1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E7766-G000-101
Study Protocol Title:	An Open-Label, Multicenter Phase 1/1b Study of **In**tratumorally Administered **ST**ING Agonist E7766 in Subjects With **A**dvanced Solid Tumors or **L**ymphomas – **INSTAL-101**
Sponsor:	Eisai Inc. 155 Tice Boulevard Woodcliff Lake, New Jersey 07677, US H3 Biomedicine Inc. 300 Technology Square, FL 5, Cambridge, Massachusetts, 02139, US
Investigational Product Name:	E7766
Indication:	Advanced Solid Tumors or Lymphomas
Phase:	1/1b
Approval Date(s):	Original Protocol 21 June 2019 Amendment 01 19 Aug 2019 Amendment 02 04 Dec 2019
IND Number:	137834
EudraCT Number:	2019-000160-17
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of the sponsors. Any viewing or disclosure of such information that is not authorized in writing by the sponsors is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

REVISION HISTORY

Amendment 02

Date: 04 Dec 2019

Change	Rationale	Affected Protocol Sections
Safety pharmacology and toxicology section was updated to include additional data.	Updated for completeness and consistency with the Global Investigator's Brochure and as per Medicines and Healthcare products Regulatory Agency (MHRA) request.	• Section 7.1.3.3
Clarified that subjects with prior immunotherapy known to have experienced severe nontolerable toxicities attributed to drug should be excluded.	The text was updated as per France Ethics Committee request.	• Synopsis: Inclusion Criterion #6 • Section 9.3.1: Inclusion Criterion #6
For Inclusion criterion#9, it was clarified that subjects with prior Hepatitis B or Hepatitis C are eligible if they have adequate liver function as described in Inclusion Criterion #13. The additional wording "Exclusion criteria#4" was removed from "Inclusion criterion#9" to avoid confusion. Participants with active Hepatitis B or Hepatitis C infection will be excluded and participants who had prior Hepatitis B or Hepatitis C infection which is inactive at the time of screening and with normal liver function are eligible to the study.	The text was updated for further clarity.	• Synopsis: Inclusion Criterion #9 • Section 9.3.1: Inclusion Criterion #9
Additional guidance was added in the protocol for selection of lesions for intratumoral E7766 injection to minimize risk of hemorrhage and inadvertent risk of intravascular systemic injection. Also, recommendations for administering local analgesic (ie, at the site of injection) with or without systemic analgesic prior to initiation of the intratumoral injection, have been added to the protocol.	Further guidance was added for clarity and as per MHRA and France Ethics Committee request.	• Synopsis: Study Treatments • Section 9.4.1.3
Additional pregnancy testing added on Day 1 of all cycles, ie, every 3 weeks (Q3W).	The change has been made per France health authority (ANSM) request.	• Section 9.5.2.1, Table 7, footnote f

Amendment 01 **Date: 19 Aug 2019**		
Change	**Rationale**	**Affected Protocol Sections**
Additional dose limiting toxicity criteria were added as follows: -Any death not clearly due to the underlying disease or extraneous causes -For patients with hepatic metastases, AST or ALT >8×ULN, or AST or ALT >5×ULN for ≥14 days -Hy's Law cases Removal from DLT exceptions of 'any laboratory abnormalities that are not clinically significant per investigator assessment'.	The change has been made per FDA requirement.	• Synopsis - Study Design • Section 9.1.1.2
Treatment is not allowed beyond confirmed disease progression per iRECIST or LYRIC.	The change has been made per FDA requirement.	• Synopsis – Study Treatment, Duration of treatment • Section 9.4.1.5 (deleted) • Appendix 2 (Appendix Table 2)
Selection of recommended Phase 2 dose (RP2D) was updated to state that although decisions regarding dose escalation will be made based on review of data from Cycle 1, late immune-related observed toxicities occurring after Cycle 1 (DLT period) and up to 90 days after last dose of E7766, will also be used to inform corrections to the MTD and aid selection of the RP2D.	The change has been made per FDA requirement.	• Synopsis: Study Design - Definition of DLT, Selection of RP2D; Statistical methods • Section 9.1.1.1 • Section 9.7.4.1
Clarified that investigators and sponsors will together conduct the evaluation and the recommended Phase 2 dose/doses and/or any modification to the dosing regimen will be agreed upon jointly.	The change has been made per FDA requirement	• Synopsis: Study design, Selection of RP2D • Section 9.1.1.3
Selection criterion for exclusion of subjects with prolongation of corrected QT interval (using Fridericia's correction factor) (QTcF) >480 msec was revised to exclude male and female subjects with prolongation >450 msec	The change has been made per FDA and other health authority requirements. QTcF is clarified for consistency with the safety assessments section.	• Synopsis: Exclusion Criterion 8 • Section 9.3.2, Exclusion Criterion 8

AE and concomitant medications collection period was increased to 90 days after last dose of study treatment from 30 days. If the subject initiates new anticancer therapy within 30 days, then AEs and concomitant medications should be collected for 30 days following the last dose of E7766. Definition for treatment-emergent adverse event (TEAE) was also updated to align with the above change.	The change has been made per FDA requirement to monitor all patients for approximately 90 days after treatment discontinuation for late immune-related toxicities that have been associated with immunotherapy products.	• Synopsis: Study design • Section 9.4.7 • Section 9.5.2.1: Table 7 (footnote w) • Section 9.5.1.5.1 • Section 9.5.4.1 • Section 9.7.1.5 • Section 9.7.1.8.2
Reporting period for SAEs was updated to 90 days after last dose of study treatment (previously 30 days after last dose). If the subject initiates new anticancer therapy within 30 days, then SAEs should be collected for 30 days following the last dose of E7766.	The change was made due to changes in AE collection period.	• Section 9.5.1.5.1 • Section 9.5.4.1

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E7766

Name of Active Ingredient: (1*R*,3*R*,15*E*,28*R*,29*R*,30*R*,31*R*,34*R*,36*R*,39*S*,41*R*)-29,41-Difluoro-34,39-bis(sulfanyl)-2,33,35,38,40,42-hexaoxa-4,6,9,11,13,18,20,22,25,27-decaaza-34λ^5,39λ^5-diphosphaoctacyclo [28.6.4.$1^{3,36}$.$1^{28,31}$.$0^{4,8}$.$0^{7,12}$.$0^{19,24}$.$0^{23,27}$]dotetraconta-5,7,9,11,15,19,21,23,25-nonaene-34,39-dione diammonia

Study Protocol Title

An Open-Label, Multicenter Phase 1/1b Study of **In**tratumorally Administered **ST**ING Agonist E7766 in Subjects With **A**dvanced Solid Tumors or **L**ymphomas – **INSTAL-101**

Investigators

Multiple investigators

Sites

Approximately 4 sites globally for Dose Escalation part, additional sites planned for Dose Expansion part.

Study Period and Phase of Development

Total study period: Approximately 36 months

Phase 1/1b

Objectives

Primary objectives

Dose Escalation part

- Assess the safety/tolerability profile of E7766 administered intratumorally in subjects with advanced solid tumors or lymphomas
- Determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of E7766 in subjects with advanced solid tumors or lymphomas

Dose Expansion part

- Assess the safety/tolerability profile of E7766 administered intratumorally in cohorts of subjects with selected tumor types
- Assess clinical activity of E7766 based on investigator assessment of objective response rate (ORR), duration of response (DOR), and disease control rate (DCR) according to modified Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 and modified RECIST 1.1 for immune-based therapeutics (iRECIST) for solid tumors, and for lymphoma (if included in Dose Expansion part), lymphoma response according to Lugano and LYmphoma Response to Immunomodulatory Therapy Criteria (LYRIC) criteria, in cohorts of subjects with selected tumor types

Secondary objectives

Dose Escalation part

- Evaluate preliminary clinical activity of E7766 based on investigator assessment of ORR, DOR, and DCR according to modified RECIST 1.1 and iRECIST for solid tumors, and Lugano and LYRIC criteria for lymphoma

- Evaluate the pharmacokinetic (PK) profile of E7766 and any metabolites in plasma, urine, and feces

Dose Escalation and Dose Expansion parts

- Evaluate the PK profile of E7766 and any metabolites in plasma
- Evaluate progression-free survival (PFS) based on investigator assessment and overall survival (OS) in subjects treated with E7766
- Evaluate tumor size changes per investigator assessment in injected lesions and in non-injected lesions

Exploratory Objectives

Dose Escalation and Dose Expansion parts

- Evaluate changes in tumor size assessed by independent imaging review (IIR) using volumetric computed tomography (CT)/magnetic resonance imaging (MRI)
- Evaluate immune pharmacodynamics effects of E7766 in the tumors and in peripheral blood
- Explore PK/pharmacodynamics relationships (safety and efficacy endpoints)
- Explore correlation of baseline tumor and peripheral blood immune phenotypes and of STING genotypes with safety and/or efficacy endpoints
- Evaluate pre-injection changes in size of injected lesion per investigator assessment in addition to the scheduled tumor assessments to characterize the kinetics of response, progression, or immune-induced flare in the injected lesion.

Study Design

This is an open label, multicenter, Phase 1/1b study to assess the safety and evaluate the clinical activity of E7766 administered intratumorally to subjects with advanced solid tumors or lymphomas. The study is a first-in-human (FIH) study for intratumoral administration route of E7766. A Dose Escalation part will enable selection of a dose of E7766 to move forward with as the RP2D in the Dose Expansion part, where clinical activity in selected tumor types or populations will also be evaluated.

