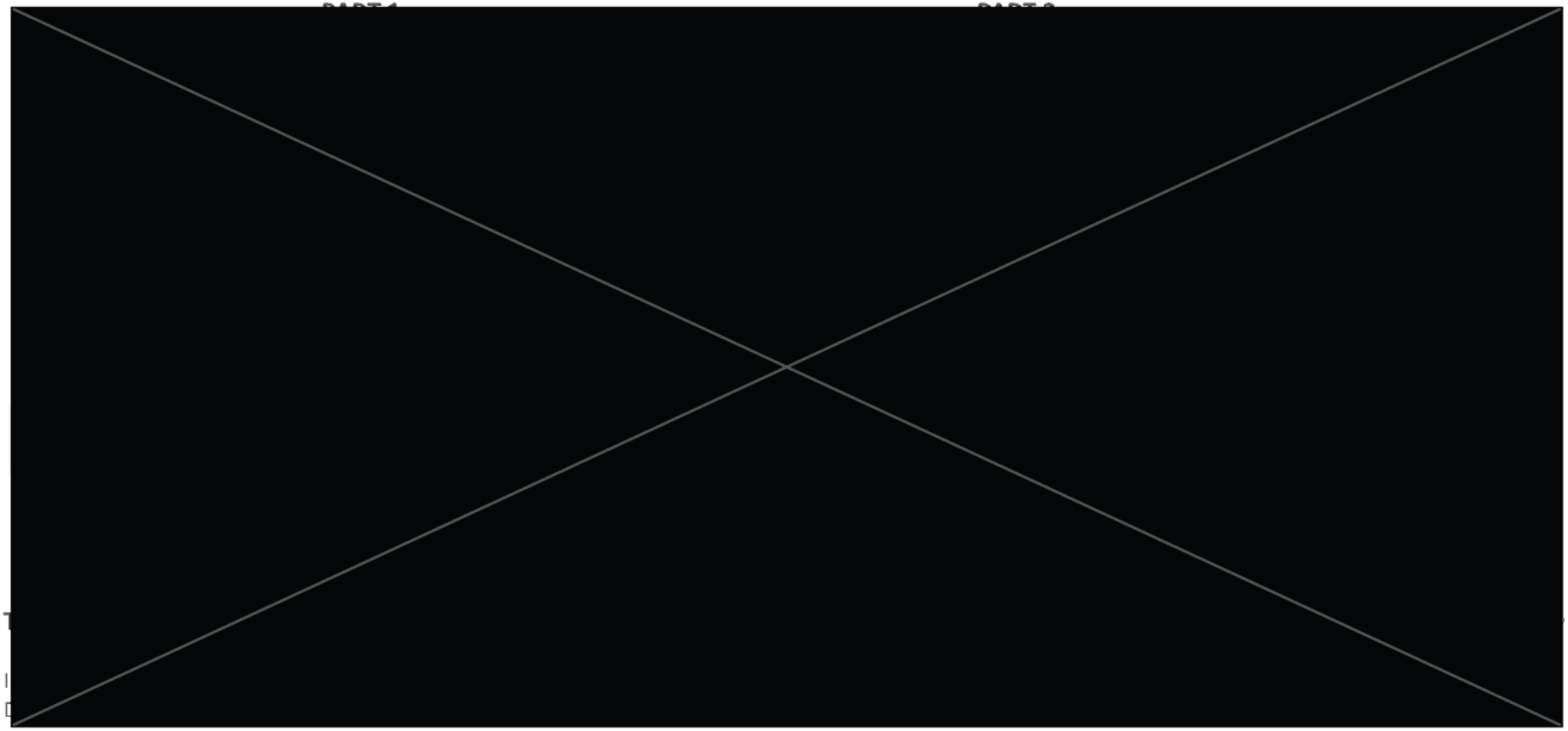
Pharmacokinetic Analyses

The PK analyses will be assessed in the Pharmacokinetic Population.

Plasma concentration-time profiles will be constructed for each patient and each dosing cohort. Plasma concentration values will be summarized at each time point using mean, standard deviation, median, and range.

Summary PK parameters will be summarized using mean, standard deviation, median, and range.

Figure 1: Schematic of Study Design (Part 1 and Part 2)



Based on review of safety and fluorescence data from previously treated cohorts, actual doses selected may be smaller increases from the dose studied in the previous cohort, or may be an intermediate dose between previously studied doses

Table 3: Schedule of Assessments and Procedures (Part 1 all cohorts)

Study Day	**-30 to -1**	**0**			**1 (±4h)**	**3 (±24h)**	**6 (±24h)**	**28 (±48h)**
	Screening[a]	**Pre-treatment**	**Study Drug Administration**	**Surgery (3±2h or an alternate imaging schedule TBD)**	**Follow-up**			
Informed consent [b]	X							
Medical history	X	X						
Vital signs	X	X	X [c]		X[d]		X	
Complete physical examination	X						X	
Height, weight, BMI calculation	X	X						
Calculate Child-Pugh score • Encephalopathy • Ascites • INR or PT prolongation in seconds	X							
12-lead ECGs		X[e]	X[e]				X	
Blood for CMP [f,]	X	X[g]			X	X	X	X
Blood for CBC with differentials	X	X[g]			X		X	X
Blood for HgbA1C	X	X[g]						
Pregnancy test [h]	X							X
Perform test for alcohol [i]		X						
Karnofsky Performance Status Scale	X	X						
Confirm study eligibility	X	X						
Administration of ONM-100 [j]			X					

Study Day	-30 to -1	0			1 (±4h)	3 (±24h)	6 (±24h)	28 (±48h)
	Screening[a]	Pre-treatment	Study Drug Administration	Surgery (3±2h or an alternate imaging schedule TBD)	Follow-up			
[redacted]				[redacted]				
[redacted]				[redacted]				
[redacted]				X				
[redacted]				X				
[redacted]				→				
Plasma for PK analyses [m]		X	X		X	X	X	
Assess for TEAEs [n]			X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X

Table 4: Schedule of Assessments and Procedures (Part 2 when ONM-100 dosing on day of surgery)

Study Day	**-30 to -1**	**0**			**1 (±8 hours)**	**10 (±5 days)**	**28 (±5 days)**
	Screening[a]	**Pre-treatment**	**Study Drug Administration**	**Surgery (TBD)**	**Follow-up**		
Informed consent [b]	X						
Medical history	X	X					
Vital signs	X	X	X [c]		X[d]	X	
Complete physical examination	X					X	
Height, weight, BMI calculation	X	X					
Calculate Child-Pugh score • Encephalopathy • Ascites • INR or PT prolongation in seconds	X						
12-lead ECGs		X[e]	X[e]			X	
Blood for CMP [f]	X	X[g]			X	X	X
Blood for CBC with differentials	X	X[g]			X	X	X
Blood for HgbA1C	X	X					
Pregnancy test [h]	X						X
Perform test for alcohol [i]		X					
Karnofsky Performance Status Scale	X	X					
Confirm study eligibility	X	X					
Administration of ONM-100 [j]			X				
[redacted]				X			
				X			

[redacted]							
[redacted][k]				X			
[redacted]				X			
[redacted]				→			
Plasma for PK analyses [m]		X	X		X		
Assess for TEAEs [n]			X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X
[redacted]							

Footnotes for Table 4

a. [redacted]

Table 4A: Schedule of Assessments and Procedures (Part 2 when ONM-100 dosing 16-80 hours before surgery)

Study Day	**-30 to -1**	**0**		**1 (or longer) [b]**	**10 (±5 days)**	**28 (±5 days)**
	Screening[a]	**Pre-treatment**	**Study Drug Administration**	**Surgery (16-80 h postdose)**	**Follow-up**	
Informed consent [c]	X					
Medical history	X	X				
Vital signs	X	X	X [d]	X[e,f]	X	
Complete physical examination	X				X	
Height, weight, BMI calculation	X	X				
Calculate Child-Pugh score • Encephalopathy • Ascites • INR or PT prolongation in seconds	X					
12-lead ECGs [g]		X	X		X	
Blood for CMP [h]	X	X[i]		X[f]	X	X
Blood for CBC with differentials	X	X[i]		X[f]	X	X
Blood for HgbA1C	X	X[i]				
Pregnancy test [j]	X					X
Perform test for alcohol [k]		X				
Karnofsky Performance Status Scale	X	X				
Confirm study eligibility	X	X				
Administration of ONM-100 [l]			X			
[redacted]				X		

Study Day	**-30 to -1**	**0**		**1 (or longer) [b]**	**10 (±5 days)**	**28 (±5 days)**
	Screening[a]	**Pre-treatment**	**Study Drug Administration**	**Surgery (16-80 h postdose)**	**Follow-up**	
[redacted]				X		
[redacted][m]				X		
[redacted]				X		
[redacted]				→		
Plasma for PK analyses [o]		X	X	X[f]		
Assess for TEAEs [p]			X	X[f]	X	X
Prior/concomitant medications	X	X	X	X[f]	X	X

[redacted]

Footnotes for Table 4A

[redacted]

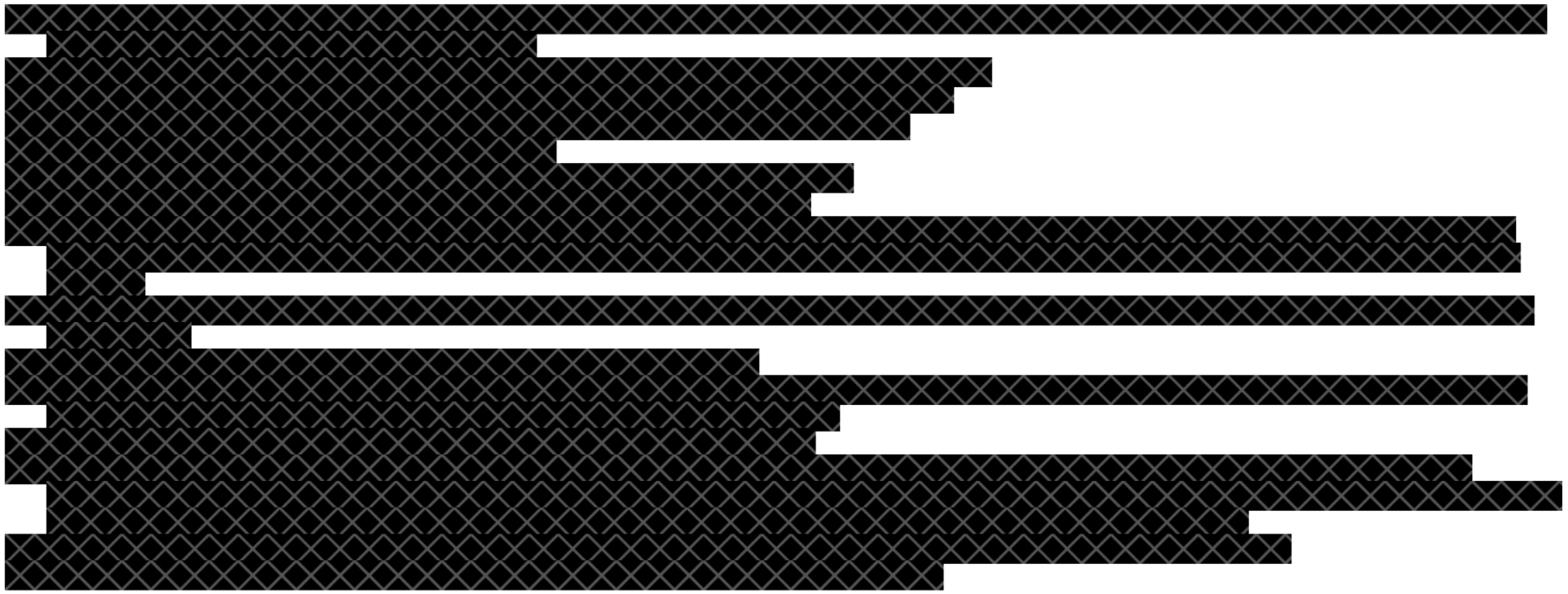
Table 5: Schedule of Assessments and Procedures (Part 3)

Study Day	-30 to -1	0		1 [b]	10 (±5 days)	28 (±5 days)
	Screening[a]	Pre-treatment	Study Drug Administration	Surgery (24 ±8 hours postdose)	Follow-up	
Informed consent [c]	X					
Medical history	X	X				
Vital signs	X	X	X [d]	X[e,f]	X	
Complete physical examination	X				X	
Height, weight, BMI calculation	X	X				
Calculate Child-Pugh score • Encephalopathy • Ascites • INR or PT prolongation in seconds	X					
12-lead ECGs [g]		X	X		X	
Blood for CMP [h]	X	X[i]		X[f]	X	X
Blood for CBC with differentials	X	X[i]		X[f]	X	X
Blood for HgbA1C	X	X[i]				
Pregnancy test [j]	X					X
Perform test for alcohol [k]		X				
Karnofsky Performance Status Scale	X	X				
Confirm study eligibility	X	X				
Administration of ONM-100 [l]			X			
[redacted]				X		
[redacted]				X		

Study Day	**-30 to -1**	**0**		**1** [b]	**10 (±5 days)**	**28 (±5 days)**
	Screening[a]	**Pre-treatment**	**Study Drug Administration**	**Surgery (24 ±8 hours postdose)**	**Follow-up**	
[redacted]				X		
[redacted]				X		
[redacted]				X		
[redacted]				→		
[redacted]			X	X[f]	X	X
Prior/concomitant medications	X	X	X	X[f]	X	X

[redacted]

Footnotes for Table 5



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3.0 LIST OF ACRONYMS, ABBREVIATIONS AND DEFINITIONS OF TERMS

ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the time-concentration curve
$AUC_{0\text{-}24}$, $AUC_{0\text{-}24hr}$	area under the time-concentration curve from time 0 to 24 hours
$AUC_{0\text{-}\infty}$	area under the time-concentration curve from time 0 to infinity
$AUC_{0\text{-}last}$	area under the time-concentration curve from time 0 to the final sample
AUC_{all}	area under the time-concentration curve from time 0 to the last time point (including concentration =0)
BC	breast cancer
BLS	bread loaf slice
BQL	below the quantitation limit
BMI	body mass index
C_{10}, C_{10m}	Concentration at 10 minutes
CBC	complete blood count
CL	Total body clearance
C_{max}	maximum plasma concentration
CMP	comprehensive metabolic panel
Conc	concentration
CRO	Contract Research Organization
CNR	contrast to noise ratio
CSE	clinically significant event
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose-limiting toxicity
EAFUS	Everything Added to Food in the United States
ECG	electrocardiogram
eCRF	electronic case report form
FDA	United States Food and Drugs Administration
FFPE	formalin-fixed and paraffin-embedded
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
H/E	haemotoxylin and eosin
HED	human equivalent dose
HgbA1C	hemoglobin A1c

HNSCC	head and neck squamous cell carcinoma
ICF	Informed Consent Form
ICG	indocyanine green
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	intravenous, intravenously
MedDRA	Medical Dictionary for Regulatory Activities
MFI	mean fluorescence intensity
MTD	maximum tolerated dose
NCI	National Cancer Institute
NIR	near infrared
NOAEL	no-observed-adverse-effect level
NPV	negative predictive value
NSCLC	non-small-cell lung carcinoma
ONM-100	poly(ethyleneoxide)-*b*-poly(dibutylaminoethyl methacrylate) copolymerindocyanine green conjugate
OTC	over-the-counter
PEG	polyethylene glycol
PI	Principal Investigator
PK	Pharmacokinetic(s)
PMMA	polymethylmethacrylate segments
PPV	positive predictive value
SAE	serious adverse event
SAER	Serious Adverse Event Report
SBR	specimen-to-background ratio
SOC	standard of care
SOP	standard operating procedure
Sponsor	The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TBD	to be determined
TBR	tumor-to-background ratio
TEAE	treatment-emergent adverse events
T_{max}	time to maximum plasma concentration
US	United States
Vss	volume of distribution at steady state

Vz	volume of distribution at terminal phase
WHO	World Health Organization

4.0 BACKGROUND AND RATIONALE

Approximately 1.7 million new cancer cases are expected to be diagnosed and approximately 610,000 Americans are expected to die of cancer in 2018 (American Cancer Society, 2018). Despite the ongoing improvements in the treatment of solid cancers, disease morbidity remains significantly high in the United States (US). Cancer is the second most common cause of death in the US, exceeded only by heart disease.

Treatment guidelines for solid cancers of all stages prominently include surgical removal of the primary tumor, as well as at risk or involved lymph nodes, in some cases preceded or followed by chemoradiation. Despite the biologic and anatomic differences between these tumor types, the post-operative margin status is one of the most important prognostic factors of local tumor control and therefore the chance for recurrent disease or tumor metastasis (Denaro, 2014; Jonkman, 2007).

Surgical excision of solid tumors is a balance between oncologic efficacy and minimization of the resection of normal tissue, and thus functional morbidity. This also holds true for lymphadenectomy performed for diagnostic and therapeutic purposes, often at the same time as the removal of the primary cancer. The presence or absence of lymph node metastasis is the most important determinant of survival for gastrointestinal cancers, breast cancer, and many other solid cancers (Ferlay, 2015; Amit, 2014; d'Alessandro, 2015). While physical examination or imaging modalities used for staging are successful in detecting enlarged or abnormal nodes and help with surgical treatment plans, for a high percentage of patients, lymph node metastasis is present at a level that is too small to be detected by current methods, which leads to under-staging. Because occult nodal metastasis is common, elective regional nodal dissection and histological examination is standard-of-care (Kim, 2006; Milenovic, 2014; Pedersen, 2015; Thompson, 2013) for many solid cancers, especially when locally advanced. This leads to overtreatment with significant potential for treatment related morbidities (Amezaga, 2007).