Dose escalation will be conducted using an improved modified toxicity probability interval (mTPI) design (Guo, et al., 2017; Yan, et al., 2017) to determine the MTD for E7766. Each subject will be assessed for tumor response (injected and non-injected lesions), PK, and pharmacodynamics (blood and tumor factors). The RP2D will be selected based on integrating results of safety (including the MTD), clinical activity, PK, and pharmacodynamics. During the Dose Escalation part, selected dose level cohorts may accrue additional subjects to provide further safety, drug administration-related, biomarker, and/or PK data needed for selection of the RP2D. Intrapatient dose escalation of study drug will be allowed in the study.

The Dose Expansion part will be initiated when the RP2D and/or MTD is available from the Dose Escalation part. In the Dose Expansion part, separate study arms will evaluate E7766 at the RP2D in selected tumor types and populations to confirm safety and assess clinical activity. The study populations will be decided based on the emerging data from the Dose Escalation part.

The overall study design is shown in Figure "Study Schematic for Dose Escalation and Dose Expansion parts."

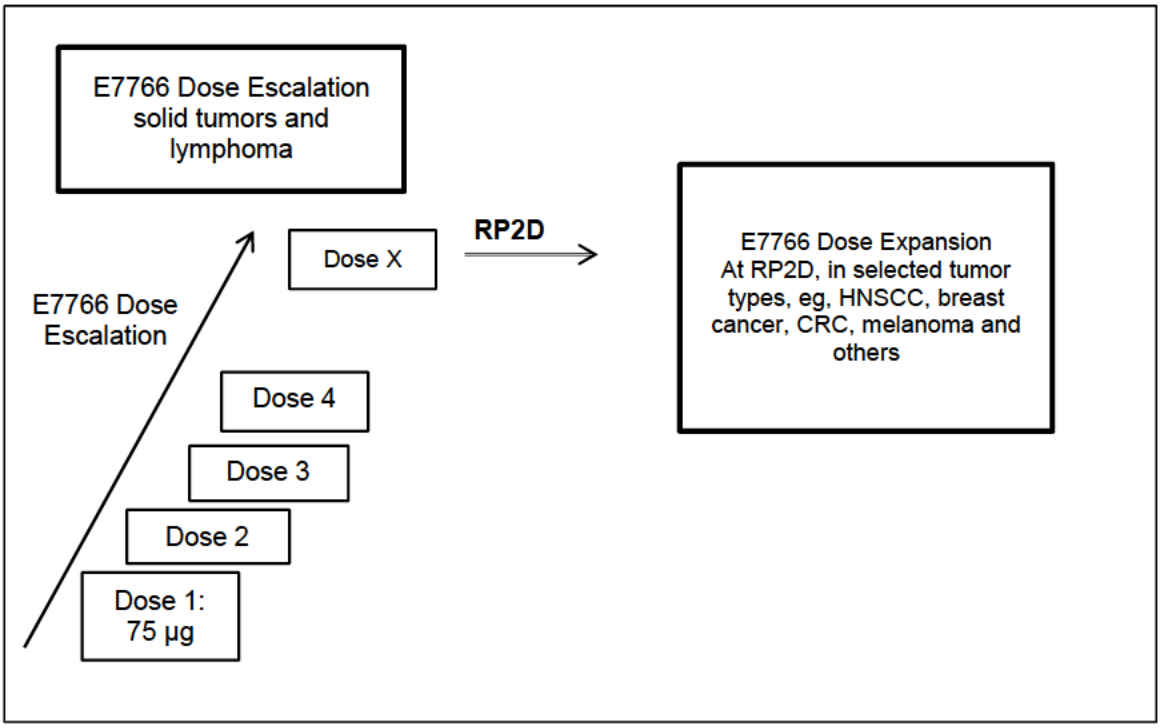
A fixed E7766 dose will be administered for each subject. There should be at least 7 days between initiating treatment of the first and second subject in each new dose escalation cohort. There will be no adjustments for subject weight. Detailed instructions for intratumoral injection of E7766 are provided under "Study Treatment."

E7766 will be administered in cycles which are 3-weeks long, with treatment as follows:

- Induction (Cycle 1): injection on Days 1, 8, and 15
- Maintenance (Cycle 2 and after): injection on Day 1 of each cycle, once in 3 weeks (Q3W).

Systemic E7766 drug levels will be measured after intratumoral injection.

Pharmacodynamic assessments will include evaluation of drug target-mediated immune pathway activation by gene expression profiling, immunohistochemistry or other appropriate methodologies in the injected tumor as well as in non-injected lesions. Pre- and posttreatment tumor biopsies will be required for the injected lesion and, if available, from one non-injected lesion (which will be predefined). Refer to Appendix 1 for further guidance. Changes in frequency, differentiation and activation status of intratumoral immune cell populations will be evaluated as well. In addition, the effect of E7766 on systemic levels of cytokines and immune cell phenotypes reflective of innate and adaptive immune activation will be assessed.



CRC = colorectal cancer, HNSCC = head and neck squamous cell carcinoma, RP2D = recommended Phase 2 dose.

Figure: Study Schematic for Dose Escalation and Dose Expansion Parts

DOSE ESCALATION

E7766 Dose Escalation

Dose assignment of subjects will be done using the improved mTPI design in order to determine the MTD of E7766. Each subject will be assigned a dose in accordance with the rules of the improved mTPI design based on a target dose-limiting toxicity (DLT) rate of 25% and its equivalence interval (EI) of 20% to 30%.

The dose assignment decision rule is pre-tabulated in the Table "Decision Rule for Dose Assignment." Two subjects will be enrolled for each tested dose level, and recruitment to the dose level will be expanded as required as described in the Table "Decision Rule for Dose Assignment." Based on the number of subjects with DLTs in each dose level, dose assignment for the next dose will be determined according to the Table "Method for Deciding the Dose of the Next Dose Group" after consultation between the investigators and the sponsor. For the lowest dose, extra subjects may be added if a DLT develops in 1 of the 2 subjects, if deemed appropriate. Subjects who are not evaluable for DLT (eg, those subjects who fail to complete at least 2 E7766 injections during Cycle 1 for reasons other than DLT occurrence) should be replaced within their dose level, if at least 2 subjects in total have not been tested at the dose level. Subject enrollment will be closed when the DLT rate at the lowest dose level greatly exceeds the target DLT rate (25%) or when the RP2D has been determined.

Additional details of the improved mTPI design are in the statistical section.

Decision Rule for Dose Assignment

		Number of Subjects Treated at Current Dose					
		2	**4**	**6**	**8**	**10**	**12**
Number of Subjects With DLTs	**0**	E	E	E	E	E	E
	1	D[a]	S	E	E	E	E
	2	D, U	D	D	S	S	E
	3		D, U	D	D	D	S
	4		D, U	D, U	D, U	D	D
	5			D, U	D, U	D, U	D
	≥6			D, U	D, U	D, U	D, U

Target DLT rate at MTD = 25% and its equivalence interval = 20% to 30%, Cohort size = 2 subjects.
Display for more than 12 subjects at the current dose is omitted. If the required rules are not available in the table, the decision will follow the rule determined by the improved mTPI design with the same settings above.
E = Escalate to the next higher dose, S = Stay at the current dose, D = De-escalate to the next lower dose, U = Current dose is unacceptably toxic (ie, Do not re-enter the current dose)
DLT = dose-limiting toxicity, MTD = maximum tolerated dose, mTPI = modified toxicity probability interval.
a: Extra subjects may be added for the lowest dose, for example if the investigators and the sponsor determine that more subjects would be required to adequately evaluate that dose level and it is considered safe to do so.

Subjects will be assigned to a dose level in the order of study entry. There should be at least 7 days between initiating treatment of the first and second subject in each new dose escalation. This would provide enough safety margin in terms of safety evaluation for any acute serious toxicities arising from activation of the immune system, which would generally be expected to occur within the first hours or 1 to 3 days of drug exposure. In cohorts where the dose is de-escalated or re-escalated, a delay in administration of E7766 between the first subject and subsequent subjects in that cohort is not required if the same or a higher dose level has already been investigated in a previous cohort.

The first E7766 dose to be administered to subjects will be 75 µg, which is a calculated pharmacologically active dose (PAD) based on nonclinical studies. The dose of subsequent dose groups will be determined based on the E7766-related adverse events (AEs) that develop in subjects in the prior dose group during 3 weeks of Cycle 1 (see "Method for deciding the dose of the next dose

group"). When escalating or de-escalating the dose to the next dose level according to the improved mTPI design, if there is a higher or lower dose level that has been tested previously, subjects should be enrolled to the previously tested dose and the "Method for deciding the dose of the next dose group" below shall not apply. In addition, intermediate doses can be further added if necessary based on the safety or PK of the previously tested dose. The addition of new dose levels will be decided based on discussions between the investigators and sponsor during dose escalation meetings.

Method for Deciding the Dose of the Next Dose Group

Dose Escalation Steps	E7766-Related Toxicity During Cycle 1
Increase ~75% to 100%	Up to Grade 1
Increase ~30% to 60%	Grade 2 in 1 subject
Increase ~10% to 30%	Grade 2 in 2 or more subjects and/or Grade 3 or higher in 1 or more subject

Intrapatient dose escalation of study drug will be allowed in the study after a minimum of 3 cycles of study therapy at the designated dose and after there is sufficient information to ensure safety at the higher dose. The decision for individual cases, if requested, will be made in agreement between the investigators and the sponsors.

Escalation of the E7766 dose will be achieved based on the concentrations and volumes administered according to the guidance in the table below entitled "Examples of Drug Dilutions and Volumes Administered."

During the Dose Escalation part, selected dose level cohorts may accrue additional subjects to provide additional safety, drug administration-related, biomarker, and/or PK data needed for selection of the RP2D.

Definition of Dose-Limiting Toxicities

DLTs are any of the following toxicities occurring during Cycle 1 and assessed by the investigator as related to study drug (any toxicities considered related to any degree to E7766):

- Clinically significant nonhematologic toxicity ≥ Grade 3 (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v.5.0), except
  - Grade 3 fatigue <5 days.
  - Asymptomatic Grade 3 or 4 laboratory abnormalities that are corrected within 72 hours.
  - ≥ Grade 3 nausea, vomiting, and diarrhea unless lasting >48 hours despite optimal supportive care.
  - Other AEs that per investigator assessment are not dose limiting nor dose related.
- CTCAE Grade 2 nonhematologic toxicities which, in the opinion of the investigator, require a dose reduction or discontinuation of study drug, or lead to the subject's failure to complete at least 2 out of 3 scheduled injections of E7766 in Cycle 1, or be considered intolerable for any other reason by the investigator, may be deemed to be dose-limiting if agreed upon by participating investigators and the sponsors.
- Nonhematologic laboratory findings of Grade ≥3 that were ≤ Grade 1 at baseline with the exception of abnormal Grade 3 laboratory values with no clinical significance that resolve within 7 days (this includes electrolyte abnormalities which respond to medical intervention)
- Hematologic toxicity:
  - Grade 4 neutropenia for >5 days, or febrile neutropenia.

- Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with hemorrhage.

- Any other toxicity assessed as related to E7766 treatment, and which in the opinion of the study investigator(s) and the study medical monitor constitutes a DLT
- A delay of initiating Cycle 2 of 7 days or more due to toxicity.
- Any death not clearly due to the underlying disease or extraneous causes
- For patients with hepatic metastases, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >8×upper limit of normal (ULN), or AST or ALT >5×ULN for ≥14 days.
- For patients with normal ALT and AST and total bilirubin (TBIL) value at baseline: AST or ALT >3.0×ULN combined with TBIL >2.0×ULN without evidence of cholestasis (ALP ≤2×ULN), with no alternative etiology (Hy's law)
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT >2×baseline and >3.0×ULN] OR [AST or ALT >8.0×ULN], whichever is lower, combined with [TBIL >2×baseline AND >2.0×ULN] without evidence of cholestasis (ALP ≤2×ULN)

A subject should have received at least 2 E7766 injections during the DLT period (Cycle 1) to be considered evaluable for a DLT, unless the subject experienced a treatment-related toxicity preventing more than 1 administration of E7766.

If a subject at a given dose level receives fewer than 2 out of 3 planned E7766 intratumoral injections during the Induction cycle (DLT period/Cycle 1) because of E7766-related AEs, the subject should be considered as potentially experiencing a DLT by the Study Safety Committee, composed of investigators and representatives of the sponsor.

A subject experiencing a DLT may continue treatment at a reduced dose if the DLT has resolved and in the opinion of the investigator the subject is benefiting from treatment. In case of recurrence of the DLT at a lower dose, E7766 treatment should be discontinued. Late immune-related toxicities occurring after Cycle 1 (DLT period) and up to 90 days after last dose of E7766, will also be used to inform corrections to the MTD and aid selection of the RP2D.

SELECTION OF THE RP2D

The RP2D of E7766 will be selected based on an integrated evaluation of safety, tolerability, clinical activity, PK data, and any available pharmacodynamics data for all dose levels or all available data according to the following guidelines:

- The RP2D must not exceed the MTD, as defined in the Dose Escalation part.
- Consideration will be given to other toxicities including: AEs assessed as related to study drug treatment but not considered dose limiting, the nature and frequency of toxicities, late immune-related toxicities (up to 90 days after last dose of the study drug), and the emergence of any specific category of toxicities.
- Consideration will be given to the tumor response(s) and antitumor activity.
- Pharmacodynamic demonstration of biologic activity, including but not limited to: activation of STING-mediated immune pathways and modulation of innate and adaptive immune response in the tumors and/or in the peripheral blood such as INFβ, CXCL10, and MCP1.

The investigators and sponsors will together conduct the evaluation, and the recommended Phase 2 dose/doses and/or any modification to the dosing regimen will be agreed upon jointly.

DOSE EXPANSION PART

Expansion arms shall be opened in specific tumor types and populations with treatment at the E7766 RP2D. Prioritized early indications, selected based on the preclinical finding and bioinformatics analysis of The Cancer Genome Atlas (TCGA) database, include melanoma, head and neck squamous cell carcinoma (HNSCC), breast cancer, colorectal cancer, and/or other tumors including lymphomas.

E7766 Expansion Arms

Safety and clinical activity of E7766 at the RP2D will be tested in separate Expansion arms with defined populations potentially including but not limited to: melanoma, HNSCC, breast cancer, colorectal cancer, and/or other tumors including lymphomas. About 40 patients will be recruited in each expansion arm.

Study Phases

There will be 4 phases for each subject in the Dose Escalation part and the Dose Expansion part: Pretreatment Phase, Treatment Phase, Extension Phase, and Follow-Up Phase.

Pretreatment Phase

This phase will last no longer than 28 days and includes:

- A Screening Period to obtain informed consent and establish protocol eligibility
- A Baseline Period to establish disease characteristics before treatment

Treatment Phase

The Treatment Phase will last for 1 treatment cycle of 21 days in the Dose Escalation part. In the Dose Expansion part, the Treatment Phase will last for 6 Cycles.

Extension Phase

In the Extension Phase, subjects who are receiving study drug at the end of the Treatment Phase will continue to receive drug treatment at the same dose, and according to the Dosing Schedule described under "Study Treatment."

In the ***Treatment*** and ***Extension Phases,*** subjects will discontinue study drug at the time of confirmed disease progression (per iRECIST or LYRIC), disappearance or nonavailability of any injectable lesions, development of unacceptable toxicity, subject request, withdrawal of consent, termination of the study program, pregnancy, or investigator decision.

Follow-Up Phase*:* The Follow-Up Phase will begin immediately after the off-treatment assessments have been completed and will continue for up to 2 years or until study subject is deceased, or until the completion of the primary analysis, whichever is earlier, unless the subject withdraws consent or until the sponsor terminates the study. Information on AEs and concomitant medications will be collected for 90 days after the last dose of study drug or start day of another anticancer therapy, whichever is earlier. If the subject initiates new anticancer therapy within 30 days, then AEs and concomitant medications will be collected for 30 days following the last dose of E7766.

Subjects who discontinue study treatment before disease progression will continue to undergo disease assessment every 6 weeks in case of solid tumors and 12 weeks in case of lymphomas until documentation of disease progression or start of another anticancer therapy.

Subjects will be followed every 12 weeks (±1week) for survival, performance status and subsequent anticancer treatments. The sponsor may decide to terminate survival follow-up anytime during the

Extension Phase or when all subjects have discontinued study treatment. Survival follow-up will be conducted in person or via phone call.

Study Assessments

Safety, tumor assessments, PK, and pharmacodynamic assessments will be performed on every subject; details are described under "Assessments" and in the Schedule of Visits and Procedures.

Number of Subjects

Approximately, 35 to 40 subjects will be enrolled in the Dose Escalation part and 80 subjects in the Dose Expansion part.

Inclusion Criteria

1. Age ≥ 18 years.
2. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
3. Life expectancy ≥12 weeks.
4. Subjects with solid tumors or lymphomas, confirmed by available histopathology records or current biopsy, that are advanced, nonresectable, or recurrent and progressing since last antitumor therapy, and for which no alternative standard therapy exists.
5. Subjects must have a minimum of one injectable lesion which is also accessible for biopsy, and if available, one other measurable lesion also accessible for biopsy.

   An injectable lesion is defined as being measureable (defined below) with a maximum of 3.0 cm longest diameter, accessible for injection as judged by the investigator, and has not been subjected to any prior intratumoral treatment or radiotherapy. Lesions selected for injection must not be too close to a major vessel, as judged by the investigator, and not be associated with increased risk of bleeding, eg, subcapsular liver lesions or hypervascular tumors.

   Measurable lesions are:

   a. Solid tumors: At least 1 lesion of ≥1 cm by longest axial diameter or ≥1.5 cm short axis diameter if a nodal lesion, which is serially measurable according to modified RECIST 1.1 using CT/MRI or photography. Lesions that have had external beam radiotherapy or locoregional therapies such as radiofrequency (RF) ablation must show evidence of progression to be deemed a target lesion (Appendix 2).
   b. Lymphoma: At least 1 lymph node with a longest diameter >1.5 cm or an extranodal lesion with a longest diameter >1.0 cm (Appendix 3).
6. Prior anticancer therapy such as chemotherapy, immunotherapy (eg, tumor vaccine, cytokine, checkpoint inhibitors), or investigational drugs, or any vaccine must have been completed at least 4 weeks before study drug administration, and all AEs must have either returned to baseline or stabilized. Subjects with prior immunotherapy known to have experienced severe nontolerable toxicities attributed to drug should be excluded.
7. Prior definitive radiation therapy must have been completed at least 6 weeks and prior palliative radiotherapy at least 2 weeks before study drug administration. Radiopharmaceuticals (eg, strontium, samarium) must be at least 8 weeks before study drug administration.
8. Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses >10 mg/day prednisone or equivalent) must have been discontinued at least 4 weeks before study drug administration.

9. Subjects with prior Hepatitis B or C are eligible if they have adequate liver function as defined by Inclusion Criterion #13.
10. Left ventricular ejection fraction (LVEF) >50% or within normal limits per institutional practice, on echocardiography or multigated acquisition (MUGA) scan.
11. Adequate renal function defined as serum creatinine <1.5× ULN (or use SI units or calculated creatinine clearance ≥50 mL/min per the Cockcroft and Gault formula) (Appendix 4).
12. Adequate bone marrow function:
    a. Absolute neutrophil count (ANC) $\geq 1000/mm^3$ ($\geq 1.0 \times 10^3/\mu L$)
    b. Platelets $\geq 75{,}000/mm^3$ ($\geq 75 \times 10^9/L$)
    c. Hemoglobin ≥9.0 g/dL
13. Adequate liver function defined by:
    a. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤1.5
    b. Total bilirubin ≤1.5 × ULN except for unconjugated hyperbilirubinemia or Gilbert's syndrome
    c. Alkaline phosphatase (ALP), ALT, and AST ≤3 × ULN (in the case of liver metastasis ≤5 × ULN) unless there are bone metastases. Subjects with ALP values >3 × ULN and known to have bone metastases can be included.
14. Willing and able to comply with all aspects of the protocol.
15. Provide written informed consent prior to any study-specific screening procedures.