While pre-operative imaging modalities such as computerized tomography, magnetic resonance imaging, and position emission tomography improve early detection and help with surgical planning, intraoperatively surgeons still largely rely on inspection and palpation to determine surgical margins in real-time with limited accuracy (Alam, 2018).

Optical imaging strategies have rapidly been adapted to image tissues intra-operatively based on cellular imaging, native autofluorescence, and Raman scattering (Dacosta, 2006; Haka, 2006; Mo, 2009; Schwarz, 2009; Vahrmeijer 2013). The potential advantages of optical imaging include real-time feedback and the availability of camera systems that provide a wide view of the surgical field (Gioux, 2010). Despite some success, one of the major limitations of optical imaging strategies is the lack of broad tumor applicability in cancer patients.

One strategy to address the challenges that physicians face during surgery and to overcome the complexity encountered due to the diversity in oncogenotypes and histologic phenotypes is to target metabolic vulnerabilities that are ubiquitous in cancer. Aerobic glycolysis, known as the Warburg effect, in which cancer cells preferentially uptake glucose and convert it into lactic acid, occurs in all solid cancers. Lactic acid preferentially accumulates in the extracellular space due to monocarboxylate transporters (Webb, 2011). The resulting acidification of the extra-cellular space promotes remodelling of the extracellular matrix for further tumor invasion and metastasis.

ONM-100, the fluorescence imaging agent in development, exploits this ubiquitous pH difference between cancerous tissue and normal tissue and provides a highly sensitive and specific fluorescence response after being taken up by the cells, thus allowing the detection of tumor tissue, tumor margin, and metastatic tumors including lymph nodes (Li, 2016; Zhao, 2016; Ma, 2014; Wang, 2014).

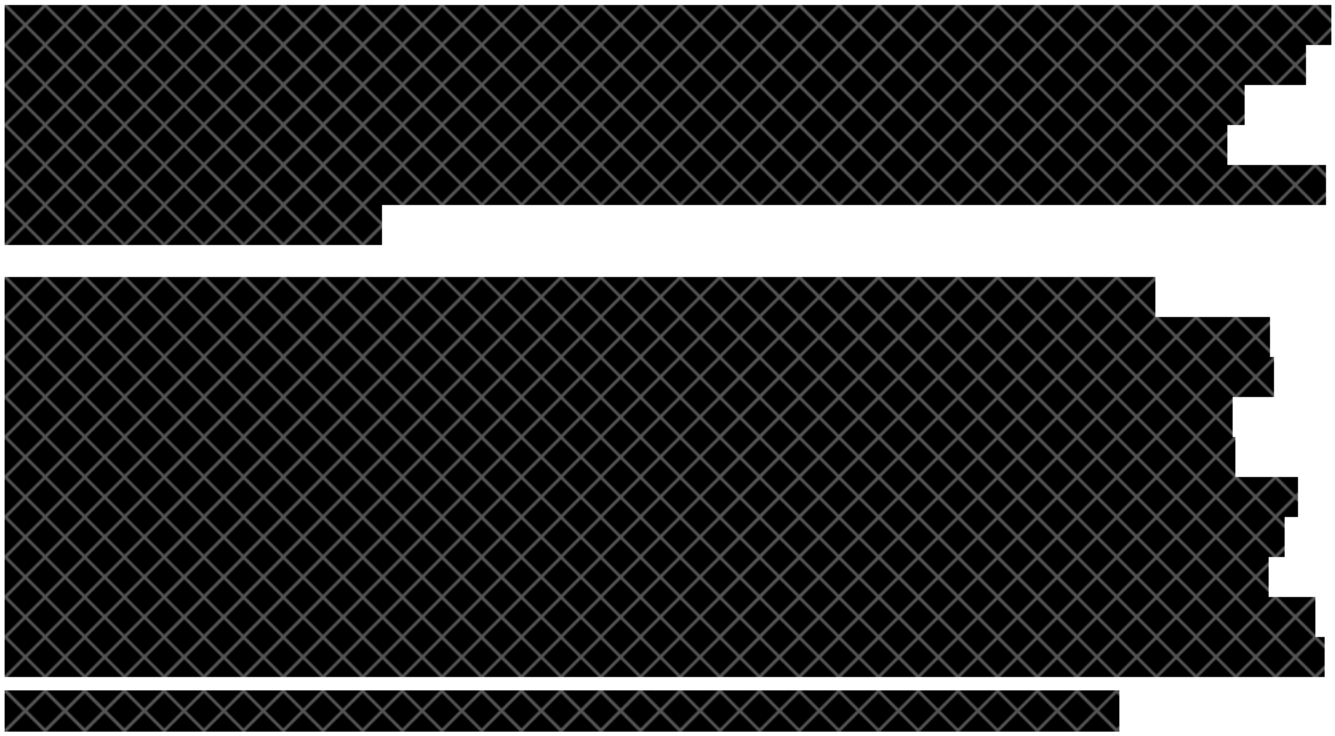
There is a clear unmet clinical need for the intraoperative detection of tumor margins and cancer-involved nodes. Solutions to these challenges would allow surgeons to more precisely remove primary cancers and directly and selectively remove only cancer-involved nodes, while avoiding the morbidity of radical surgery and false negative rates associated with proxy tests such as imaging and sentinel lymph node biopsy.

4.1 Nonclinical Studies

4.1.1 Primary Pharmacology

Upon systemic administration, ONM-100 circulates as a large micelle [redacted] at physiologic pH (7.35-7.45), with indocyanine green (ICG) dyes sequestered within the micelle core leading to fluorescence quenching (eg, during blood circulation). When the ONM-100 micelle encounters an acidic environment, such as tumor tissues, the micelles dissociate into individual polymers with an average molecular weight of [redacted] allowing the activation of fluorescence signals from the ICG dye, causing the tumor to specifically fluoresce.

The intense fluorescent response is a result of the sharp phase transition that occurs between the hydrophobicity-driven micellar self-assembly (non-fluorescent OFF state) and the cooperative dissociation of these micelles (fluorescent ON state) at predefined low pH (Ma, 2014; Li, 2016). This leads to a clear demarcation between tumor and surrounding normal tissues, an absolute necessity when aiming for tumor margins negative for cancer cells. [redacted]



4.1.2 Nonclinical Pharmacokinetics

[redacted] (Alexis, 2008; Kumar, 2010), and a similar profile is observed for ONM-100. MPS clearance of ONM-100 was confirmed by the fluorescent microscopy analysis [redacted]

4.1.3 Toxicology

[redacted]

[redacted]

[redacted]

[redacted]

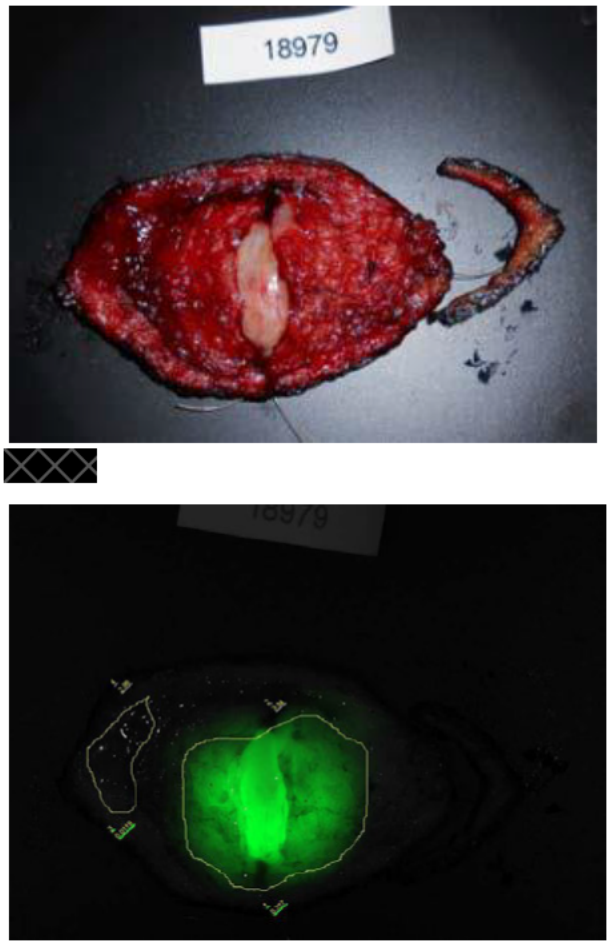
[redacted]

Additional nonclinical toxicology data are available in the Investigator's Brochure.

4.1.4 Dog Patient Study

Figure 2. Representative White Light and Fluorescence Image of a Mast Cell Tumor from a Dog Patient after ONM-100 Administration

Panel A



Panel A: white light image. Panel B: fluorescence image.

4.2 Clinical Data

This is the second clinical study of ONM-100 in humans. A first-in-human Phase 1 clinical trial was completed in The Netherlands. Clinical results from the completed Phase 1 study are available and presented below.

4.2.1 Phase 1 Study (ON-1001)

4.2.1.1 Study Design

Study ON-1001 is a completed Phase 1, single-Principal Investigator (PI), non-randomized, open-label, single-arm, cross-sectional study to evaluate the safety, PK profile, and imaging feasibility of ONM-100 in patients with solid cancers who require surgical excision. The main purpose of this study is to investigate the safety, PK, and feasibility of ONM-100 as an intra-operative optical imaging agent to detect tumors and metastatic lymph nodes in solid cancers. The s[redacted]. This study was conducted in The Netherlands.

This study was planned to enroll up to 33 patients with solid cancers [redacted] who have a biopsy-confirmed diagnosis of the respective tumor types and who are scheduled to undergo surgical resection of the tumor. The study design includes [redacted]

Phase 1a of the study is complete. Phase 1a was a dose-finding study performed in 5 cohorts of 3 patients each. The dose levels evaluated were 0.3, 0.5, 0.8, 0.1, and 1.2 mg/kg, in this sequence. Inter-cohort dose escalation took place after the last patient in the previous cohort completed the Day 10 safety assessment. The protocol planned dose levels of 1.6 mg/kg and 2.0 mg/kg were not evaluated in Phase 1a since a separate clinical study (ON-1002) is planned to further investigate dose levels >1 mg/kg to obtain optimal doses and imaging schedules.

Safety, PK, and imaging feasibility are evaluated in both the Phase 1a and 1b portions of the study. Patient safety is assessed during the study and for up to 10 days postdose.

During surgery, intraoperative images of ONM-100's fluorescence were obtained [redacted] using NIR camera(s). [redacted] No patient management decisions were made based on ONM-100 fluorescence imaging in the Phase 1a portion of the Phase 1 study.

Tumor specimens were processed for histology according to the routine pathology practice used in clinical cancer care. [redacted]

4.2.1.2 Disposition and Demographic Characteristics

All patients received a single dose of ONM-100 and completed the study. All patients were included in the imaging, PK, and safety analyses.

Demographic results for the Phase 1a dose-escalation portion of the completed Phase 1 study are available for all 15 patients; 3 patients in each of the 5 cohorts (data cut-off date of 15SEP2018). Overall, patients were predominately female (80.0%), White (100%), and not Hispanic or Latino (100%), with a mean age of 58.1 years and a mean body mass index (BMI) of 26.9 kg/m^2 (Table 5).

Table 5: Demographic and Baseline Characteristics

Demographic or Baseline Parameter	Cohort 1 0.3 mg/kg (N = 3)	Cohort 2 0.5 mg/kg (N = 3)	Cohort 3 0.8 mg/kg (N = 3)	Cohort 4 0.1 mg/kg (N = 3)	Cohort 5 1.2 mg/kg (N = 3)
Cancer Type, n					
Breast	3	1	2	0	1
HNSCC	0	2	1	3	2
Age, years					
Mean	53.3	56.7	61.3	68.3	50.7
Range	35-63	50-69	53-78	46-80	34-70
Gender, n (%)					
Male	0	1	0	1	1
Female	3	2	3	2	2
Ethnicity, n (%)					
Hispanic or Latino	0	0	0	0	0
Non-Hispanic or Latino	3	3	3	3	3
Race, n (%)					
White	3	3	3	3	3
Mean body mass index, kg/m^2					
Mean	30.3	27.8	31.1	22.7	22.4

HNSCC = head and neck squamous cell carcinoma

4.2.1.3 Safety Results

[redacted]

The safety profile was comparable at all the dose levels studied and did not raise any specific safety concerns or trends at higher doses.

ONM-100 was well tolerated and showed no dose-limiting toxicity (DLT) or study drug related serious adverse events (SAEs). All patients had ≥1 treatment-emergent adverse events (TEAEs) (Table 6).

[redacted] o patient had an abnormal electrocardiogram (ECG) that was considered clinically meaningful, had an SAE that was considered related to study drug by the Investigator, had a suspected unexpected serious adverse reaction (SUSAR), withdrew from the study due to a TEAE, or died.

[redacted]

Table 6. Overview of Adverse Events

	Cohort 1 0.3 mg/kg (N = 3) n (%)	Cohort 2 0.5 mg/kg (N = 3) n (%)	Cohort 3 0.8 mg/kg (N = 3) n (%)	Cohort 4 0.1 mg/kg (N = 3) n (%)	Cohort 5 1.2 mg/kg (N = 3) n (%)
Patients with ≥1 TEAE	3 (100)	3 (100)	3 (100)	3 (100)	3 (100)
Patients with ≥1 TEAE related to study drug	3 (100)	0	0	0	0
Patients with ≥1 SAE	0	0	1 (33.3)	0	0
Patients with ≥1 SAE related to study drug	0	0	0	0	0
Patients with ≥1 severe TEAEs	0	1 (33.3)	1 (33.3)	0	0
Patients with ≥1 severe TEAEs related to study drug	0	0	0	0	0
Patients with ≥1 SUSAR	0	0	0	0	0
Patients withdrawn from study due to a TEAE	0	0	0	0	0
Deaths	0	0	0	0	0

SAE = serious adverse event; SUSAR = suspected unexpected serious adverse reaction; TEAE = treatment-emergent adverse events.

Table 7: Serious and Severe (Grade 3) Adverse Events in Cohorts 1 to 5

Cohort	Patient Number	Adverse Event	Study Day Onset	Study Day of Resolution	Serious	Severity Grade[a]	Relationship to Study Drug	Action Taken
2 (0.5 mg)	ON 1104	ALT increased	1	16	No	3	Not related	None
		AST increased	1	10	No	3	Not related	None
3 (0.8 mg)	ON 1108	Tracheal fistula	12	15	Yes	3	Not related	Surgery

ALT = alanine aminotransferase; AST = aspartate aminotransferase
a. Severity Grade 1 = mild; Severity Grade 2 = moderate; Severity Grade 3 = severe