Exclusion Criteria

1. Other malignancy active within the previous 2 years except for basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast that has completed curative therapy.
2. Subjects with any active autoimmune disease (Appendix 5) or a documented history of autoimmune disease, except for subjects with vitiligo or resolved childhood asthma/atopy.
3. Known human immunodeficiency virus (HIV) infection.
4. Active infection requiring therapy, including known positive tests for Hepatitis B surface antigen or Hepatitis C ribonucleic acid (RNA).
5. Major surgery within 4 weeks before the first dose of study drug.
6. Concurrent medical condition requiring the use of immunosuppressive medications or immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses >10 mg/day prednisone or equivalent).
7. Brain metastases that are untreated or in the posterior fossa or involve the meninges. Subjects with stable or progressing brain metastases (except in the posterior fossa or involving the meninges) previously treated with brain stereotactic radiotherapy (SRT), whole-brain radiotherapy (WBRT) and/or surgery are allowed as long as the subject is asymptomatic neurologically and does not require immediate local intervention (radiotherapy and/or surgery). In addition, subjects must be off immunosuppressive doses of systemic steroids (>10 mg/day prednisone or equivalent) for at least 4 weeks before study drug administration.

8. Prolongation of corrected QT (QTcF) interval to >450 msec for males and females, when electrolytes balance is normal
9. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months of the first dose of study drug, or cardiac arrhythmia requiring medical treatment (including oral anticoagulation).
10. Subjects on oral anticoagulants including low dose aspirin. To meet eligibility, these subjects can be switched to receive preventive dose of low molecular weight heparin (LMWH). It is recommended that their LMWH treatment is stopped 24 hours before the intratumoral injection and resumed again 24 hours after the injection.
11. Any history of a medical condition or a concomitant medical condition that, in the opinion of the investigator, would compromise the subject's ability to safely complete the study.
12. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
13. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception (total abstinence [if it is their preferred and usual lifestyle], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 180 days after study drug discontinuation. For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide. If currently abstinent, the subject must agree to use a highly effective method as described above if she becomes sexually active during the study period or for 180 days after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 28 days before dosing and must continue to use the same contraceptive during the study and for 180 days after study drug discontinuation.
14. Male subjects who are partners of women of childbearing potential must use a condom and spermicide and their female partners if of childbearing potential must use a highly effective method of contraception (see methods described above in Exclusion Criterion #13) beginning at least 1 menstrual cycle prior to starting study drug(s), throughout the entire study period, and for 180 days after the last dose of study drug, unless the male subjects are totally sexually abstinent or have undergone a successful vasectomy with confirmed azoospermia or unless the female partners have been sterilized surgically or are otherwise proven sterile. No sperm donation is allowed during the study period or for 180 days after study drug discontinuation.
15. Known hypersensitivity to E7766 or any of the excipients or prior therapy with E7766 or any other STING agonist.
16. Use of illegal recreational drugs.
17. Currently enrolled in another clinical study or used any investigational drug or device within

28 days preceding informed consent.

Study Treatments

E7766 is provided as a sterile clear and colorless aqueous solution with 2.5 mg of E7766 in a 1 mL fill volume per vial.

DRUG ADMINISTRATION

A fully equipped and functional crash cart must be available in the unit where a subject is to be administered E7766.

In the Dose Escalation part, on Day 1 of Induction Cycle (ie, first dose only) subjects will remain at the study clinic for at least 30 hours after E7766 administration for monitoring of safety and can be discharged on Day 2 if there are no safety concerns.

Escalation of E7766 dose will be performed based on the concentrations administered according to the guidance in Table below "Examples of Drug Dilutions and Volumes Administered." The recommended injected volume is 1 mL.

For drug administration, E7766 drug product will be diluted with saline to achieve a final volume of 1 mL solution. Some examples of drug volumes and required volumes of normal saline to make up to a final injectable volume of 1 mL of a target drug dose are shown in the following table.

CCI

DOSING SCHEDULES

A fixed E7766 dose will be administered to each subject.

E7766 will be administered in 3-week cycles, with treatment as follows:

- Induction (Cycle 1): Days 1, 8, 15
- Maintenance (Cycle 2 and after): on Day 1 of each cycle, Q3W

CCI

CCI [redacted]

INTRATUMORAL INJECTION

Lesions selected for injection must be at least 1.0 cm for solid tumors and >1.5 cm for lymphoma in the longest diameter, so as to be measureable by RECIST (solid tumors) or Lugano criteria (lymphoma). The maximum size of any injected lesion is 3.0 cm in the longest diameter for both solid tumors and lymphoma. Lymph nodes for injection must be at least 1.5 cm in the short axis for solid tumors and >1.5 cm in the longest diameter for lymphoma.

Investigators will define which lesions are appropriate for E7766 injection. Preference in the initial dose levels will be given to easier to access lesions. Intratumoral injection approaches for lesions that are proximal to major vessels or those deemed to have a risk of bleeding should be discussed in a multidisciplinary setting with regards to safety of the approach in order to avoid a risk of vascular catastrophe and/or inadvertent risk of intravascular systemic injection. Lesions in the vicinity of major vessels with a high risk of bleeding (eg, the common, internal, or external carotid arteries or their branches), or other situations with a risk of vascular catastrophe such as tumor-encased large vessels, subcapsular liver lesions, hypervascular tumors, lesions that have been previously irradiated, lesions with macroscopic intravascular tumor invasion (eg, liver lesions with tumor infiltration into the main portal vein, hepatic vein or vena cava) should be excluded from intratumoral injection. To avoid potential risk of bleeding and systemic exposure, Doppler ultrasound guidance is recommended for intratumoral injections with E7766 to ensure that the injection is not carried out within a vessel (Marabelle, et al., 2018). Lesions selected for injections must not have been subjected to any prior intratumoral therapy.

Local (at site of injection) plus or minus systemic analgesic treatments should be anticipated and are recommended to be initiated at least 30 minutes before undertaking intratumoral injection procedure. Skin analgesia at the site of injection can be administered using topical xylocaine (4%) or other local anaesthetic agents. The options for systemic analgesia are recommended to include the full range of analgesia from paracetamol/acetaminophen to opioids, depending on the precise details of the procedure and the subject's underlying symptoms (Marabelle, et al., 2018).

The same lesion will be injected at each administration. In the event that the injected lesion shrinks and/or is no longer injectable (ie, no longer accessible, not appropriate for injection, or for other reasons), additional lesions may also be considered for injection and the same guidance for injection of these lesions will apply in terms of accessibility, injectability, and follow-up. The sequence of lesion selection for injection should be agreed in advance by the investigator and treating team. If no other injectable lesions are available, treatment will stop.

Additional guidance for direct and ultrasound/CT guided injection will be provided in a separate manual.

DOSE ADJUSTMENTS

E7766 Dose Adjustments

- In the Dose Escalation part, dose adjustments may be allowed at the discretion of the

investigator after discussion with the sponsors. Subject may be allowed to continue study drug at a reduced dose, if this is judged to be in their best interest. E7766 dose reductions and interruptions should be carried out as outlined in "E7766 Dose Reduction and Interruption Instructions."

Guidelines for dose adjustments after Cycle 1

E7766 dose reduction and interruption for subjects who experience therapy-related toxicity (as assessed by the investigator) will be in accordance with the dose modification guidelines described in the "E7766 Dose Reduction and Interruption Instructions."

- Subjects who experience toxicities that could have been qualified as DLTs may, at the discretion of the investigator and after discussion with the sponsor, be allowed to continue study drug at a reduced dose according to these dose modification guidelines, if this is judged to be in their best interest.

For subjects who require dose interruption due to E7766-related toxicity in Cycle 2 or beyond, the treatment may re-start once the toxicity has been resolved to Grade ≤1 or the baseline value according to the Dose Reduction and Interruption Instructions in the table below."

E7766 Dose Reduction and Interruption Instructions

E7766-Related Toxicity[a]	During Therapy	Approximate Dose Adjustment
Grade 1		
All occurrences	Continue E7766 treatment. If CRS, then interrupt E7766 until Grade 0.	Maintain dose level.
Grade 2[b]		
1st occurrence	Interrupt E7766 until resolved to Grade ≤1 or baseline. If CRS, then interrupt E7766 until Grade 0[c].	Maintain dose level. If CRS, consider dose reduction.
2nd occurrence (same toxicity)	Interrupt E7766 until resolved to Grade ≤1 or baseline. If CRS, then interrupt E7766 until Grade 0[c].	Consider reduction by 1 dose level of starting dose, if dose delayed. If CRS, then consider further dose reduction.
3rd occurrence (same toxicity)	Interrupt E7766 until resolved to Grade ≤1 or baseline[c]. If CRS, then discontinue E7766.	Reduce by 1 or 2 dose levels of starting dose, if appropriate.
4th occurrence (same toxicity)	Interrupt E7766 until resolved to Grade ≤1 or baseline[c].	Discuss with sponsors.
Grade 3[b]		
1st occurrence	Interrupt E7766 until resolved to Grade ≤1 or baseline[c]. If CRS, then discontinue E7766.	Reduce by 1 dose level of starting dose
2nd occurrence (same toxicity)	Interrupt E7766 until resolved to Grade ≤1 or baseline[c].	Reduce by 2 dose levels of starting dose
3rd occurrence (same toxicity)	Discontinue E7766 treatment.	Not applicable
Grade 4[d]: Discontinue E7766		

CRS = cytokine release storm.
For grading, see Common Terminology Criteria for Adverse Events (CTCAE v. 5.0)

a: Excluding alopecia, anemia, lymphocytopenia, and asymptomatic neutropenia. Initiate optimal medical management for nausea, vomiting, diarrhea, and/or fever before any E7766 interruption or dose reduction.
b: Applicable only to those Grade 2 toxicities judged by the subject and physician to be intolerable and to all Grade 3 toxicities.
c: Interruption of E7766 treatment for more than 21 days (due to E7766-related toxicities) will require a discussion with the sponsors before treatment can be resumed.
d: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

Management of Cytokine Release Storm

Cytokine release storm (CRS) has been identified as a potential safety risk in immunotherapies, especially drugs that act as agonists for immune activation. A full guidance for identification and management of CRS is provided in the "Management of Cytokine Release Storm and Organ Toxicity" table below. IL-6 levels will be assessed by the site as clinically indicated. For E7766 dose adjustments and interruptions for the management of CRS, refer to "E7766 Dose Reduction and Interruption Instructions." table.

Management of Cytokine Release Storm and Organ Toxicity

CRS Grade (CTCAE)	Sign/Symptom	Management
Grade 1	Fever or Grade 1 organ toxicity	• Acetaminophen and hypothermia blanket as needed for fever • Ibuprofen if fever is not controlled with above; use with caution or avoid if thrombocytopenic • Assess for infection with blood and urine cultures, and chest x-ray • Consider antibiotics and filgrastim (if neutropenic) • IV fluids as needed • Symptomatic management of constitutional symptoms and organ toxicities • Consider IL-6 antagonist[1] for persistent (greater than 3 days) or refractory fever
Grade 2	Hypotension	• IV fluid bolus of 500 – 1,000 mL normal saline; repeat as necessary to maintain SBP greater than 90 mmHg • Consider IL-6 antagonist[1] for hypotension refractory to fluid boluses • If hypotension persists after two fluid boluses and IL-6 antagonist[1], start vasopressors, transfer patient to ICU, and obtain ECHO • In patients at high-risk for severe CRS[2], if hypotension persists after IL-6 antagonist[1], if there are signs of hypoperfusion[3] or if there is rapid deterioration in the opinion of the clinician, may use dexamethasone 10 mg IV every 6 hours • Manage fever and constitutional symptoms as in Grade 1 CRS
	Hypoxia	• Use supplemental oxygen as needed • Use IL-6 antagonist[1] with or without corticosteroids as in hypotension • Manage fever and constitutional symptoms as in Grade 1 CRS
	Grade 2 organ toxicity	• Manage organ toxicity as per standard guidelines • Use IL-6 antagonist[1] with or without corticosteroids as in hypotension

		• Manage fever and constitutional symptoms as in Grade 1 CRS
Grade 3	Hypotension	• IV fluid boluses as needed as in Grade 2 CRS • IL-6 antagonist[1] as in Grade 2 if not administered previously • Use vasopressors as needed • Transfer patient to ICU and obtain ECHO if not performed already • Start dexamethasone 10 mg IV every 6 hours; increase to 20 mg IV every 6 hours if refractory • Manage fever and constitutional symptoms as in Grade 1 CRS
	Hypoxia	• Use supplemental oxygen including high-flow oxygen delivery and noninvasive positive pressure ventilation • Use IL-6 antagonist[1], corticosteroids as above and supportive care
	Grade 3 organ toxicity or Grade 4 increased transaminases	• Manage organ toxicity as per standard guidelines • Use IL-6 antagonist[1], corticosteroids as above and supportive care • Manage fever and constitutional symptoms as in Grade 1 CRS
Grade 4	Hypotension	• IV fluids, IL-6 antagonist[1], vasopressors, and hemodynamic monitoring as in Grade 3 • High-dose methylprednisolone[1] • Manage fever and constitutional symptoms as in Grade 1
	Hypoxia	• Mechanical ventilation • Use IL-6 antagonist[1], high-dose methylprednisolone[1] and supportive care
	Grade 4 organ toxicity, excluding increased transaminases	• Symptomatic management of organ toxicity as per standard guidelines • Use IL-6 antagonist[1], high-dose methylprednisolone[1] and supportive care

CRS = cytokine release storm, CTCAE = Common Terminology Criteria for Adverse Events, ECHO = echocardiogram, ICU = intensive care unit, IL-6 = interleukin 6, IV = intravenous, SBP = systolic blood pressure.

[1] See Appendix 6 for Interleukin-6 Antagonist and Corticosteroid Dosing Tables.

[2] High risk for CRS includes any of the following:

- High tumor burden
- Early onset CRS (less than 3 days from cell infusion)
- Co-morbidities (a score of 3 or greater using the Hematopoietic Cell Transplantation Comorbidity Index; for solid tumor patients – prior solid tumor will not be counted)

[3] Signs of hypoperfusion include:

- Decreased urine output (less than 0.5 mL/kg/hour)
- Lactate greater than or equal to 4 mmol/L, rising lactate, and/or poor lactate clearance (less than 10%) despite adequate fluid resuscitation.

Source: Adapted from MD Anderson Cancer Center CAR cell therapy toxicity assessment and management protocol (Teachey et al., 2016; MD Anderson Cancer Center, 2017).

Duration of Treatment

A subject will remain on study treatment until 1 or more of the following events occur(s):

- Confirmed progressive disease (PD) per iRECIST (iCPD)/LYRIC

  Note: Subjects will be permitted to continue treatment beyond initial modified RECIST 1.1 (or Lugano) defined progression as discussed further in Appendix Table 2

- Disappearance or nonavailability of any injectable lesions
- Unacceptable toxicity
- Subject request
- Withdrawal of consent
- Termination of the study by the sponsors
- Pregnancy
- Investigator decision

Concomitant Drug/Therapy

The following are prohibited:

- Other investigational drugs.
- Other antitumor therapies such as chemotherapy, radiotherapy, antitumor interventions (surgical resection), or antitumor immunotherapy. Palliative radiotherapy may be allowed in up to 2 nontarget lesions upon discussion between investigator and sponsors. Patients may continue the use of bisphosphonates or denosumab for bone disease provided the dose is stable before and during the study and they were started at least 2 weeks prior to study drug. Additionally, cases where these drugs may be indicated should be discussed and agreed upon between investigator and sponsors.
- Systemic steroid therapy or any other form of immunosuppressive therapy. Any such therapy should be stopped at least 7 days prior to the first dose of study treatment. The use of physiologic doses of corticosteroids (up to 10 mg/d of prednisone or equivalent) may be approved after consultation with the sponsors.
- CCI [redacted]

Other restrictions and prohibitions:

- It is recommended that subjects should avoid prolonged exposure to sunlight, and use sunscreens, umbrellas, and protective long sleeved clothing to minimize Sun exposure, pending completion of test to assess E7766's phototoxicity potential.

Assessments

Efficacy Assessments

Solid Tumors

Tumor assessments will be performed based on modified RECIST 1.1 followed by iRECIST, if appropriate. Investigator-determined response assessments will be performed at each assessment time point. All tumor assessment scans and photographs will be sent to an imaging core laboratory designated by the sponsor for quality assessment, tumor lesions volumetric assessment, and archival for potential independent efficacy review.

These tumor assessments will be carried out during the Pretreatment Phase and then every 6 weeks counting from Cycle 1 Day 1 during treatment cycles in both the Treatment and Extension Phases. Similarily, CT scans (with oral and intravenous contrast) of chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to Cycle 1 Day 1), then every 6 weeks (± 7 days) as above, and as indicated clinically. Skin lesions may be considered as target lesions if documented with color photographs with a millimeter ruler in the same plane as the lesion, as nontarget lesions if photographic and measurement documentation is not available, or as

new lesions if they meet the minimum size criteria for a measurable lesion. Subjects with HNSCC must also have head and neck scans performed. Historical standard of care scans that are performed with scanning parameters consistent with the requirements for this protocol within 28 days prior to dosing are acceptable. A pretreatment biopsy will be obtained during the Screening Period (Day -28 to Day -1) from the lesion selected for injection (mandatory) and, from one prespecified non-injected lesion, if available. If the non-injected lesion is not accessible for biopsy, the biopsy may be omitted (Appendix 1).

MRI scans may be used instead of CT scans for head, neck, abdomen and pelvis; however, chest lesions must be assessed using CT. Chest disease may not be followed using chest x-ray. The same method of assessment used at Screening must be used at all subsequent time points.

For subjects with triple-negative breast cancer (TNBC) and non-small-cell lung carcinoma (NSCLC), or other tumor types where bone metastases are common, bone scans will be performed at Screening, every 24 weeks, or sooner if clinically indicated, and at confirmation of response. Lesions identified on bone scans must be verified with correlative cross-sectional imaging. Cross sectional imaging will be used to follow response in target and nontarget lesions.

A brain MRI (pre- and post-gadolinium contrast) must be performed at Screening to assess potential central nervous system (CNS) disease and/or metastases. For subjects with protocol-eligible treated brain metastases, a brain scan must be performed at all tumor assessment time points. For all subjects, a follow-up brain scan must be performed to confirm a complete response (CR) within 1 week following response confirmation, or if clinically indicated.

Responses should be confirmed no less than 4 weeks following the initial response (generally at the next 6 weekly scheduled tumor assessment visit).