4.2.1.4 Pharmacokinetic Results

P

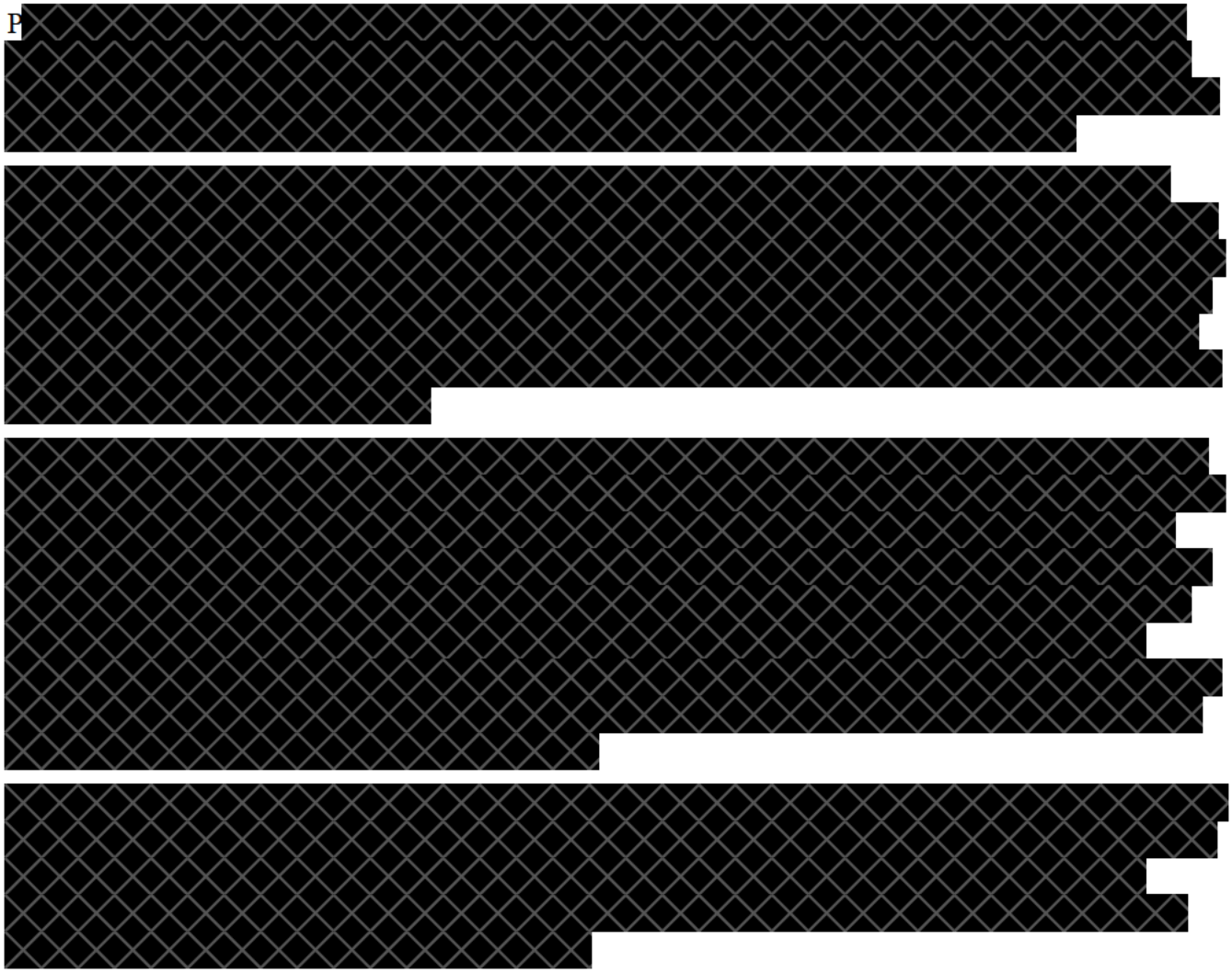
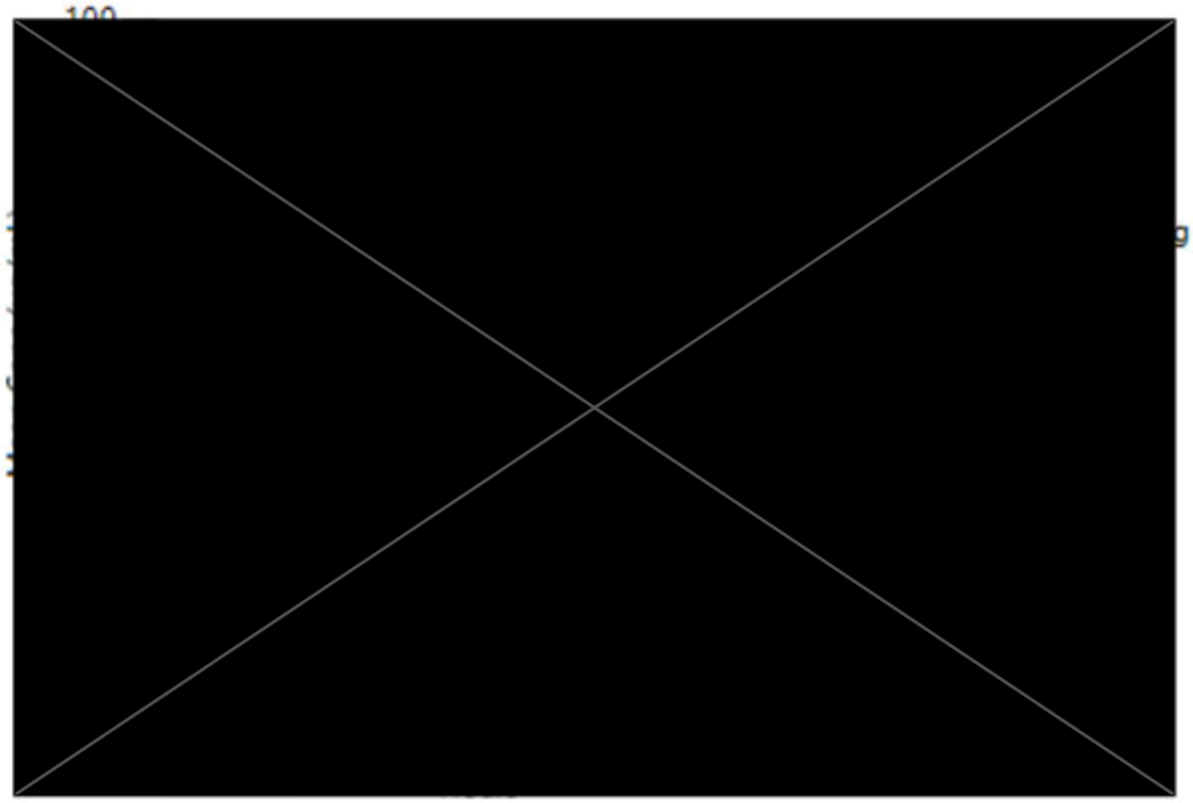


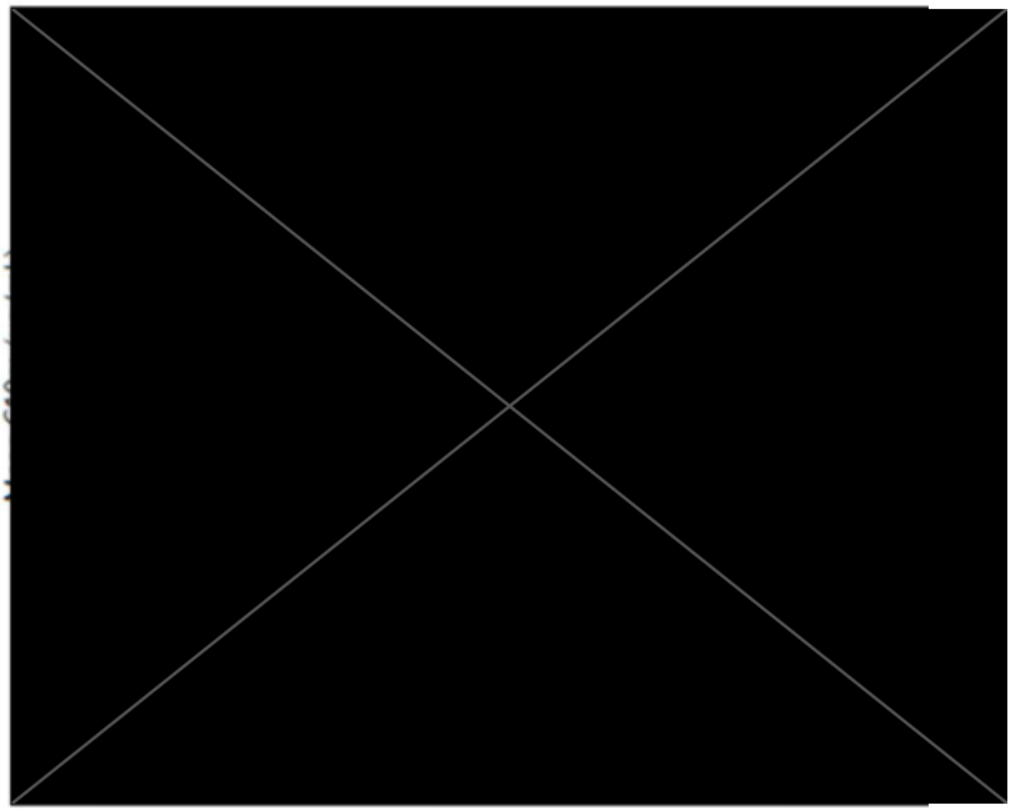
Figure 3: Mean ONM-100 Plasma Concentration versus Time following a Single Intravenous Dose of ONM-100



Conc = concentration

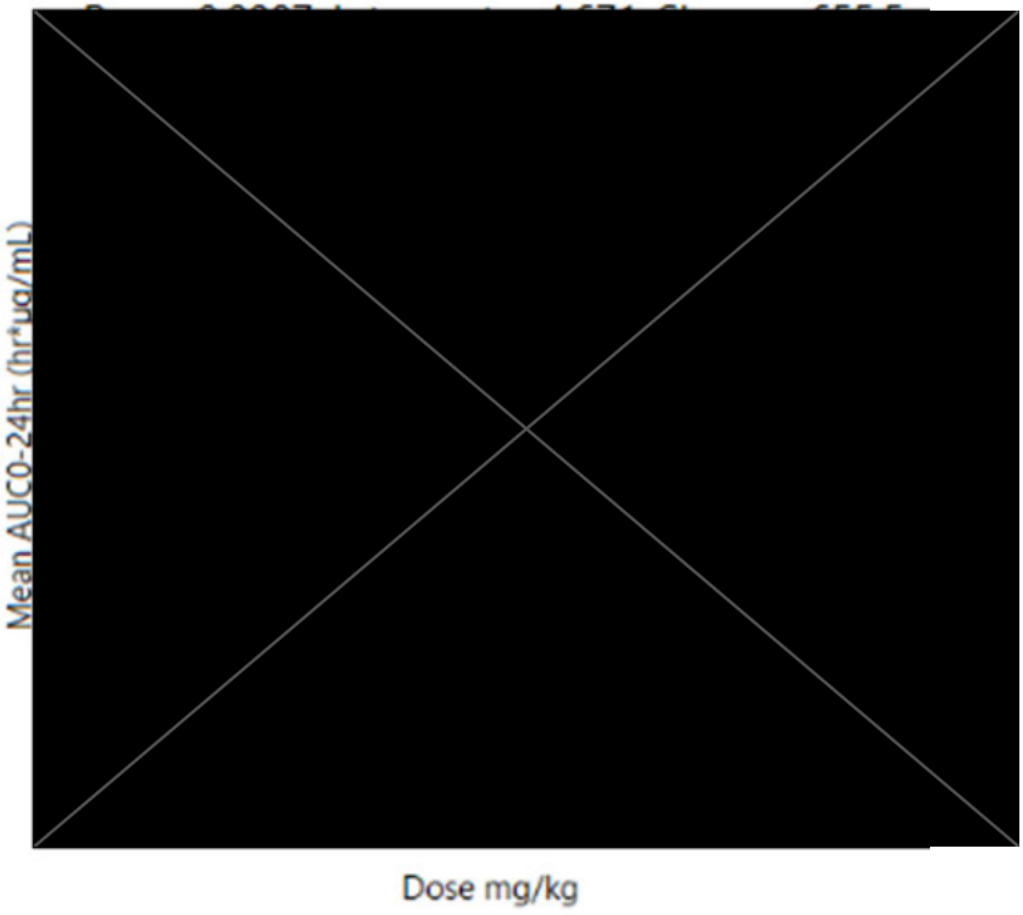
[redacted]

Figure 4: Correlation Between Mean ONM-100 Concentration at 10 minutes and Dose



C10m = ONM-100 concentration at 10 minutes

Figure 5: Correlation Between Mean AUC_{0-24} and Dose



AUC_{0-24hr} = area under the time-concentration curve from time 0 to 24 hours

4.2.1.5 Fluorescence Imaging Data

[redacted]

Figure 6: Intraoperative Images from 3 Patients in Cohort 2 (ONM-100, [redacted]) using [redacted]

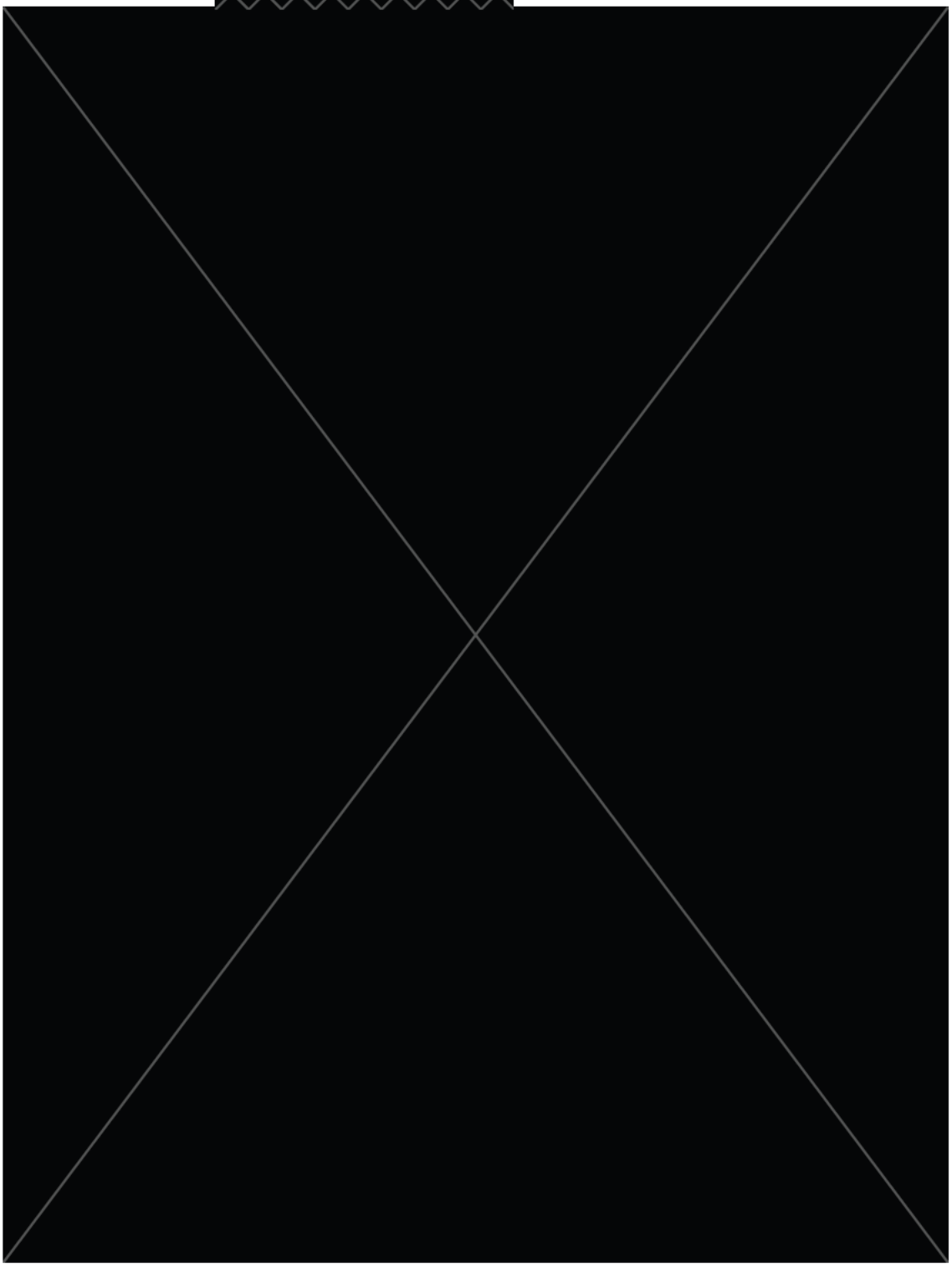
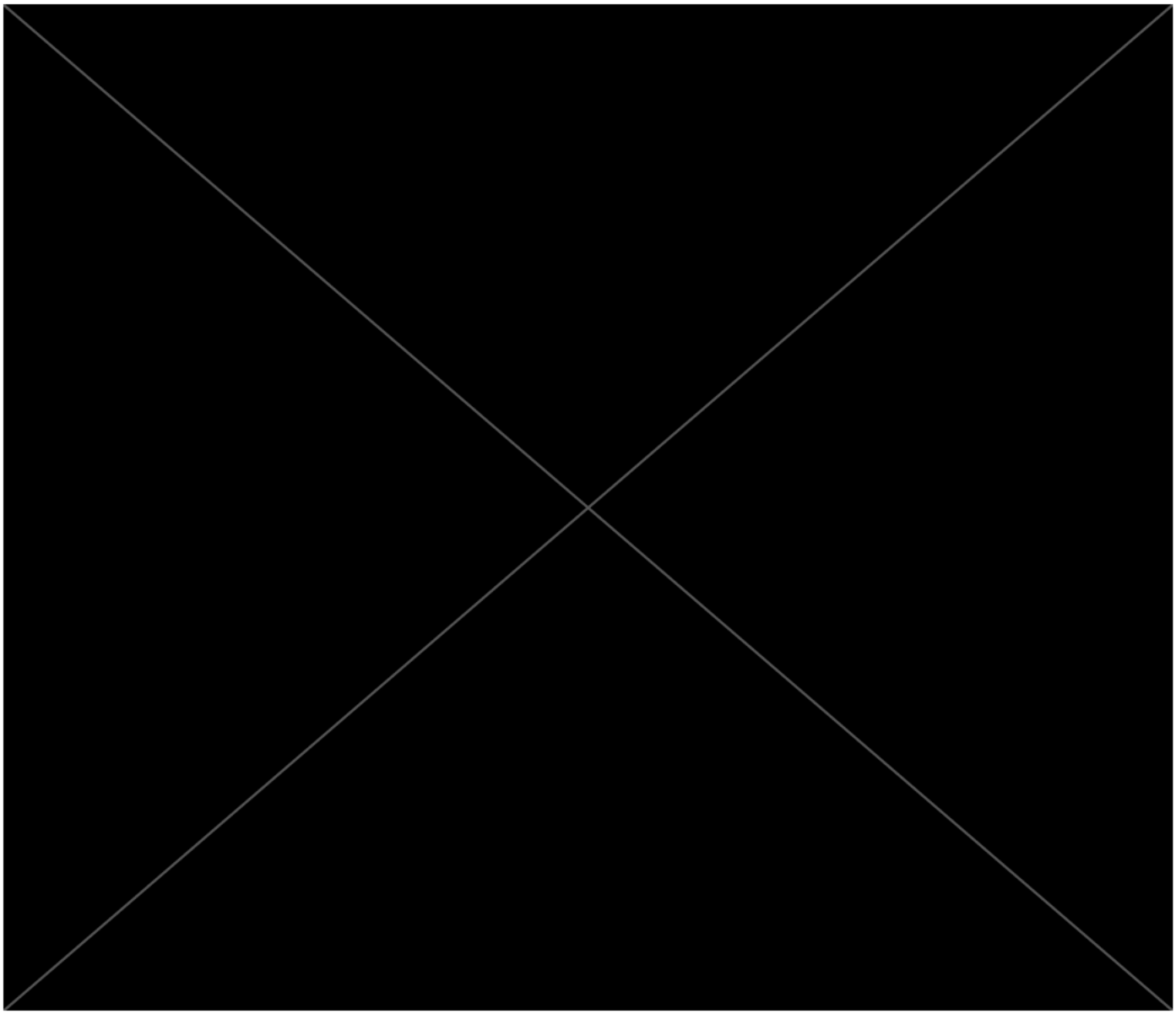
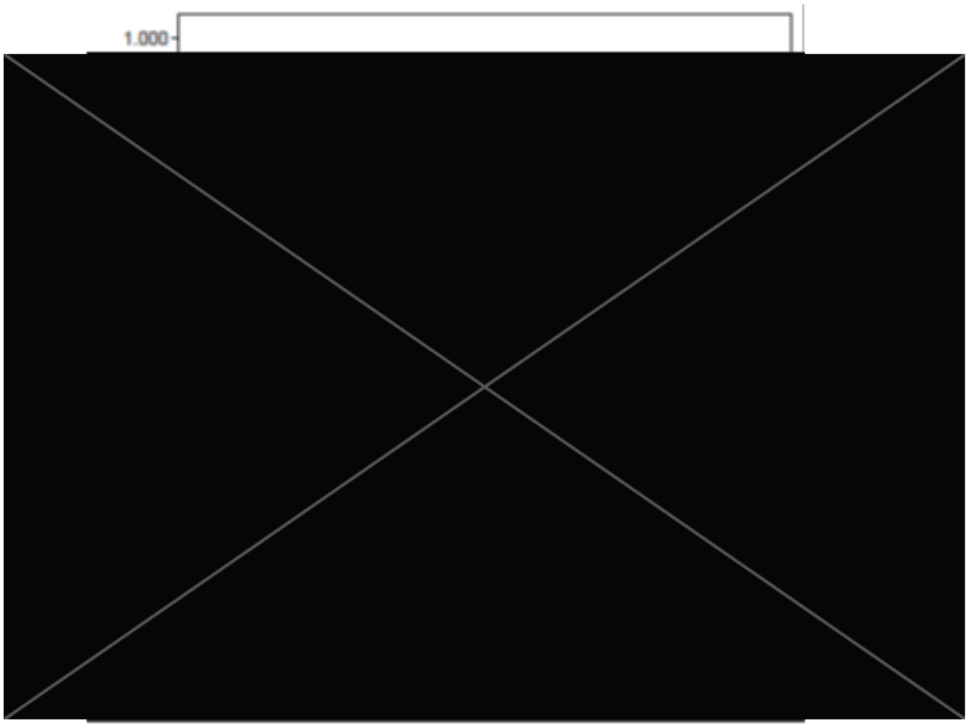