Tumor assessments should initially proceed according to modified RECIST 1.1. Tumor assessments per modified RECIST 1.1 will follow Eisenhauer, et al (2009); however, up to 10 target lesions, up to 5 per organ, may be selected (as opposed to a maximum of 5 target lesions, up to 2 per organ).

Per iRECIST, disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of progressive disease in clinically stable subjects. Subjects who have unconfirmed disease progression per iRECIST (iUPD) may continue on treatment at the discretion of the investigator until progression is confirmed by the site, provided they have met the following conditions.

When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules (Appendix 2). This allowance to continue treatment despite initial radiologic progressive disease takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. These data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Subjects who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging

if it is scheduled less than 4 weeks later; tumor imaging should resume at the subsequent scheduled imaging time point, if clinically stable. Subjects who have confirmed disease progression by iRECIST or LYRIC, as assessed by the site, will discontinue study treatment. Exceptions may be discussed with the study medical monitor.

Subjects going off study without disease progression will also undergo tumor assessments every 6 weeks until disease progression is documented or another anticancer therapy is initiated.

Lymphoma

Tumor assessments will be performed based on Lugano (Cheson, et al, 2014) followed by LYRIC criteria (Cheson, et al., 2016) for confirmation of disease progression (Appendix 3). Investigator-determined response assessments will be performed at each assessment time point.

Tumor assessments will be carried out during the Pretreatment Phase, at Week 9 (during the 9th week counting from Cycle 1 Day 1), and then every 12 weeks during treatment cycles in both the Treatment Phase and the Extension Phase. ^{18}Fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET)-CT (PET-CT) scans (contrast-enhanced diagnostic quality CT) of neck, chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to Cycle 1 Day 1), using the above tumor assessment schedule, and as indicated clinically. While diagnostic quality contrast-enhanced PET-CT is preferred, if contrast-enhanced images are not obtainable, noncontrast PET-CT will be acceptable. Historical standard of care scans that are performed with scanning parameters consistent with the requirements for this protocol within 28 days prior to dosing are acceptable.

Tumor assessments should initially proceed according to Lugano criteria.

If the investigator believes that, at the time of Lugano progressive disease, a subject is experiencing clinical stability or improvement, they will be considered as having an immune response (IR), and continue to be followed according to LYRIC criteria. The subject must be considered likely to tolerate continued treatment and not at risk of serious complications should further tumor growth occur. For a subject categorized as having IR, repeat imaging is mandatory after an additional 12 weeks (or sooner if clinically indicated) to assess whether they have true progressive disease.

All subjects

In additional to the individual lesion measurement data that will be collected for all lesions, the specific lesion injected at each time point/dose administration should be recorded. In addition, lesions that are biopsied should be recorded as such (at the time point) to allow evaluation of exploratory efficacy endpoints such as the effect on injected versus non-injected lesions.

Pharmacokinetic Assessments

Samples of blood, urine, and feces for PK analyses will be collected as described in the Schedule of Procedures/Assessments.

Blood, urine, and fecal samples may also be used for exploratory analysis of metabolites and pharmacodynamic assessments.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Pharmacodynamic Assessment

Pharmacodynamics biomarkers of E7766 include Proof of Mechanism (POM) biomarkers and Proof of Principle (POP) biomarkers, which will be measured to evaluate modulation of the STING

pathway and of both innate and adaptive immune response, respectively, by E7766 treatment in human patients. To measure the STING pathway modulation, expression of a specific panel of STING pathway genes by E7766 identified from preclinical studies will be examined in the tumor biopsies and in the blood. To measure the innate and adaptive immune response, immune gene profiling will be performed for the available tumor biopsies and in blood. Immune cytokines and immune cell phenotyping may be analyzed in the blood as well. Results from the pharmacodynamics biomarker studies may be used to aid the selection for the RP2D and to monitor drug biological activity. Blood and tumor tissue samples will be collected from study subjects at protocol-specified time points as indicated in the Schedule of Procedures/Assessments. It is worthwhile to note that when new research results emerge, the parameters and methods for the pharmacodynamics biomarker analysis may change.

Biomarker Sample Collection:

Mandatory paired pre- and on-treatment tumor biopsies will be obtained from injected lesions and one predefined non-injected lesion (if available), with appropriate subject consent, to examine the potential intratumoral STING pathway modulation and antitumor immune response enhancement upon E7766 treatment at both local and systemic levels. CCI [redacted] Subjects should have the biopsy with the same image-guided procedure as E7766 injection. The on-treatment biopsy should be performed after the E7766 injection. In the event that E7766 administration is delayed, the biopsy time will be moved as well, to coincide with drug administration.

Blood biomarker samples from study subjects may be analyzed for immune cytokine expression monitoring by ELISA, multiplex bead-based immunoassay, or other assays/methods and new technology. Whole blood (peripheral blood mononuclear cell [PBMC]) may be subjected to immune gene expression profiling and flow cytometric analysis as well. Blood biomarker samples will be collected both prior the first administration and during the treatment process.

Archived, fixed tumor tissue will be collected (if available). These tissues may be used for assessment of mutations and other genetic alterations or immune cell infiltration status and their relationship with tumor response to E7766.

In the event that a subject is required to have additional tumor biopsy(s) for medically indicated reasons while on study, formalin-fixed paraffin embedded (FFPE) tissue will be requested for shipment for exploratory biomarker analysis.

<u>Exploratory Imaging Biomarkers</u>

Tumor volume (3-dimensional size as opposed to measuring a single diameter) changes (per independent imaging review) as assessed using all CT/MRI scans will also be explored as a continuous variable.

Time course changes in pre-injection sizes of injected lesions per investigator assessment will be evaluated.

<u>Pharmacogenetic (PG) Assessment</u>

Whole blood DNA and RNA samples (and optionally archived fixed tumor tissues) will be collected

for STING genotype and gene expression analyses, respectively. The DNA samples may be used also for PG analysis. The role of DNA sequence variability on the absorption, distribution, metabolism, and elimination (ADME) of E7766 may be evaluated in this study. Variation in E7766 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or pharmacodynamics data.

Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual.

Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all CTCAE 5.0 AEs (for both increasing and decreasing severity), and serious adverse events (SAEs); regular laboratory evaluation for hematology, blood chemistry, and urine values; and periodic measurement of vital signs, echocardiograms/MUGA scans, safety ECGs, and physical examinations.

Additionally, QTc intervals will be evaluated in the Dose Escalation part only, unless a signal indicates the need for continued monitoring in the Dose Expansion part. The effects of E7766 on cardiac repolarization will be evaluated via 24-hour, 12-lead continuous Holter/ECG monitoring during Baseline, Cycle 1 Day 1, Cycle 1 Day 14, and Cycle 1 Day 15 of the Dose Escalation part of the study only. Replicate 12-lead ECGs will be extracted from the Holter recordings at specified time points and will be evaluated by a central laboratory. QT intervals will be measured from Lead II and will be corrected for QTc using Fridericia's correction factor (QTcF). The primary QTc parameter will be QTcF. Secondary parameters (heart rate, PR interval and QRS) and treatment emergent T wave abnormalities and U-waves will be evaluated. Potential effects of E7766 will be evaluated as change-from predose baseline heart rate, PR interval, QRS and QTcF by postdosing time point. For purposes of QT assessment, exposure response analysis will be performed of the relationship between E7766 plasma levels and ΔQTcF.

In preclinical studies, intratumorally or subcutaneously administered E7766 upregulated expression of certain cytokines in the blood suggesting a possibility of inducing CRS in patients who will receive E7766 treatment. In case a CRS-like symptom occurs, tocilizumab (anti-IL6R) and standard practice by clinical sites may be given to the subjects according to the "Management of Cytokine Release Storm and Organ Toxicity" table shown above.

Bioanalytical Methods

E7766 in plasma, urine, and feces will be determined using validated liquid chromatography–mass spectrometry (LC-MS/MS) assays. If appropriate, assay of plasma, urine, and fecal samples for any metabolites of E7766 may be explored.

Gene expression, cytokine expression, immune cell phenotyping, and intratumoral cell phenotyping will be measured using qualified assays and appropriate technologies.

Statistical Methods

Improved Modified Toxicity Probability Interval Design in Dose Escalation Part

The improved mTPI design, which uses a Bayesian statistical framework and a beta-binomial hierarchical model, will be employed to determine the MTD and/or RP2D of E7766.

Decision rules for dose assignment will be based on the improved mTPI design with the target DLT rate of 25% and its EI of 20% to 30%, and a set of equal-width intervals as EI below/above EI (ie, below EI: 0% to 10%, 10% to 20%; above EI: 30% to 40%, ... , 90% to 100%). The posterior

probabilities of each interval will be calculated with non-informative beta prior distribution Beta (1, 1). The location of the interval with the largest posterior probability – below EI, EI, or above EI – guides the decision for the next dose level to be assigned, ie, Dose Escalation (E), Staying at the current dose (S), or dose De-escalation (D), respectively. This dose assignment rule minimizes the posterior expected penalty in the Bayes' rule under a decision-theoretic framework with the equal prior expected penalties for E, S, and D. The entire dose assignment decision rule can be pre-tabulated as presented above.

The subject enrollment will be closed when the lowest dose has a >95% posterior probability of being above the target DLT rate of 25% (ie, an unacceptable DLT rate beyond the target DLT rate) or when the RP2D has been determined.

MTD is defined as the dose with the smallest difference between the target DLT rate of 25% and an estimate of DLT rate at each dose among all the tested doses with a ≤95% posterior probability of being above target DLT rate of 25%. The isotonically transformed posterior mean under the beta posterior distribution with non-informative beta prior distribution Beta (0.005, 0.005) will be used to determine the estimate of DLT rates at each dose. The pooled adjacent violators algorithm (PAVA) will be used to maintain monotonically the increase of DLT rate with increasing dose level. Late immune-related toxicities occurring after Cycle 1 (DLT period) and up to 90 days after last dose of E7766, will also be used to inform any corrections to the MTD and aid selection of the RP2D.