Figure 7: Postoperative Specimen Images from 3 Patients (ONM-100, [redacted])

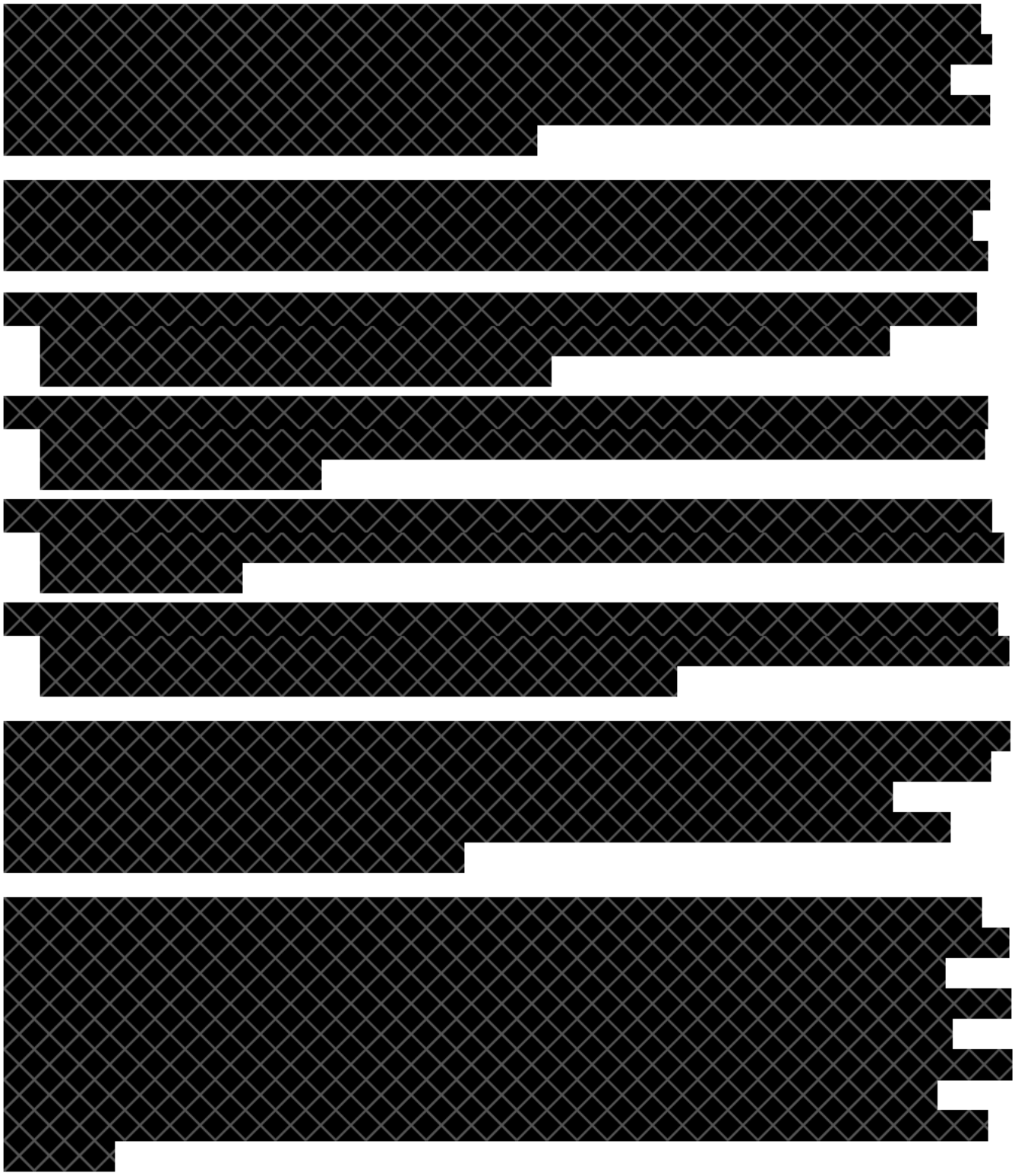


Histology confirmed tumor and normal tissue specimens showed clear demarcation (no overlap) of mean fluorescence intensity (MFI) for each patient (n=15) when plotted against each patient's plasma concentration at 10 minutes. Tumor fluorescence increased with increasing initial plasma concentration (Figure 8).

Figure 8: Fluorescence by Estimated Initial Concentration at the Specimen Level



C10 = ONM-100 concentration at 10 minutes
Postoperative ex-vivo mean fluorescence intensity of the histology confirmed tumor (red dots) and normal (black dots) tissues for the pathologist selected bread loaf slice specimens for each patient versus plasma C_{10}.



4.2.1.6 Summary of Phase 1a Results

4.3 Summary of Benefits and Risks

4.3.1 ONM-100

ONM-100 is a novel, micelle-based, fluorescence imaging agent. The micelles are comprised of a [redacted] of [redacted] covalently conjugated to ICG, [redacted]

In GLP toxicology studies, no adverse effects were observed in either rats or dogs at the maximum dose studied (30 mg/kg). Nonclinical toxicology of ONM-100 is presented in Section 4.1.3 and described in the Investigator's Brochure.

One Phase 1 clinical trial was completed in The Netherlands. Safety data from Phase 1a portion of the Phase 1 study (ON-1001) are presented in Section 4.2.1. No patient had an abnormal ECG that was considered clinically meaningful, had an SAE considered related to study drug by the Investigator, had a SUSAR, withdrew from the study due to a TEAE, or died.

[redacted]

4.3.2 Constituents of ONM-100

[redacted]

4.3.3 Imaging Devices

Only approved cameras for visualizing ICG will be used in this study. These may include the following cameras, as well as other approved NIR cameras that can detect ICG fluorescence.

- [redacted]

[redacted]

4.3.5 ONM-100 Fluorescence-detected Tumors Not Detected by Routine Surgery or Pathology

[redacted]

4.4 Justification for the Study Design, Dose, and Imaging Schedule

ONM-100 is being developed as an intraoperative imaging tool to aid the surgeons during routine surgical procedures.

[redacted]

A starting dose of [redacted]

In nonclinical GLP toxicology studies, the NOAEL was found to be 30 mg/kg in dogs and rats (the maximum feasible dose). Because the dog is the most sensitive species, the conversion to human equivalent doses are based on dog data (Table 8). The acceptable maximum dose for human dosing is 7.5 mg/kg, [redacted]

Table 8. Exposure/Dose Exaggerations for the Clinical Dose Range Compared to the NOAEL in the Dog (30 mg/kg)

Dog (30 mg/kg NOAEL)	Acceptable Maximum Dose = 15 mg/kg (50% NOAEL)	Planned Maximum Dose = 14 mg/kg (46.7% NOAEL)
HED (mg/kg)	7.5 [a]	7.0 [a]
AUC based HED Exaggeration Factor vs. Dog NOAEL	2.0-fold [c]	2.1-fold [c]
C_{max} Based HED Exaggeration Factor vs. Dog NOAEL	2.0-fold [c]	2.1-fold [c]

AUC = Area under the time-concentration curve; C_{max} = Concentration maximum; HED = Human equivalent dose; NOAEL = No-Observed-Adverse-Effect Level

a. Based on AUC, projected human total body clearance is approximately half of dog CL.
b. C_{max} and AUC exaggeration are based on the dog 0.5 mg/kg
c. C_{max} and AUC exaggeration are based on the dog 30 mg/kg

[redacted]

The IV route of ONM-100 administration is the same as the established route of administration of other fluorescence imaging agents. All of the animal studies were performed with IV dosing (Section 4.1).

[redacted]

4.5 Population to be Studied

[redacted]

4.6 Rationale for Trial Analyses

The imaging and diagnostic performance analyses are objective measures that reflect the real-world performance of ONM-100 as an agent for helping surgeons [redacted]

4.7 Statement of Compliance

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), the ethical principles of the Declaration of Helsinki (2013), and applicable regulatory and IRB or Independent Ethics Committee (IEC) requirements.

5.0 STUDY PURPOSE AND OBJECTIVES

The main purpose of this study is to investigate whether ONM-100 can be used to image primary tumors and metastatic lymph nodes at an imaging schedule earlier than 24 ±8 hours postdose in patients undergoing routine surgery of their solid cancers and whether the diagnostic performance to detect metastatic lymph nodes can be improved by optimizing the dose and the imaging schedule.

Part 1 Primary Objectives:

- Evaluate the dose(s) at which ONM-100 fluorescence imaging is feasible [redacted]
- Evaluate safety at the dose(s) used to assess imaging feasibility and select the dose(s) and imaging schedule(s) [redacted]

Part 2 Primary Objectives:

- Verify the safety and diagnostic performance of ONM-100 compared to standard pathology [redacted]

Part 1 and Part 2 Secondary Objective

- Evaluate the PK profile of ONM-100 [redacted]

Part 3 Primary Objective:

- Assess the safety and efficacy [redacted]

Part 3 Primary Endpoints:

- [redacted]

Part 3 Secondary Endpoints:

- [redacted]

Part 3 Exploratory Endpoints:

- [redacted]
- [redacted]
- [redacted]

6.0 STUDY DESIGN

6.1 Description of the Study

This is a non-randomized, open-label, multi-center, safety, PK, and imaging feasibility study of ONM-100, an intraoperative fluorescence imaging agent. The study consists of 3 parts (Part 1, Part 2 and Part 3).

- Part 1 will be performed in a dose-escalation design (maximum of 5 cohorts of 3 patients each) to determine the dose(s) at which ONM-100 fluorescence can be used to image metastatic lymph nodes and primary tumors [redacted]

- Part 2 will be a verification of the dose(s) and imaging schedule(s) from Part 1. Approximately 10 to 20 patients will be enrolled in Part 2. Eligible patients will have a confirmed diagnosis (or high clinical suspicion in the opinion of the Investigator) from among the following list of solid tumor types [redacted] The Sponsor will inform Investigators which tumor types are open to enrollment during the conduct of Part 2.
- Part 3 will investigate the safety, s[redacted] Approximately 20 to 30 patients will be enrolled. Eligible patients will have a confirmed diagnosis [redacted]r.

All included patients will satisfy the inclusion and exclusion criteria of Part 1, Part 2 or Part 3.

The starting dose level of ONM-100 [redacted]n this study is based on the safety, plasma exposure, and fluorescence imaging results from the Phase 1a portion of the completed Phase 1 study (ON-1001). Standard dose-escalation safety rules will be used for ONM-100 doses >1 mg/kg; note that the highest dose studied and determined to be safe in the Phase 1 Study ON-1001 was 1.2 mg/kg. Safety at each dose level will be assessed for 28 days (±48 hours) postdose in Part 1 and 28 days (±5 days) postdose in Part 2 and Part 3, and reviewed. [redacted] If needed, a smaller step change or an intermediate dose level may be selected as the next dose. Dose levels >3 mg/kg will be evaluated only as needed.

The dose escalation phase (Part 1) is anticipated to be completed with up to 5 cohorts (up to 15 patients) of the 6 potential cohorts (Table 9). Part 1 will begin with Cohort A, in which 3 patients will be administered a single dose of ONM-100 at 1 mg/kg and will undergo surgery and fluorescence imaging at [redacted]

this study, or in Study ON-1001, may be enrolled for the purposes of evaluating an alternate imaging schedule postdose, in parallel to another cohort being evaluated. All dosing decisions will be made after discussing all available data between the Sponsor and PIs and documenting the decision.

Table 9: ONM-100 Doses and Surgery/Imaging Schedules Evaluated in Part 1

Study Part	Cohort	ONM-100 Single Dose[a], mg/kg	Surgery / Imaging Time, hours	Number of Patients	Tumor Types[b]
Part 1	A	[redacted]		[redacted]	
	B	[redacted]		[redacted]	
	C (if needed)	[redacted]		[redacted]	
	D (if needed)	[redacted]		[redacted]	
	E (if needed)	[redacted]	[redacted]	[redacted]	[redacted]
	F (if needed)	[redacted]		[redacted]	

[redacted]

In Part 2, up to 3 ONM-100 doses and imaging schedules will be evaluated to verify the diagnostic performance of ONM-100 fluorescence imaging for detecting primary tumors and metastatic lymph nodes (Table 2).

[redacted]

In Part 2, enrollment will begin [redacted]. Based on ongoing review of imaging data obtained, the Sponsor may open enrollment in additional tumor types and/or selectively close enrollment in one or more tumor types. All the available data to date will be used to decide the

additional tumor type(s), number of patients per tumor type, and number of Group(s) to be enrolled.

Table 10: Doses and Surgery/Imaging Schedules Evaluated in Part 2

Study Part	Group	ONM-100 Single Dose, mg/kg	Surgery / imaging time, hours	Tumor Types[a]
Part 2	1			
	2			
	3			

The Sponsor will inform Investigators when each Group has been opened to enrollment and provide the dose and, as applicable, dose schedule to be used in each Group, and when any tumor type is activated or deactivated for enrollment. Any Group in Part 2 may begin dosing at any time during Part 1 if the safety and observed detection of metastatic lymph nodes or the primary tumors at the same or higher dose level has been demonstrated in Part 1.

Schematics of the study designs for Part 1 and Part 2 are presented in Figure 1. The Schedule of Assessments and Procedures for Part 1 (all cohorts) (

Table 3), Part 2 for Groups dosing on Day of surgery (Table 4), and Part 2 for Groups dosing ≥1 days (16-80 hours) before surgery (Table 4A) are presented. Note that the timing provided for postdose assessments and procedures begins after infusion of study drug has been completed (ie, time = 0 begins at the end of study drug infusion).

On Day 0, each patient will receive a single IV dose of ONM-100. The ONM-100 dose level, surgery time, and imaging schedule will be based on the Cohort in Part 1 or Group in Part 2 in which each patient is enrolled. The patient will undergo anesthesia in accordance with standard surgical practice. The surgery with tissue excision will occur as per routine surgical standards and the surgical specimens will be collected for pathologic evaluations.

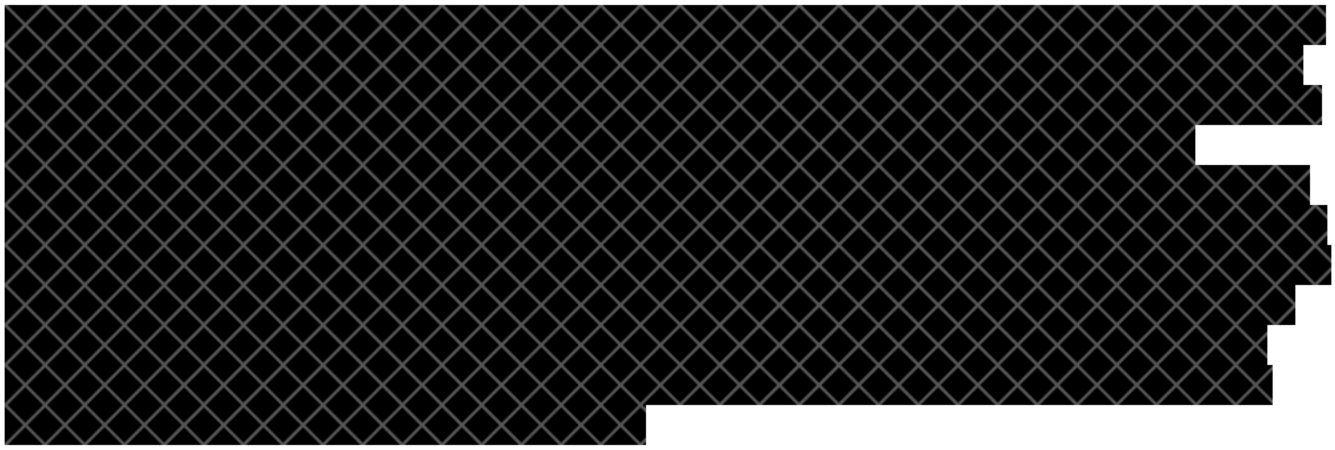
ONM-100 fluorescence imaging of [redacted]

Any ONM-100 fluorescence [redacted] Note that none of the ONM-100 florescence imaging results will be used for any therapeutic or patient management decisions intraoperatively or post operatively.

[redacted]

After surgery, the patient will be strictly observed following the standard, respective, postoperative protocol. Patients will be monitored for safety assessments and PK sample procurement.

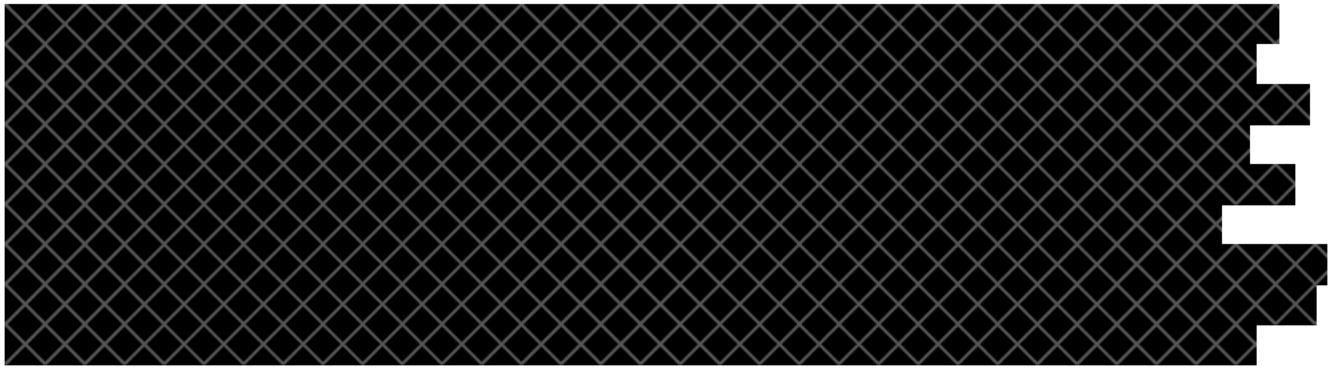
Medical history, prior medication use, hemoglobin, and Karnofsky performance status will be evaluated at Screening and pretreatment on Day 0. Pregnancy tests will be performed at Screening and at Day 28 (±48 hours) in Part 1 and at Day 28 (±5 days) in Part 2. Electrocardiograms (ECGs) will be performed pretreatment and at 30 ±10 minutes postdose on Day 0.

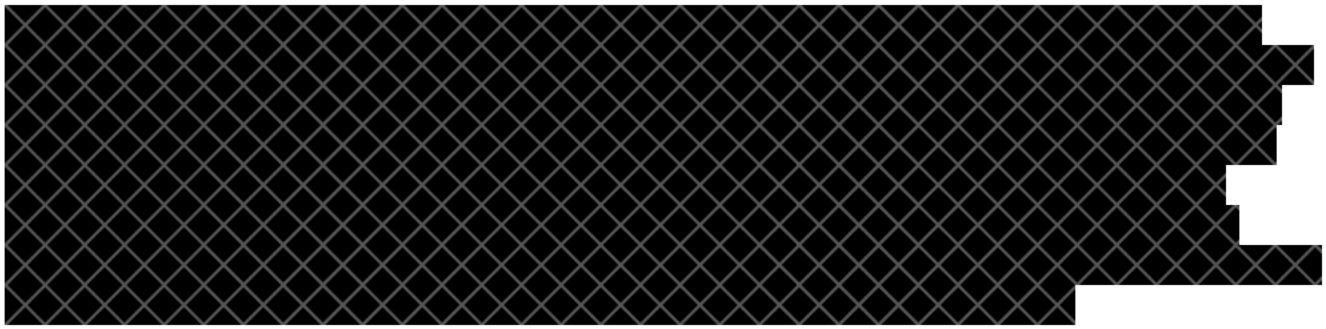


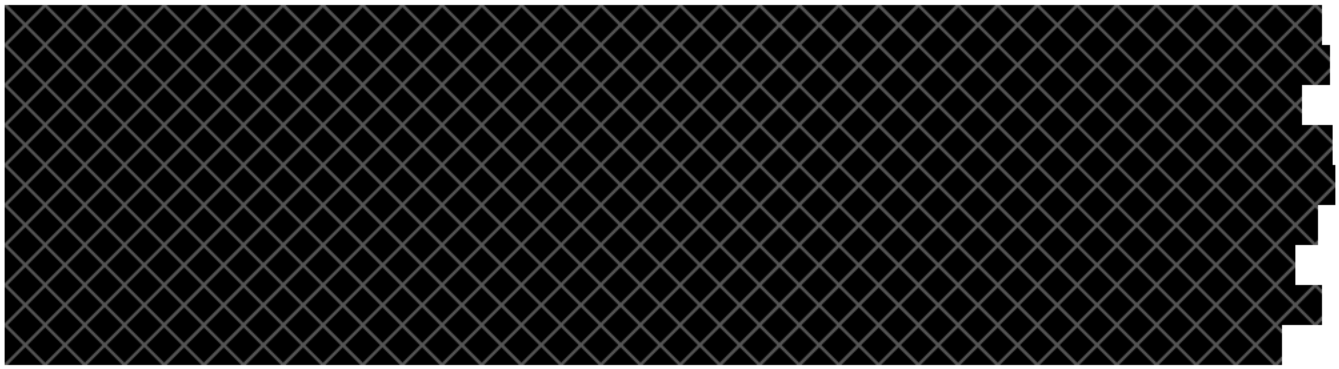
Plasma samples for PK analyses will be collected from all patients pretreatment and at various time points up to Day 6 (±24 hours) in Part 1 and up to Day 1 (±8 hours) in Part 2.

The Schedule of Assessments and Procedures for Part 3 are presented in Table 5. Note that the timing provided for postdose assessments and procedures begins after infusion of study drug has been completed (ie, time = 0 begins at the end of study drug infusion).

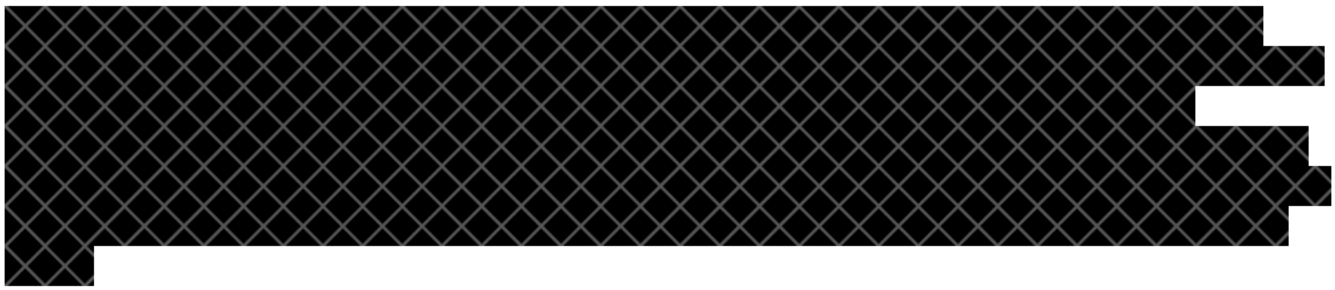
On Day 0, each patient will receive a single IV dose of ONM-100. The patient will undergo anesthesia in accordance with standard surgical practice.







All the ONM-100 fluorescence images will be saved per the Imaging Manual.



After surgery, the patient will be strictly observed following the standard, respective, postoperative protocol. Patients will be monitored for safety assessments.

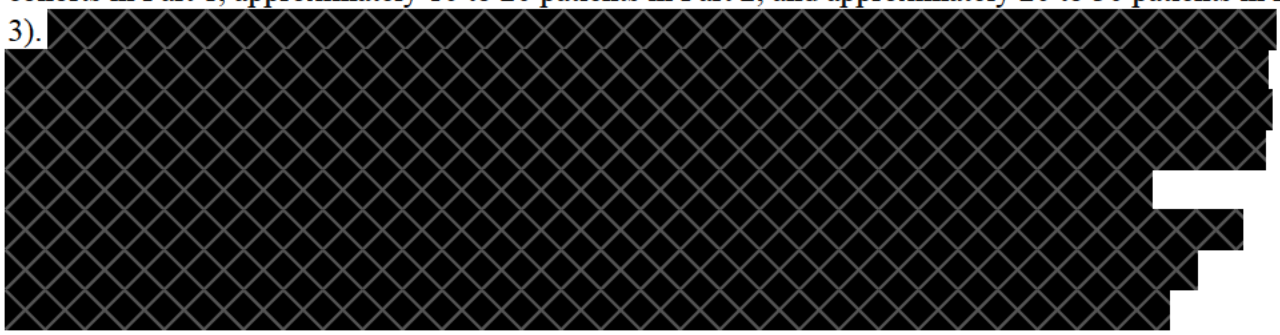
Medical history, prior medication use, hemoglobin, and Karnofsky performance status will be evaluated at Screening and pretreatment on Day 0. Pregnancy tests will be performed at Screening and

at Day 28 (±5 days). Electrocardiograms (ECGs) will be performed pretreatment, at 30 ±10 minutes postdose on Day 0, and on Day 10 (±5 days).

Patient safety will be assessed for 28 days (±5 days). All patients will be monitored for vital signs and physical examination pretreatment and at various time points up to Day 10 (±5 days). All patients will be monitored for comprehensive metabolic panel (CMP) and complete blood count (CBC) with differentials pretreatment and at various time points up to Day 28 (±5 days). All patients will be monitored for TEAEs and concomitant medication use from the start of dosing up to Day 28 (±5 days). TEAEs will be followed closely during the study.

6.2 Number of Patients

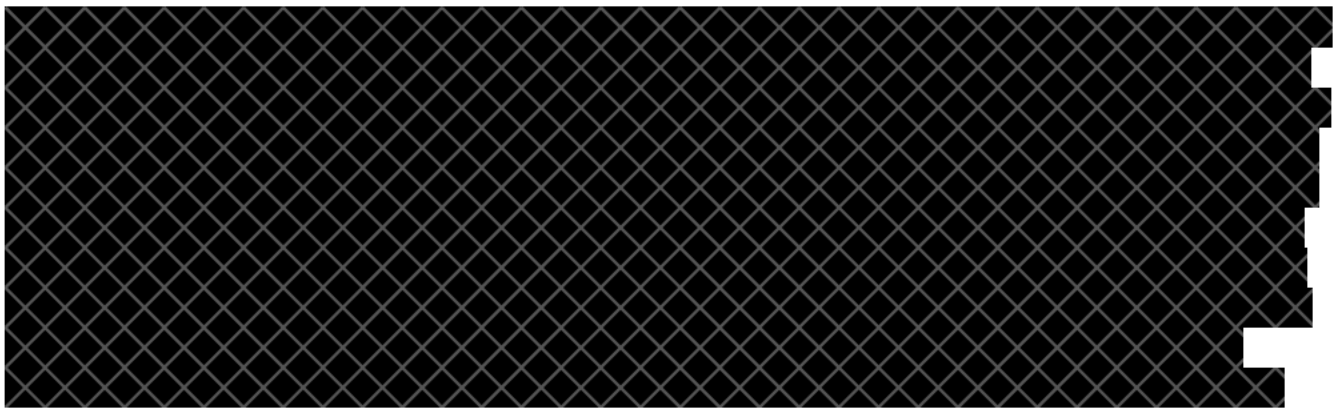
Up to 60 patients will be enrolled in this study (with planned allocation of up to 15 patients in up to 5 cohorts in Part 1, approximately 10 to 20 patients in Part 2, and approximately 20 to 30 patients in Part 3).



6.3 Measures Taken to Minimize Bias

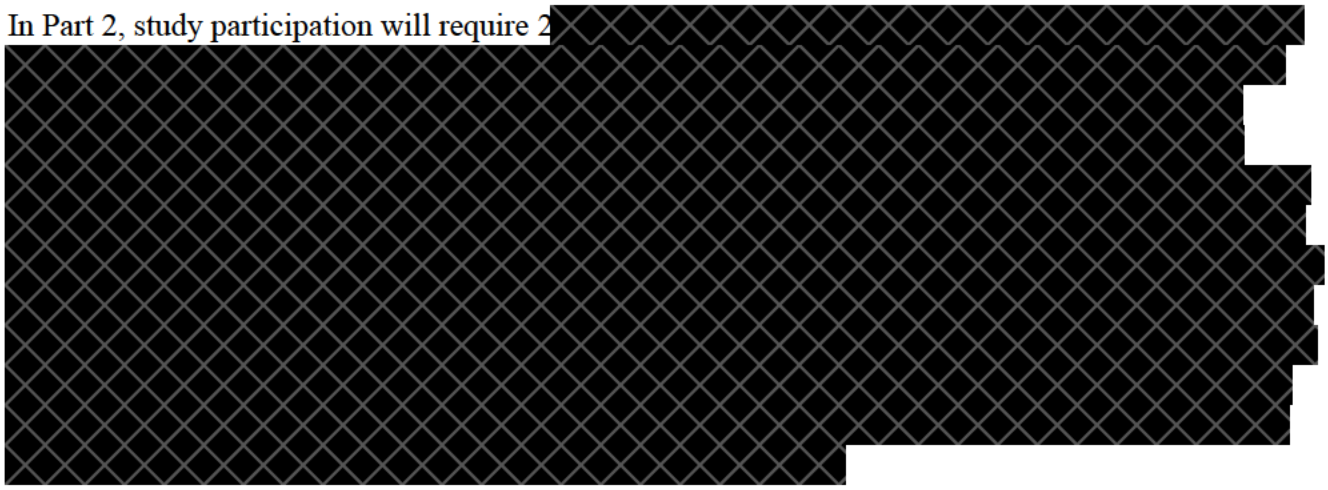
Randomization, treatment allocation, and blinding are not applicable since this is a single-arm, single-dose, open-label study. However, surgeons will be blinded to the presence or absence of fluorescence during standard of care surgery. Also, all pathology analyses will be blinded to the presence or absence of fluorescence, including surgical bed biopsies, tumor specimens, lymph nodes, lymph node bundles, bread loaf slices, and formalin-fixed and paraffin-embedded (FFPE) blocks.

6.4 Expected Duration of Patient Participation

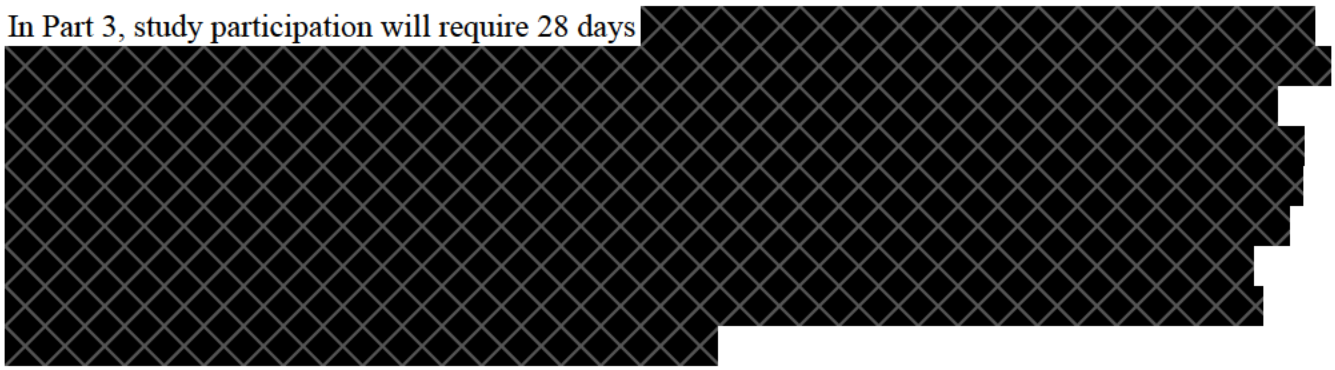


will be repeated on Day 28 (±48 days). All TEAEs and abnormal laboratory findings that are considered at least possibly related to ONM-100 will be followed until resolved or stabilized.

In Part 2, study participation will require 2



In Part 3, study participation will require 28 days



6.5 Method of Treatment Assignment and Blinding

Treatment assignment and blinding are not applicable since this is a single-arm, single-dose, open-label study.

7.0 SELECTION, DISCONTINUATION, AND WITHDRAWAL OF SUBJECTS

To be enrolled in this study, all patients must meet all of the following inclusion criteria and none of the exclusion criteria.