Primary Endpoints:

- Safety-related endpoints, including DLT
- ORR according to modified RECIST 1.1 and iRECIST, or Lugano and LYRIC, defined as the proportion of subjects achieving a best overall response of confirmed partial or complete response (PR + CR). Subjects who do not have a tumor response assessment for any reason will be considered nonresponders and will be included in the denominator when calculating the response rate (Dose Expansion part only)
- DOR according to modified RECIST 1.1 and iRECIST, or Lugano and LYRIC, defined as the time from the date of first documented PR or CR until the first documentation of confirmed disease progression or death, whichever occurs first (Dose Expansion part only)
- DCR according to modified RECIST 1.1 and iRECIST, or Lugano and LYRIC, defined as the proportion of subjects achieving PR or CR or stable disease (SD) (Dose Expansion part only).

Secondary Endpoints:

- ORR, DOR, and DCR according to iRECIST and modified RECIST 1.1, or Lugano and LYRIC (Dose Escalation part only)
- PK profile in plasma, urine, and feces (Dose Escalation part) and plasma only (in Dose Expansion part)
- PFS, defined as the time from the date of first dose to the date of the first documentation of confirmed disease progression or death, whichever occurs first
- OS, defined as the time from the date of first dose to the date of death from any cause
- Change in tumor size in injected lesions and in distant non-injected lesions

Exploratory Endpoints:

- Changes in tumor size assessed by IIR using volumetric CT/MRI

- Immune pharmacodynamics effects in the tumors and in the peripheral blood
- PK/pharmacodynamic relationships (safety and efficacy endpoints)
- Baseline immune phenotypes and its relationship with the response to E7766
- STING genotypes and its relationship with the response to E7766
- Changes in pre-injection size of injected lesion per investigator assessment

Analysis Sets

DLT Analysis Set is the group of subjects in the Dose Escalation part who have completed Cycle 1, without incurring certain major protocol deviation (for instance those related to dosing or others identified before database lock), with at least 2 E7766 injections during Cycle 1, and are evaluable for DLT, or subjects who have experienced a DLT during Cycle 1. This will be the analysis set to evaluate tolerability.

Full Analysis Set is the group of subjects who received at least 1 dose of study drug. This will be the primary analysis set for efficacy evaluations, as well as for demographic and baseline characteristics.

Safety Analysis Set is the same group as Full Analysis Set. This will be the analysis set for all safety evaluations except DLT results.

Efficacy Analysis Set is the group of subjects who received at least 1 dose of study drug and had a baseline tumor assessment.

Pharmacokinetic (PK) Analysis Set is the group of subjects who have received at least 1 dose of study drug and have at least 1 evaluable plasma concentration.

Pharmacodynamic Analysis Set is the group of subjects who have received at least 1 dose of study drug and have evaluable pharmacodynamic data.

Pharmacokinetic/Pharmacodynamic Analysis Set is the group of subjects in the Safety Analysis Set that also have evaluable serum PK and pharmacodynamics pretreatment assessment and at least one posttreatment assessment.

Efficacy Analyses

Evaluation of clinical activity will be primarily performed on the Full Analysis Set. Summary of clinical activity on the Efficacy Analysis Set will also be provided as needed. Objective response rate (ORR), DOR, DCR, PFS, assessed by the investigator, and OS will be listed and descriptively summarized as appropriate. If applicable, a waterfall plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions at post-baseline nadir (ie, maximum tumor shrinkage).

- **ORR** will be calculated with exact 95% CI using the Clopper and Pearson method. Summary of best overall response will also be presented.
- **DOR** will be summarized using Kaplan-Meier estimates as appropriate. Median, Q1, Q3, and their 95% CIs will be presented and Kaplan-Meier estimates will be plotted over time. The DOR will be based on subjects achieving a best overall response of confirmed PR + CR.
- **DCR** will be calculated with exact 95% CI using the Clopper and Pearson method.
- **PFS** will be summarized using Kaplan-Meier estimates. Median, Q1, Q3, and their 95% CIs will be presented and Kaplan-Meier estimates will be plotted over time. Subjects without progression of disease or death will be censored at the time of the last tumor assessment.

- **OS** will be summarized using Kaplan-Meier estimates. Median, Q1, Q3, and their 95% CIs will be presented and Kaplan-Meier estimates will be plotted over time. Subjects who are lost to follow-up or withdrew consent will be censored at the last known alive date, or the data cutoff date, whichever occurs first. Subjects who remained alive will be censored at the time of data cutoff.

The analysis using the tumor assessment by lesions, such as injected lesions and non-injected lesions, will be collected and conducted separately. Time course changes in pre-injection size of injected lesion will also be provided separately.

Pharmacokinetic Analyses

Plasma concentrations of E7766 will be tabulated and summarized by dose level, day, and protocol time. E7766 PK parameters will be derived from plasma concentrations by noncompartmental analysis using actual times. Minimally, the following PK parameters will be calculated: maximum drug concentration (C_{max}), time to reach maximum concentration following drug administration (t_{max}), area under the concentration × time curve (AUC), and if data permit, terminal elimination half-life (t½), apparent body clearance (CL/F), apparent volume of distribution (Vd/F), renal clearance (CLr), accumulation ratio (R), and fraction excreted (fe). Recovery of E7766 in urine and feces will be tabulated and summarized by dose level, day, and protocol time.

If exploratory characterization/identification of metabolites in plasma, urine, and feces are attempted after administration of E7766, the results will be presented in a separate report.

Pharmacokinetic/Pharmacodynamic Analyses

Exploratory/graphical analyses will be conducted for PK/pharmacodynamics evaluations and may be followed by model-based analyses. The analyses may be detailed and reported in a separate analysis plan.

When conducting population analysis, the population PK analysis plan and its report will be made separately.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacodynamics biomarkers of E7766 include POM biomarkers and POP biomarkers, which will be measured to evaluate modulation of the STING pathway and of both innate and adaptive immune response, respectively, by E7766 treatment in human patients. To measure the STING pathway modulation, expression of a specific panel of STING pathway genes by E7766 will be examined as part of immune gene profiling in the tumor biopsies and in the blood. To measure the innate and adaptive immune response, immune gene profiling will be performed for the available tumor biopsies and blood. Immune cytokines and immune cell phenotyping will be analyzed in the blood as well. Results from the pharmacodynamic biomarker studies may be used to aid the selection for the RP2D and to monitor drug biological activity. Blood and tumor tissue samples will be collected from study subjects at protocol-specified time points as indicated in the Schedule of Procedures/Assessments.

Tolerability/Safety Analyses

Evaluation of DLTs will be performed on the DLT Analysis Set. The number and percentage of subjects with a DLT will be calculated. Evaluation of safety will be performed on the Safety Analysis Set. Safety data to be evaluated include AEs, clinical laboratory results, vital signs, ECGs, and the results of physical examinations. QTc intervals will be evaluated in the Dose Escalation part

only.

Safety parameters will be summarized using descriptive statistics (mean, standard deviation, median, Q1, Q3, and range for continuous variables; numbers and percentages for categorical measures).

Interim Analyses

No formal interim analyses are planned. Interim monitoring using a snapshot of the database will be conducted to determine the MTD and/or RP2D, or to confirm safety and detect efficacy signals in subjects with selected disease indications before the analysis for a clinical study report (CSR). Database locks are not required to perform these interim evaluations.

The data cutoff date for the CSR will be after 6 months of the last subject in, and may be conducted before the last subject discontinues study treatment in this study.

Sample Size Rationale

It is anticipated that selection of the RP2D will be based on integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamic data. The total number of subjects for the Dose Escalation part will depend on the observed data including safety profile, which will determine the number of subjects per dose level, as well as the number of dose levels tested before the RP2D is established. Therefore, a formal statistical calculation of sample size is not applicable. The anticipated sample size in the Dose Escalation part will be approximately 35 subjects, assuming approximately 10 dose levels and at least 2 subjects per dose level will be tested to achieve the MTD and then approximately 4 subjects for the selected 1 to 3 dose levels may be additionally enrolled for the RP2D selection.

The total number of subjects for the Dose Expansion part will depend on the number of arms by the disease-specific indications, and the number of subjects per arm. The anticipated sample size for the Dose Expansion part will be approximately 80 subjects, assuming 2 arms, and a maximum of 40 subjects per arm will be enrolled.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AEs	adverse events
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BP	blood pressure
CA	Competent Authority
CL/F	apparent body clearance
CLr	renal clearance
C_{max}	maximum drug concentration
CNS	central nervous system
CR	complete response
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CRS	cytokine release storm
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
EC50	50% effective concentrations
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EI	equivalence interval
fe	fraction excreted
FIH	first-in-human
FOB	functional observational battery
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HNSCC	head and neck squamous cell carcinoma

Abbreviation	Term
HNSTD	highest nonseverely toxic dose
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCPD	confirmed progressive disease per iRECIST
IEC	Independent Ethics Committee
IFN	interferon
IIR	independent imaging review
IR	immune response
IRB	Institutional Review Board
iRECIST	modified RECIST 1.1 for immune-based therapeutics
iUPD	unconfirmed disease progression per iRECIST
K_d	dissociation constant
LMWH	low molecular weight heparin
LVEF	left ventricular ejection fraction
LYRIC	LYmphoma Response to Immunomodulatory Therapy Criteria
MABEL	minimally anticipated biological effect level
MRI	magnetic resonance imaging
MRP2	multidrug resistance-associated protein 2
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
MUGA	multigated acquisition
OATP	organic anion transporting polypeptide
ORR	objective response rate(s)
OS	overall survival
PAD	pharmacologically active dose
PD	progressive disease
PET-CT	^{18}fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET)-CT
PFS	progression-free survival
PG	pharmacogenetic, pharmacogenomic
PK	pharmacokinetics
POM	Proof of Mechanism
POP	Proof of Principle
PR	partial response

Abbreviation	Term
Q3W	once in 3 weeks (dosing)
QTc	corrected QTc interval
QTcF	corrected for QTc interval using Fridericia's correction factors
R	accumulation ratio
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	stable disease
STING	stimulator of interferon genes
$t_{1/2}$	terminal elimination half-life
TBIL	total bilirubin
t_{max}	time to reach maximum concentration
TNF	tumor necrosis factor
ULN	upper limit of normal
V_d/F	apparent volume of distribution
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with ICH E6 (Good Clinical Practice), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number[s]). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The definition of the end of the study is the date of the data cutoff for the final analysis or last subject/last visit, including discontinuation from the study for any reason, whichever occurs later. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- A waiver from the IRB(s)/IEC(s) will be obtained before study initiation for non-US studies conducted under an Investigational New Drug (IND) application.
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator must explain to each subject or guardian/legally authorized representative the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject or the subject's legally acceptable representative should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion.