7.1 Patient Inclusion Criteria

Patients must meet ALL of the following inclusion criteria to be enrolled:

1. Adults ≥18 years of age
2. Biopsy-confirmed diagnosis for primary or recurrent disease (or high clinical suspicion in the opinion of the Investigator)
   a. Part 1: Stage 0 to 4 [redacted]
   b. Part 2:
      - Stage 0 to 4 [redacted]
      - Stage 2 to 4 [redacted]
   c. Part 3:

      Stage 2 to 4 [redacted]
3. Acceptable hematologic status (as respective standard surgery protocol requires, as determined by the Investigator), kidney function, and liver function. Elevations of creatinine, ALT, AST, alkaline phosphatase [AP], or total bilirubin ≥1.5× upper limit of normal (ULN) must be determined to be not clinically significant by the Investigator and approved by the Medical Monitor.
4. Documented negative serum pregnancy test for women of childbearing potential (ie, premenopausal women with intact reproductive organs and women <2 years after menopause)
5. Male patients and female patients of child-bearing potential (ie, premenopausal women with intact reproductive organs and women <2 years after menopause) must agree to and comply with using medically acceptable contraception including surgical sterilization (eg, hysterectomy, bilateral oophorectomy, bilateral tubal ligation), intrauterine device, oral contraceptive, contraceptive patch, long acting injectable contraceptive, partner's vasectomy, double-barrier method (condom or diaphragm plus spermicide or condom plus diaphragm), or abstinence during the trial and for 6 months thereafter.
6. Agree to abstain from alcohol consumption [redacted]
7. Adequate potential for follow up

8. Willing and able to provide written informed consent

7.2 Patient Exclusion Criteria

Patients must NOT meet any of the following exclusion criteria:

1. Histologically diagnosed by an excisional biopsy procedure
2. Tumors at sites of which the surgeon would assess that in vivo intraoperative imaging would not be feasible.
3. Life expectancy <12 weeks
4. Karnofsky Performance Status <70% (Appendix 1)
5. [redacted]
6. Lab values or any sign, symptom, or medical condition that in the opinion of the PI would prevent surgical resection.
7. Medical or psychiatric conditions that compromise the patient's ability to give informed consent
8. Pregnant or lactating women
9. [redacted]
10. [redacted]
11. [redacted]ry
12. Receiving or planned to receive, during the duration of the study, concomitant medication with a high chance o[redacted] as judged by the PI based on standard protocols within the study center
13. Alcohol consumption within 72 hours before ONM-100 administration
14. Received an investigational agent within the shorter of 5 half-lives or 30 days before ONM-100 dosing
15. Inability to adhere to the schedule of assessments or any circumstance that would interfere with the validity of assessments performed in the study
16. The PI considers that the patient should not participate in the study

7.3 Requalification for Entry

Patients not fulfilling the entry criteria and not enrolled may be rescreened for participation if their eligibility characteristics have changed.

7.4 Patient Withdrawal Criteria

7.4.1 Withdrawal from Study Protocol

[redacted]

7.4.2 Early Discontinuation from Study Drug Administration

[redacted]

7.5 Replacement of Patients

Patients withdrawn from the study will be replaced.

7.6 Study Termination by Sponsor and Termination Criteria

The Sponsor reserves the right to terminate an investigational site or this clinical study at any time. Reasons for termination may include, but are not limited to, the following:

- [redacted]

8.0 STUDY DRUGS

All patients in this study will be administered a single dose of ONM-100.

[redacted]

8.1 ONM-100

ONM-100 drug substance is comprised of a [redacted] conjugated to ICG, [redacted]

[redacted]

[redacted]

[redacted] When the ONM-100 [redacted], allowing the [redacted]

The product is limited to investigational use only.

8.1.1 Directions for Use

[redacted]

Please refer to the Pharmacy Manual for detailed information on study drug preparation.

8.1.2 Drug Storage

[redacted]

Please refer to the Pharmacy Manual for detailed information on study drug storage.

8.1.3 Dose Expansion and Escalation

[redacted]

Dose escalation may be stopped at a dose before reaching MTD if an optimal dose range with adequate TBR and safety coverage is determined (as assessed by the PI).

8.1.4 Dose Adjustment

Dose adjustments are not allowed in this study.

8.2 Comparator

There is no comparator imaging agent used in this study.

8.3 Compliance

Treatment compliance will be documented in the eCRF by recording the date, start time, and whether the dose of study drug was completely infused.

8.4 Previous and Concomitant Medications and Substances

[redacted]

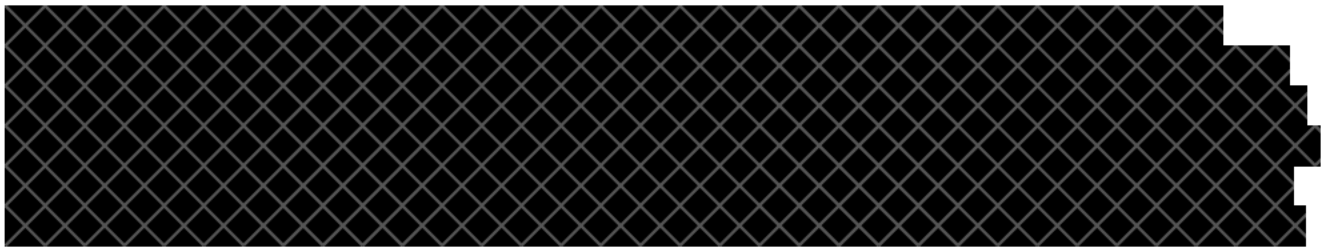
8.5 Accountability Procedures

The pharmacy or study personnel are responsible for ensuring that a current record of ONM-100 inventory and accountability is maintained.

A Pharmacy Monitor will be responsible for checking drug accountability at the site. Inventory records must be readily available for inspection by regulatory authorities at any time. Each shipment of ONM-100 will contain an Investigational Drug Transmittal and Receipt Form to assist in maintaining current and accurate inventory records. Upon receipt of ONM-100, the pharmacy or study personnel will visually inspect the shipment and verify the number and condition of vials received.

Refer to the Pharmacy Manual for additional information.

8.6 Study Drug Handling and Disposal



9.0 STUDY PROCEDURES

Study procedures should be completed within the windows provided in the Schedule of Assessments and Procedures for Part 1 (Figure 1,

Table 3) Part 2 (Figure 1,

Table 4, 4A) and Part 3 (Table 5) . However, if a patient is unable to attend a visit within the specified windows, the PI (or qualified designee) should discuss appropriate scheduling with the Medical Monitor (or appropriate designee).

Note that the timing provided for postdose assessments and procedures begins after infusion of study drug has been completed (ie, time =0 begins at the end of study drug infusion). General clinical practice will have priority over study procedures at all times.

9.1.1 Patient Restrictions

Patients are required to:

- [redacted]

9.1.2 Screening (Day -30 to Day -1)

Note that procedures and assessments collected as standard-of-care within 30 days before surgery can be used for Screening, when available. However, serum pregnancy test must be performed within 7 days before surgery.

- Obtain signed informed consent prior to initiating any study-related assessments or procedures
- Obtain a complete medical history
- Clinical assessments
  - Conduct complete physical examination
  - Record weight and height, calculate BMI
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate)
  - Determine Karnofsky Performance Status (Appendix 1)
  - Calculate Child-Pugh score (Appendix 2)
- Laboratory assessments
  - [redacted]
  - Perform serum pregnancy test on female patients <2 years postmenopausal
- Record all prior medications including prescription, over-the-counter (OTC), and herbal medications
- Confirm that the patient meets all study inclusion and exclusion criteria

9.1.3 Study Drug Dosing: Day 0

9.1.3.1 Predose procedures

- Clinical assessments
  - Record weight and height, calculate BMI
  - Record medical signs and/or symptoms since Screening visit
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate)
  - Perform 12-lead ECG during pre-operative screening anesthesia
  - Determine Karnofsky Performance Status (Appendix 1)
  - Install an IV line
- Laboratory assessments
  - [redacted]
    - [redacted]
  - Perform test for alcohol only for patients who have a known medical history of alcohol abuse; serum or urine test for alcohol is acceptable. If urine test is used and tests positive, a confirmatory serum test may be used to rule out false positive results.
  - Obtain predose blood sample for PK analyses and blood volume (Part 1 & 2 Only)
- Record all prior medications since Screening visit
- Confirm that the patient meets all study inclusion and exclusion criteria

9.1.3.2 Dosing and Postdose Procedures

- Study Drug Administration
  - [redacted]
- Clinical assessments (postdose)
  - [redacted]
  - Perform 12-lead ECG at 30 ±10 minutes after ONM-100 administration
  - [redacted]
- Laboratory assessments (postdose)
  - Obtain blood sample for PK analyses and blood volume (Part 1 & 2 Only)
    - Part 1 (all cohorts): at 10 (±1) minutes and 3 (±2) hours postdose (ie, after infusion has been completed)
    - Part 2 (all Groups): 10 (±1) minutes and 3 (±2) hours postdose (ie, after infusion has been completed)
- Record all concomitant medications including prescription, OTC, and herbal medications
- Assess, identify, and record any TEAEs or SAEs

9.1.4 Surgery: Day 0 (Part 1 all cohorts; Part 2 Groups assigned to dosing on day of surgery), Day 1 or longer [redacted] (Part 2 Groups assigned to dosing ≥1 day prior to surgery) or Day 1 (Part 3)

- Surgery (Section 9.1.4.1)
  - [redacted] for Part 1 Cohorts A and B
  - 6 [redacted] for Part 1 Cohorts C and D
  - An alternate imaging schedule postdose (to be determined) for Part 1 Cohorts E and F
  - An alternate imaging schedule postdose (to be determined) for Part 2 Groups assigned to dosing on day of surgery
  - [redacted]
  - [redacted]

9.1.4.1 Intraoperative ONM-100 Fluorescence Imaging and Biopsy

The ONM-100 Fluorescence Imaging Instruction Manual and training will be provided to the surgical team before site initiation. The following intraoperative in vivo and ex vivo procedures will be performed in, or close to, the operating room using the intraoperative NIR camera designated for the study and working with the surgical staff. ONM-100 images will be taken by a separate study technician or physician assistant. The basic methodology and conceptual framework for fluorescence imaging is provided in Koller (2018) and Rosenthal (2016).

A brief description is provided below:

<u>Part 1 and Part 2</u>

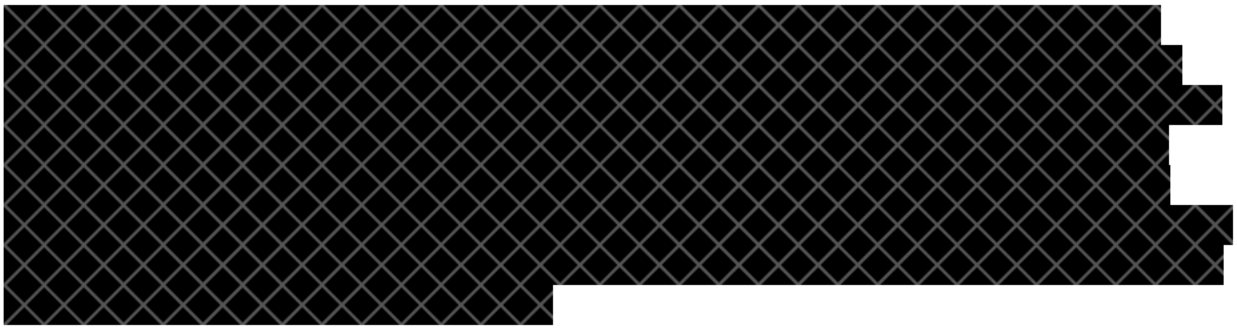
- Anesthetize patient per standard protocol
- [redacted]
- Perform cancer surgery as per routine surgery standard procedures [redacted]
  - [redacted]

- [redacted]

- Save all the ONM-100 fluorescence images as directed in the ONM-100 Fluorescence Imaging Instruction Manual

Part 3

- Anesthetize patient per standard protocol
- [redacted]

- 

- Save all the ONM-100 fluorescence images per the Imaging Manual.

9.1.4.2 End of Surgery

- Complete surgical procedures according to routine surgical practice
- After surgery, bring the patient to the nursing ward and strictly observe following the standard, respective, post-operative protocol; decisions on post-operative strategies will not be influenced by this study
- Record all concomitant medications including prescription, OTC, and herbal medications
- Assess, identify, and record any new TEAEs

9.1.4.3 Post-operative Procedures : Pathologic Specimen Preparations, ONM-100 Fluorescence Imaging, and Pathologic Evaluations

The ONM-100 Fluorescence Imaging Instruction Manual, Standard Pathology Assessment Instruction Manual, and training will be provided to the surgical team before site initiation. The following procedures will be performed in the pathology suite or equivalent space, working with the pathology team.

Part 1 and Part 2:

ONM-100 fluorescence imaging will be performed by a designated study technician or physician assistant using the [redacted]. The basic methodology and conceptual framework for fluorescence imaging is provided [redacted]

A brief description is provided below:

- [redacted]
  - [redacted]
- Store the images, videos, quantitative fluorescence data, and pathology results to the assigned database
- Archive the tissue specimens as per standard practice or as directed by the Sponsor

Part 3:

- [redacted]

- All tissue specimens will be archived per standard practice or as directed by the Sponsor.

9.1.5 Day 1 [redacted]

[redacted]

- Clinical assessments
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate) only if abnormal on Day 0
- Laboratory assessments
  - [redacted]
  - Obtain blood sample for PK analyses and blood volume (Parts 1 & 2)
- Record all concomitant medications including prescription, OTC, and herbal medications
- Assess, identify, and record any new TEAEs

9.1.6 Day 3 (±24 hours) (Part 1 only)

- Laboratory assessments
  - [redacted]
  - Obtain blood sample for PK analyses and blood volume (Part 1 & 2 Only)
    - Part 1 (all cohorts): 72 (±24) hours postdose (ie, after infusion has been completed)
- Record all concomitant medications including prescription, OTC, and herbal medications
- Assess, identify, and record any new TEAEs

9.1.7 Day 6 (±24 hours) in Part 1 ;and Day 10 (±5 days) in Part 2 and Part 3

- Clinical assessments
  - Measure vital signs (temperature, heart rate, blood pressure, and respiratory rate)
  - Perform 12-lead ECG
  - Conduct complete physical examination
- Laboratory assessments
  - [redacted]
  - Obtain blood sample for PK analyses and blood volume (Parts 1 & 2)
    - [redacted]
- Record all concomitant medications including prescription, OTC, and herbal medications
- Assess, identify, and record any new TEAEs

9.1.8 Day 28 (±48 hours) in Part 1; Day 28 (±5 days) in Part 2 and Part 3

- Laboratory assessments
  - [redacted]
  - Perform serum pregnancy test on female patients <2 years postmenopausal
- Record all concomitant medications including prescription, OTC, and herbal medications
- Assess, identify, and record any AEs

10.0 STUDY ASSESSMENTS

10.1 Intraoperative In Vivo and Ex Vivo Imaging Assessments

[redacted]

10.1.1 [redacted]

[redacted]

10.1.2 [redacted]

[redacted]

10.1.3 [redacted]

[redacted]

10.1.4 [redacted]

[redacted]

10.1.5 [redacted]

[redacted]

10.2 Post-operative Ex Vivo Imaging Assessments

Post-operative ex vivo imaging will be conducted [redacted]

10.2.1 [redacted]

[redacted]

10.3 Pathologic Assessments

Tumor specimens will be processed for histology according to the routine pathology practice used in clinical cancer care. If an ONM-100 fluorescence tissue is not selected by routine pathological sampling, select additional samples from the fluorescence tissue for pathological correlations. As needed, an independent central pathology reading will be used for pathology assessments when data required for analysis are not provided in the standard of care report.

10.4 Pharmacokinetic Assessments

10.4.1 Plasma Concentrations

Plasma samples will be collected, processed, and analyzed for ONM-100 concentrations as outlined in the Pharmacokinetic Laboratory Manual. Note that the timing provided for postdose assessments and procedures begins after infusion of study drug has been completed (ie, time =0 begins at the end of study drug infusion). Standard curves will be used to estimate ONM-100 patient sample concentrations at different time points.

[redacted]

10.4.2 Plasma Concentrations and Blood Volumes over Time

[redacted]

10.4.3 Pharmacokinetic Summary Parameters

For each plasma concentration-time curve, the following PK summary parameters will be estimated using standard non-compartmental methods:

- Maximum plasma concentration (C_{max})
- Time to C_{max} (T_{max})
- Area under the time-concentration curve (AUC)
- Total body clearance (CL)
- Volume of distribution (V_z)
- Volume of distribution at steady state (V_{ss})
- Elimination rate constant (λz)
- Terminal elimination half-life ($t_{1/2}$)

10.5 Safety Assessments

10.5.1 Safety Parameters

Safety will be assessed from the signing of the Informed Consent Form (ICF) to Day 28 (±48 hours) in Part 1 and to Day 28 (±5 days) in Part 2 and Part 3 postdose through the evaluation of TEAEs, physical examinations, vital signs, ECGs, and conventional clinical laboratory data (CMP and CBC with differentials) according to the schedule of Assessments and Procedures (Figure 1,

Table 3,

Table 4/4A, Table). Note that the timing provided for postdose assessments and procedures begins after infusion of study drug has been completed (ie, time =0 begins at the end of study drug infusion).

10.5.2 Adverse Events

TEAEs will be collected for all patients starting from the start of dosing and through Day 28 (±48 hours) in Part 1 and through Day 28 (±5 days) in Part 2 and Part 3. The Investigator will assess all TEAEs and SAEs and will record the following information on the appropriate eCRF page:

- Date of onset
- Date of resolution or stabilization
- Severity
- Relationship to study drug
- Action taken with study medication

Medically indicated laboratory tests (emergency or unscheduled tests) should be conducted at the local laboratory. The Investigator should employ best medical judgment in determining how to manage TEAEs and SAEs. Any questions regarding TEAE or SAE management should be directed to the Medical Monitor.

10.5.3 Adverse Event Reporting

The Sponsor has requirements for expedited reporting of SAEs meeting specific criteria to worldwide regulatory authorities. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after informed consent.

All SAEs must be reported to the Medical Monitor by phone or email within 24 hours of the investigational site's knowledge of the event.

The study site will also transmit a Serious Adverse Event Report (SAER) to the safety vendor by facsimile or email within 24 hours. Contact details will be provided to all sites. An optional initial report can be made via telephone, but a completed SAER must still be provided within 24 hours of the site's knowledge of the event. The Investigational site will be provided with SAER forms wherein the following information is requested.

- Patient identification, Investigator name, and site number
- SAE information: event term, onset date, severity, and causal relationship
- The outcomes attributable to the event (eg, death, a life-threatening TEAE, inpatient hospitalization, prolongation of existing hospitalization, a persistent or significant disability or incapacity, or other important medical event[s])
- A summary of relevant test results, pertinent clinical laboratory data, and any other relevant medical history
- The date of study drug administration
- Indicate if the study drug was discontinued or the study drug administration schedule modified
- Supplemental information may include the following hospital records: laboratory results, radiology reports, progress notes, admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates

In addition, relevant eCRF pages should be appended to communicate relevant study drug and patient outcome information. The SAER should be faxed or emailed within 24 hours with as much of the above information as available at the time. The following minimum information is required for reporting an SAE: patient identification, reporting source, and an event or outcome. Supplemental information may be transmitted using a follow-up report and should not delay the initial report. The Sponsor may contact the investigational site to solicit additional information or follow up on the event.

The Investigator must take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the patient's eCRF.

10.5.4 Definitions

10.5.4.1 Adverse Event

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. A TEAE (also referred to as an adverse experience) can be any unfavorable and unintended sign (eg, a clinically meaningful abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug and does not imply any judgment about causality. A TEAE can arise with any use of the drug (eg, off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

Laboratory abnormalities should not be recorded as TEAEs or SAEs unless they are associated with clinical signs or symptoms or require medical intervention. However, each laboratory abnormality (eg, clinically meaningful changes detected on hematology, CMP) independent from any underlying medical condition that requires medical or surgical intervention, or that leads to interruption of study drug infusion or discontinuation, must be recorded as a TEAE or SAE if applicable. If the laboratory abnormality is part of a clinical condition or syndrome, it should be recorded as the syndrome or diagnosis rather than as the individual laboratory abnormality. In addition, laboratory abnormalities or other abnormal test assessments (eg, ECGs) that are associated with signs or symptoms must be recorded as TEAEs or SAEs if they meet the definition of a TEAE (or SAE) as described in Section 10.5.4.1 (or Section 10.5.4.4).

Conditions resulting from the surgical resection will be considered TEAEs if they meet the criteria described above.

10.5.4.2 Suspected Adverse Reaction

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

10.5.4.3 Life-Threatening Adverse Event or Life-Threatening Suspected Adverse Reaction

A TEAE or suspected adverse reaction is considered ‘‘life threatening’’ if, in the view of either the Investigator or Sponsor, its occurrence places the patient or patient at immediate risk of death. It does not include a TEAE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

10.5.4.4 Serious Adverse Event or Serious Suspected Adverse Reaction

A TEAE or suspected adverse reaction is considered ‘‘serious’’ if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening TEAE (see definition of TEAE provided in Section 10.5.4.1)
- 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 that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

As the study population consists of oncologic patients, progression of a patient’s pre-existing disease will not be considered an SAE. In addition, an elective hospital admission will not be considered an SAE. Conditions resulting from the surgical resection will be considered SAEs if they meet the criteria described above.

10.5.4.5 Unexpected Adverse Event or Unexpected Suspected Adverse Reaction

A TEAE or suspected adverse reaction is considered ‘‘unexpected’’:

- If it is not listed in the Investigator’s Brochure or is not listed at the specificity or severity that has been observed, or
- If an Investigator’s 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, as amended
- If it is not listed in the prescribing information (for marketed products)

For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents.

''Unexpected,'' as used in this definition, also refers to TEAEs or suspected adverse reactions that are mentioned in the Investigator's 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.

10.5.5 Adverse Event Classification

10.5.5.1 Relationship to Investigational Drug

The Investigator's assessment of causality must be provided for all TEAEs (serious and non-serious) (Table 11). An Investigator's causality assessment is the determination of whether there exists a reasonable possibility that the study drug caused or contributed to a TEAE.

These criteria, in addition to good clinical judgment, should be used as a guide for determining the causal assessment. If the event is believed to be unrelated to study drug administration, then an alternative explanation should be provided.

Table 11: Guidelines for Assessing Relationship of Event to Study Drug

Not related	The event is most likely produced by other factors such as the patient's clinical condition, intercurrent illness, or concomitant drugs, and does not follow a known response pattern to the study drug, or the temporal relationship of the event to study drug administration makes a causal relationship unlikely.
Possibly related	The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study drug, but is more likely produced by other factors such as the patient's clinical condition, intercurrent illness, or concomitant drugs.
Probably related	The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study drug, but could be explained by other factors such as the patient's clinical condition, intercurrent illness, or concomitant drugs.
Definitely related	The event follows a reasonable temporal sequence from the time of drug administration, and/or follows a known response pattern to the study drug, and cannot be reasonably explained by other factors such as the patient's clinical condition, intercurrent illness, or concomitant drugs.

10.5.5.2 Severity

All TEAEs will be graded for severity. Adverse events will be graded by the Investigator using a numerical score according to the defined National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0 (2017). Adverse events not specifically defined in the NCI CTCAE will be scored on the Adverse Event log according to the general guidelines provided by the NCI CTCAE and as outlined in Table 12.

The Investigator will use the terms: Mild, Moderate, Severe, Life Threatening, or Death to describe the maximum intensity of the TEAE. For purposes of consistency, these intensity grades are defined as follows:

Table 12: Guidelines for Severity Assessments

Grade 1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Grade 4	Life threatening	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death	Death related to an adverse event

ADL = activities of daily living

a. Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

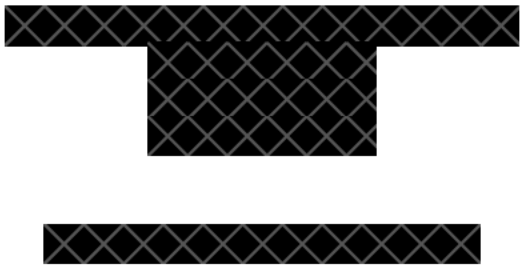
b. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.5.5.3 Serious Adverse Events

Any adverse experience occurring at any dose of study medication that occurs between the time of receiving study medication and within 28 days (±48 hours) in Part 1 or 28 days (±5 days) in Part 2 after administration of study drug that results in any of the following outcomes:

- Death
- Life-threatening situation (patient is at immediate risk of death)
- In-patient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a patient who received study drug
- Events that jeopardize the patient sufficiently that medical or surgical intervention may be required to prevent one of the above outcomes. Examples may include, but are not limited, to:
  - Intensive treatment in an emergency room or at home for allergic bronchospasm
  - Blood dyscrasias that do not result in hospitalization
  - Seizures that do not result in hospitalization

ALL SERIOUS ADVERSE EVENTS MUST BE REPORTED TO THE CONTRACT RESEARCH ORGANIZATION'S DRUG SAFETY DESK WITHIN 24 HOURS USING THE DESIGNATED SERIOUS ADVERSE EVENT REPORTING FORM



10.5.5.3.1 Serious Adverse Event Definition Clarifications

- Death is an outcome of an AE, and not an AE in itself
- All deaths during study drug administration or occurring within 21 (±1) days after administration of study drug, regardless of cause or relationship, must be reported
- "Occurring at any dose" does not imply that the patient is actively receiving study drug at the time of the event
- "Life-threatening" means that the patient was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, had it occurred with greater severity.
- Complications that occur during hospitalizations are AEs. If an AE prolongs hospitalization, it is an SAE.
- "In-patient hospitalization" means the patient has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department (although an emergency department visit may define a medically important event, which is also considered an SAE).
- The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and other clinical information. In such cases, the diagnosis should be documented as the TEAE or SAE, rather than as the individual signs or symptoms.

10.5.5.4 Suspected Unexpected Serious Adverse Reactions

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered. Unexpected adverse reactions are SUSARs if the following 3 conditions are met:

1. The event must be serious (Section 10.5.5.3)
2. There must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose
3. The adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in
    a. Summary of Product Characteristics for an authorized medicinal product
    b. Investigator's Brochure

The sponsor or sponsor designee will report SUSARs according to details provided in the study's Safety and Medical Management Plan (or equivalent). The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life-threatening cases, the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

10.5.6 Dose-limiting toxicity

DLT is defined as any TEAE of Grade 2 or greater that is considered by the Investigator to be possibly related, probably related, or definitively related to ONM-100 treatment (Section 10.5.5.1) and not to surgery, anesthesia, or other study procedures. Toxicity will be graded according to the NCI-Common Terminology Criteria for Adverse Events (CTCAE) (Sibille 2010). TEAEs will be followed closely during the study to identify any potential DLTs. In Part 1, safety results for each cohort will be reviewed by the Internal Safety Review Committee. Escalation to doses higher than those previously tested will not occur until the safety of lower doses has been confirmed following review by the Internal Safety Review Committee.

10.5.7 Adverse Event Follow-up

All unresolved TEAEs ("ongoing" at end of study) will be followed by the study staff until resolution or deemed stable.

For total bilirubin >1.5×ULN on ≥2 consecutive assessments, assess fractionated bilirubin. If liver function tests (ALT, AST, AP, total bilirubin, fractionated bilirubin) show an abnormal elevation (>1.5×ULN), retest weekly until the values have returned to baseline or stabilized.

10.5.8 Adverse Events of Special Interest

There were no TEAEs of special interest in the Phase 1 study (Section 4.2.1.3).

10.5.9 Toxicity Management

The Investigator should employ best medical judgment in determining how to manage TEAEs. Any questions regarding TEAE management should be directed to the Medical Monitor.

10.5.10 Risks for Women of Child-Bearing Potential or During Pregnancy

The risks of ONM-100 administration during pregnancy have not been evaluated. Pregnant and lactating females are excluded from this study.

Male patients and female patients of child-bearing potential (ie, premenopausal women with intact reproductive organs and women <2 years after menopause) must agree to and comply with using medically acceptable contraception including surgical sterilization (eg, hysterectomy, bilateral oophorectomy, bilateral tubal ligation), intrauterine device, oral contraceptive, contraceptive patch, long acting injectable contraceptive, partner's vasectomy, double-barrier method (condom or diaphragm plus spermicide or condom plus diaphragm), or abstinence during the trial and for 6 months thereafter.

Patients must be instructed to inform the Investigator *immediately* if they or their partner become pregnant during the study. Female partners of male patients must complete informed consent to allow the investigator to follow them for the outcome of the pregnancy.

In the event of a confirmed pregnancy, the following actions should be taken:

- Study drug should be discontinued immediately
- The pregnancy should be reported to the Medical Monitor within 24 hours of notification using the applicable Pregnancy Report Form
- The Investigator should counsel the patient regarding the possible effects of prior ONM-100 exposure on the fetus and the need to inform the study site of the outcome of the pregnancy
- The patient must be monitored until the immediate postnatal period or until termination of the pregnancy. The outcome should be reported to the Medical Monitor using the Pregnancy Outcome or Abnormal Pregnancy Outcome form.

Pregnancy is not an AE, in and of itself. However, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE. A spontaneous abortion is always considered an SAE and will be reported as described in the TEAE and SAE sections. Furthermore, any SAE occurring as an adverse pregnancy outcome poststudy must be reported to the Medical Monitor.

11.0 STATISTICAL METHODS

This is a pilot study with the intention of gathering data to assess feasibility and imaging metrics. Therefore, no formal statistical hypothesis testing will be performed for making development decisions. Considerations for outcome assessment are described in Appendix 3.

11.1 Data Management

All data generated by the sites for this study will be entered by the Investigator (or designee) onto a validated eCRF provided for this study by the Contract Research Organization (CRO). Study Data Tabulation Model datasets will be prepared from the eCRF data by the CRO using validated software. Details will be provided in the study's Data Management Plan and Statistical Analysis Plan (or equivalents).

11.2 Analysis Populations

The analysis populations that will be used in the statistical analysis are defined below:

- [redacted]

A patient is considered to have completed the study if the patient has completed all phases of the study, including the last visit or the last scheduled procedure (Figure 1,

Table 3,

Table 4/4A, and Table).

11.3 Study Population and Patient Characteristics

The study population and patient characteristics will be analyzed in the Safety population.

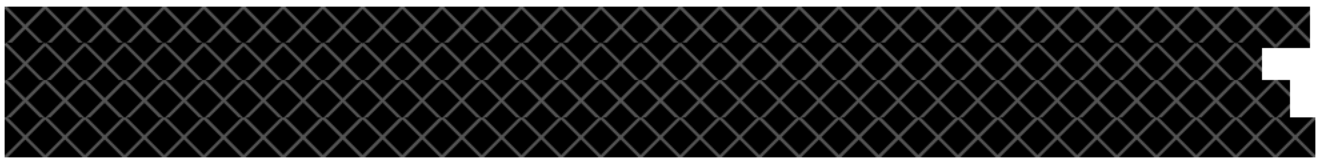
Demographics (including age, gender, race, ethnicity, and BMI), medical history (prior therapies with dates, histology, localization and classification of cancer, prior treatment outcome), and administration of study drug will be summarized using descriptive statistics.

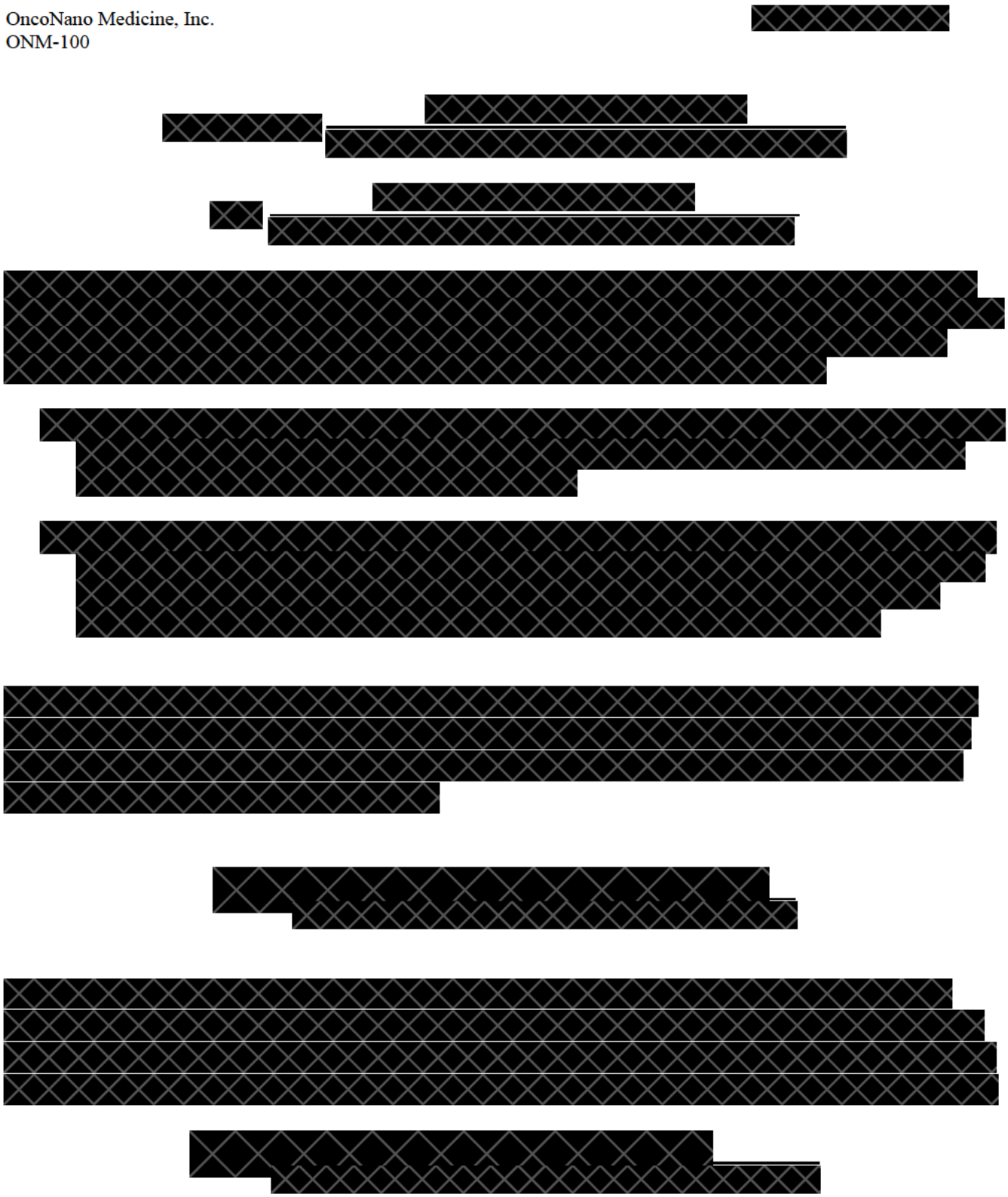
Surgical care (including type, duration, and outcome) and tumor characteristics (including morphology, size, and margin status) will be summarized using descriptive statistics.

11.4 Efficacy Analyses

This is a pilot study with the intention of gathering data to assess feasibility and imaging metrics for the efficacy analysis. Therefore, no formal statistical hypothesis testing will be performed for making development decisions. Considerations for outcome assessment are described in Appendix 3.

Imaging and diagnostic performance analyses will be analyzed using graphical methods and descriptive statistics.





11.5 Safety Analyses

The safety analyses will be assessed in the Safety Population.

Adverse events, vital signs, ECGs, and conventional clinical laboratory data (CMP and CBC with differentials) will be summarized using descriptive statistics.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.1. The incidence of TEAEs will be presented by system organ class and preferred term, by relationship to study drug, by severity, and by whether or not they resulted in alteration of administration of or discontinuation of study drug. A TEAE is defined as an AE that occurs during or after study drug administration and up through 28 days (±48 hours) in Part 1 or 28 days (±5 days) in Part 2 after administration of study drug. In addition, the incidence of SAEs and TEAEs leading to discontinuation of study drug will be presented by system organ class, preferred term, and relationship to study drug.

Descriptive statistics for clinical laboratory test results and vital signs, and for changes from Baseline, will be presented by time point. Baseline is defined as the measurement closest to, but before, the administration of study drug. Incidences of potentially clinically meaningful clinical laboratory results and vital signs, determined based on normal ranges and percentage changes from Baseline, will also be summarized by time point. The number and percentage of abnormal ECGs will be provided by time point.

11.6 Pharmacokinetic Analyses

The PK analyses will be assessed in the Pharmacokinetic Population.

Plasma concentration-time profiles will be constructed for each patient and each dosing cohort. Plasma concentration values will be summarized at each time point using mean, standard deviation, median, and range.

Summary PK parameters will be summarized using mean, standard deviation, median, and range.

11.7 Determination of Study Sample Size

11.8 Handling of Dropouts and Missing, Unused, and Spurious Data

All data will be analyzed. Data identified as spurious will be treated as missing unless they can be definitively corrected.

The incidence of missing data is expected to be quite low due to the structure of the trial. Therefore, complete case analysis will be performed. Sensitivity analysis will be performed to assess the potential impact of any missing data on trial results.

11.9 Termination Criteria

Enrollment and withdrawals from the study and from study drug will be summarized.

11.10 Deviation Reporting

Protocol deviations will be summarized. Protocol deviations are defined as any variation from the protocol, including enrollment of a patient who did not meet all inclusion and exclusion criteria and failure to perform the assessments and procedures within the required time frame.

12.0 INVESTIGATOR REQUIREMENTS

12.1 Protocol Adherence

The Investigator must adhere to the protocol as detailed in this document and agree that the Sponsor must approve any change to the protocol before seeking approval from the IRB/IEC. The Investigator will be responsible for enrolling only those patients who have met the protocol inclusion and exclusion criteria.

12.2 Electronic Case Report Forms

The eCRF will be supplied by the contract research organization or designee for the recording of all information and study data as specified by this protocol. All eCRFs must be completed by trained study personnel. The Investigator is responsible for ensuring that the eCRF data are entered and completed in a timely manner.

Once all data queries and issues have been resolved for each patient, the Investigator will electronically sign each patient's eCRF to attest to the accuracy of the data.

12.3 Source Document Maintenance

Source documents are defined as documentation related to original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, study- or patient-specific e-mail correspondence, computer printouts, clinical laboratory data, and recorded data from automated instruments. All source documents produced in this study will be maintained by the Investigator and made available for inspections by the Sponsor and by regulatory authorities. The original signed ICF for each participating patient shall be filed with records kept by the Investigator, and a signed and dated copy will be given to the patient. In all cases, subject confidentiality must be maintained in accordance with local regulatory requirements.

12.4 Study Monitoring Requirements

An authorized Sponsor representative will conduct site visits to inspect study data, patients' medical records, and eCRFs in accordance with ICH guidelines, GCPs, and the foreign regulations and guidelines, as applicable. A monitor will be utilized for monitoring ongoing drug accountability and adherence to protocol procedures.

The Investigator will allow representatives of the Sponsor and regulatory authorities to inspect facilities and records relevant to this study.

12.5 Study Completion

The Sponsor requires the following data and materials before a study can be considered complete or terminated:

- Laboratory findings, clinical data, and all special test results from Screening throughout the study until the Follow-up visit
- eCRFs (including data queries) properly completed by appropriate study personnel and signed and dated by the Investigator
- Copies of complete drug accountability records (drug inventory log and an inventory of returned or destroyed clinical material)
- Copies of protocol amendments and IRB/IEC approval and notification, if appropriate
- A summary of the study prepared by the Investigator (an IRB/IEC summary letter is acceptable)

13.0 QUALITY CONTROL AND QUALITY ASSURANCE

Written standard operating procedures (SOPs) will be followed to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. Quality control will be applied to each stage of data handling. Regular monitoring, as defined in ICH GCP, Section 1.8, "The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s)", will be conducted throughout the conduct of the study.

The purpose of monitoring is to verify that:

- Rights and well-being of the human patients are protected
- The reported study data are accurate, complete, and verifiable from source documents
- The conduct of the study is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirements
- Monitoring is an integral role in the quality control of a clinical trial and is designed to verify the quality of the study

To fulfill the Quality Assurance requirements of GCP, audits will be conducted to assess and assure the reliability and integrity of a study's quality control systems and recognized standards.

The purpose of an audit is to:

- Ensure participant safety
- Assure compliance to study protocol procedures, regulatory requirements, and SOPs
- Assure data quality

14.0 PROTECTION OF HUMAN SUBJECTS

This study will be conducted in compliance with the ICH Technical Requirements for Registration of Pharmaceuticals for Human Use including ICH E6 GCP (2016), the ethical principles of the Declaration of Helsinki (2013), US FDA Code of Federal Regulations Title 21 Food and Drugs (2018), and any additional national or IRB/IEC-required procedures.

14.1 Informed Consent

This study will be conducted in compliance with ICH E6 GCP (2016): Consolidated Guidelines pertaining to informed consent. Patients will give written consent to participate in the study at the first visit, before initiation of any study-related procedures, after having been informed about the nature and purpose of the study, participation and termination conditions, risks, and benefits. If a patient is unable to provide written informed consent, the patient's legally acceptable representative may provide written consent, as approved according to institution-specific guidelines. The ICF must be signed and dated by the patient, or the patient's legally acceptable representative, before study participation. A copy of the ICF must be provided to the patient or the patient's legally acceptable representative. If applicable, it will be provided in certified translation for non-English-speaking patients. Signed ICFs must remain in the patient's study file and be available for verification by Sponsor at any time.

14.2 IRB/IEC Approval

This protocol, the ICF, and all relevant supporting data must be submitted to the IRB/IEC for approval. The protocol, ICF, and any advertisement used to recruit study patients must be approved by the IRB/IEC. Approval by the IRB/IEC of the protocol and ICF must be obtained before the study may be initiated.

The Investigator is responsible for informing the IRB/IEC of any changes made to the protocol, and to advise them, at least once a year, about the progress of the study. The Investigator is also responsible for notifying the IRB/IEC of any significant TEAEs that occur during the study.

15.0 DATA HANDLING AND RECORD KEEPING

Training sessions, regular monitoring of Investigators by Sponsor-designated personnel, instruction manuals, data verification, crosschecking, and data audits will be performed to ensure quality of all study data. Investigator meetings will be performed to prepare Investigators and other study personnel for appropriate collection of study data.

The Sponsor will review and validate study data as defined in the monitoring plan.

It will be the responsibility of the Investigator to ensure that the essential documents are available at the Investigator or institutional site. Any or all of these documents may be pertinent to, and should be available for, monitoring by the Sponsor or inspection by the regulatory authorities as defined in the monitoring plan.

15.1 Direct Access to Source Data/Documentation

The Investigator agrees by his/her participation that the results of this study may be used for submission to national or international registration. If required, these authorities will be provided with the name of the Investigator and his or her address, qualifications, and extent of involvement. It is understood that the Investigator is required to provide Sponsor with all study data, complete reports, and access to all study records.

Data generated by this study must be available for inspection by any regulatory authorities, by Sponsor and by the IRB/IEC as appropriate. At a patient's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare. Medical information obtained from patients during the course of this study is confidential and disclosure to third parties other than those noted above is prohibited.

15.2 Study Drug Accountability

15.3 Retention of Records

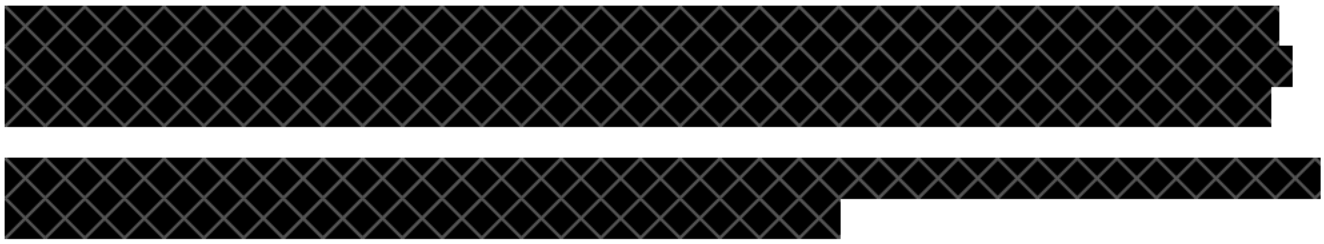
Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product and shipment and delivery of the drug for investigational use is discontinued. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements of specific ICH and non-ICH countries, or by an agreement with the Sponsor. The Sponsor will inform the Investigator/institution as to when these documents no longer need to be retained.

16.0 FINANCING AND INSURANCE

The financing and insurance for this study are outlined in the Clinical Trial Agreement.

17.0 PUBLICATION POLICY

18.0 REFERENCES



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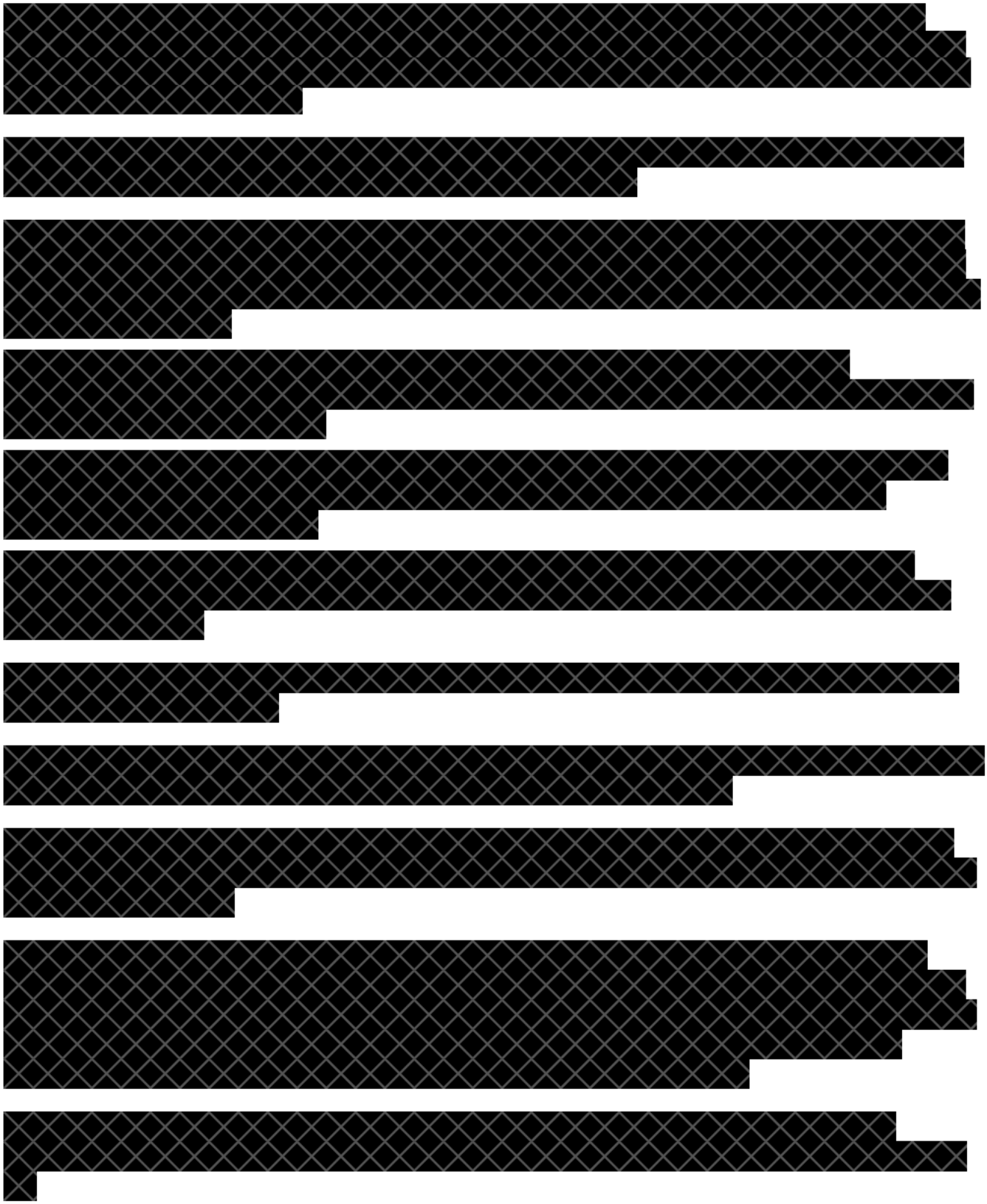

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19.0 APPENDICES

APPENDIX 1: KARNOFSKY PERFORMANCE STATUS SCALE

Karnofsky Status	Karnofsky Grade
Normal, no complaints	100
Able to carry on normal activities. Minor signs or symptoms of disease	90
Normal activity with effort	80
Care for self. Unable to carry on normal activity or to do active work	70
Requires occasional assistance, but able to care for most of his needs	60
Requires considerable assistance and frequent medical care	50
Disabled. Requires special care and assistance	40
Severely disabled. Hospitalization indicated though death nonimminent	30
Very sick. Hospitalization necessary. Active supportive treatment necessary	20
Moribund	10
Dead	0

APPENDIX 2: CHILD-PUGH SCORE

The Child-Pugh score employs 5 clinical measures of liver disease. Each measure is scored 1 to 3, with 1 indicating the least severe and 3 indicating the most severe score. The sum of the 5 measures is the total Child-Pugh point score.

Parameter	Points		
	1	**2**	**3**
Ascites	None	Medically controlled	Poorly controlled
Encephalopathy [a]	None	Medically controlled	Poorly controlled
Total bilirubin (mg/dL)	<2	2 – 3	>3
Albumin (g/dL)	>3.5	2.8 – 3.5	<2.8
International Normalized Ratio OR PT prolongation in seconds	<1.7 <4	1.7 – 2.3 4 – 6	>2.3 >6

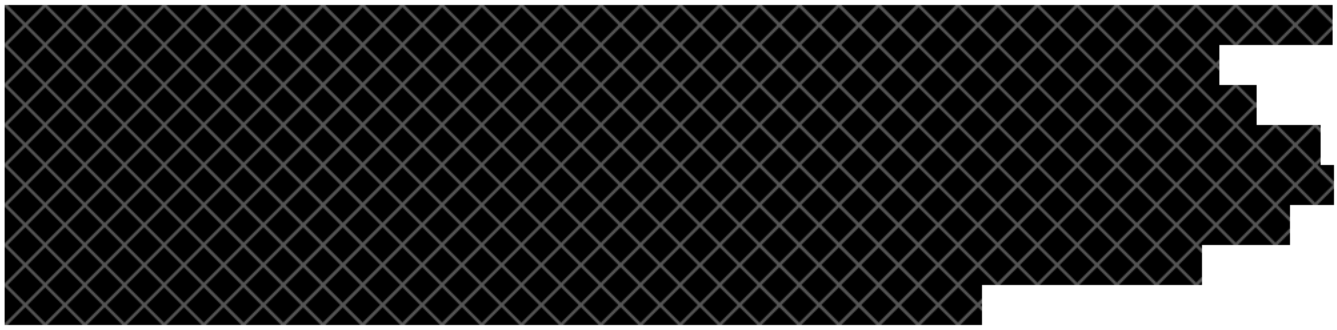
a. If sedated, use last known encephalopathy status before sedation.

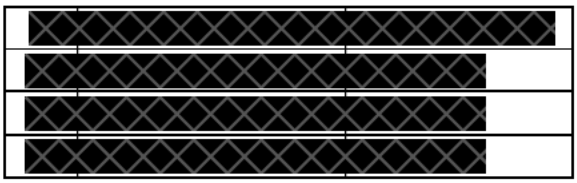
APPENDIX 3: CONSIDERATIONS FOR OUTCOME ASSESSMENT

[redacted]

Sample size considerations

[redacted]





APPENDIX 4: INVESTIGATOR AND SPONSOR SIGNATURES

By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board/Ethics Committee procedures, instructions from OncoNano Medicine Inc. representatives, the Declaration of Helsinki, International Council on Harmonization Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

INVESTIGATOR SIGNATURE:

_____ _____

Investigator Signature [redacted]

_____

Investigator Printed Name

_____

Site Name

_____

Site Address

SPONSOR SIGNATURE:

[redacted]

Sponsor Signatu[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]