After the ICF and any other written information to be provided to subjects is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site.

The subject or the subject's legally authorized representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai and H3biomedicine (the sponsors) at approximately 4 investigational sites globally for the Dose Escalation part with additional sites for the Dose Expansion part.

The name and telephone and fax numbers of the study medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File provided to each site.

7 INTRODUCTION

7.1 E7766 Background

7.1.1 E7766 Mechanism of Action

E7766 is a potent and specific agonist of stimulator of interferon genes (STING) that is being investigated as an immunotherapy for cancer treatment. STING is an important innate immune sensor that bridges the innate immune system and adaptive immunity and has been shown to play a critical role in controlling cancer progression by activating both type I IFN and canonical NF-kB pathways (Figure 1) (Woo, et al., 2014). Intratumoral stimulation of STING by a synthetic STING agonist was shown to generate a potent antitumor response in multiple nonclinical models (Corrales, et al., 2015).

As a potent STING agonist, E7766 is intended to be developed as a new cancer immunotherapy. In this study it will be injected intratumorally, where it is hypothesized that

it will directly activate an antitumoral innate immune response in the injected tumor's microenvironment followed by inducing an adaptive tumor antigen-specific immune response to counter tumors systemically. It is believed that such intratumoral administration will reduce systemic drug exposure and nontumor-specific immune activation.

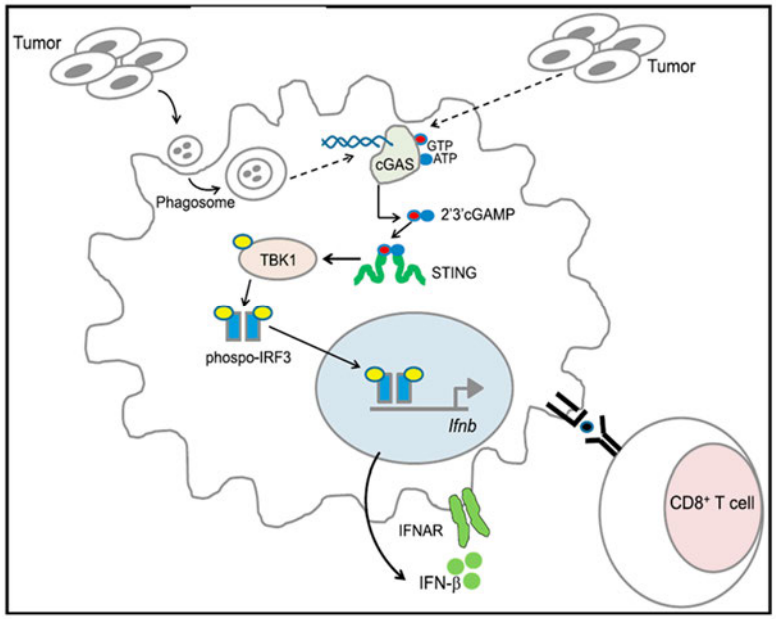

Figure 1 STING pathway activation

ATP = adenosine triphosphate, cGAMP = cyclic GMP-AMP, cGAS = cyclic GMP-AMP synthase, IFN = interferon, IRF = interferon regulatory factor, STING = stimulator of interferon genes, TBK1 = tank-binding kinase 1.

Intratumorally injected E7766 demonstrated potent, immune-mediated, long lasting antitumor activity in multiple nonclinical tumor models of different tissue origins both locally (ie, injected sites) and systemically (non-injected sites), including in tumors in the brain (Section 7.1.3.1).

Further details of the mechanism of action of E7766 are provided in the Investigator's Brochure.

7.1.2 Therapeutic Indication

The initial clinical development of E7766 will be focused in selected tumor types with identified high unmet medical need, following scientific rationale and available emerging nonclinical information.

Subjects with solid tumors or lymphomas that are advanced, nonresectable, or recurrent and progressing since last antitumor therapy, and for which no alternative standard therapy exists will be enrolled in the Dose Escalation part.

Preclinical studies indicated that tumor types with a geno-immunophenotype of high mutation burden and high Type I IFN signature were sensitive to E7766. As a result, prioritized early indications for the Dose Expansion part, selected based on the preclinical finding and bioinformatics analysis of the The Cancer Genome Atlas (TCGA) database, include melanoma, head and neck squamous cell carcinoma (HNSCC), breast cancer, and colorectal cancer. Other tumors may be selected later. The tumor types will be selected based on emerging data from the Dose Escalation part and will be tested in separate expansion arms.

7.1.3 Nonclinical Experience With E7766

7.1.3.1 Pharmacodynamics

CCI

CCI [redacted]

[redacted]

7.1.3.2 Pharmacokinetics

CCI [redacted]

[redacted]

7.1.3.3 Toxicology and Safety Pharmacology

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI

[redacted]

CCI

[redacted]

CCI

Details of single-dose toxicity studies are available in the Investigator's Brochure.

7.2 Study Rationale

Study E7766-G0001-101 is planned as a FIH study for the intratumoral administration route. The objective of the study is to evaluate the safety, tolerability, and preliminary activity of E7766 in subjects with advanced, nonresectable, or recurrent solid tumors and lymphomas, for which no alternative standard therapy is available.

While immunotherapy with monoclonal antibodies targeting various immune checkpoint inhibitors is currently being investigated for oncology, and has shown considerable success at improving clinical outcomes across a wide range of cancers, the therapies are limited by the small number of patients who achieve an objective response, their systemic immune-related toxicities (especially when used in combination), their cost, and the need to overcome intratumoral resistance. Hence other modalities like intratumoral immunotherapy, defined by direct injection of immunostimulatory agents into the tumor itself are being investigated. Intratumoral injection could result in superior priming of the antitumor response and could reduce systemic exposure, off-target toxicities, and the amounts of drug used. Intratumoral injection may also induce stronger antitumor activity in the injected tumor as well as in distant non-injected tumors (Marabelle, et al., 2018).

E7766 has demonstrated potent activity in tested animals in multiple murine syngeneic tumor models bearing 2 tumors of the same origin at different locations following single or multiple

intratumoral injections into one of the tumors. Intratumoral injection of E7766 induced a robust and effective innate and adaptive immune response including but not limited to induction of type I IFN genes and activation of resident cytotoxic T cells, which led to antitumor activity in both the injected tumor and the nontreated distant tumor, including tumors in the brain (Section 7.1.3.1). Notably, most of the animals whose tumors were eradicated by E7766 treatment rejected re-challenge of the same tumor type without any further treatment, indicating development of a protective memory immune response. Thus, E7766 has the potential to produce clinical activity in a variety of human cancer types and stages of disease including early and advanced metastatic cancer.

Systemic administration of this potent agonist is likely to bring unwanted immune effects. E7766 administration directly to the tumor lesion may allow induction of tumor-specific immune response at both the local and systemic level while minimizing AEs and nontumor-specific immune responses.

Early clinical development will be focused in selected tumor types with identified high unmet medical need and the potential for response to a STING agonist. As a result, advanced cancers including melanoma, HNSCC, breast cancer, and colorectal cancer will be prioritized initially. New immunotherapeutic approaches exploring modalities that stimulate the human immune system to attack tumors in the brain have shown early but promising results in the clinic and could be of significant importance in patients with brain metastases (Venur and Ahluwalia, 2017). In this regard, E7766 may potentially have clinical activity against central nervous system (CNS) metastases as a result of its abscopal immunomodulatory action. Tumor-specific lymphocytes activated by injection of E7766 into tumors outside of the CNS are expected to migrate into the CNS and exert an antitumor effect. This hypothesis is supported by results from a nonclinical model in which an intracranial tumor was successfully eradicated by injecting E7766 into a concurrent subcutaneous tumor (Section 7.1.3.1). Eisai thus plans to study E7766's clinical activity in metastatic or advanced cancer in subjects who have limited treatment options, including those with brain metastasis.

Risk Benefit assessment

In the current study, E7766 is being evaluated for the treatment of solid tumors or lymphomas, that are advanced, nonresectable, or recurrent and progressing since last antitumor therapy, and for which no alternative standard therapy exists. E7766 is a new agent with a novel mechanism of action and has demonstrated a potent and long lasting antitumor activity in nonclinical tumor models with nonsevere toxicity through intratumoral administration. Based on the antitumor activity of E7766 observed in nonclinical tumor models, E7766 is expected to demonstrate clinical activity and response in these subjects, for whom no alternative standard therapy exists and the prognosis is poor.

Nonclinical safety assessments were conducted in mice and cynomolgus monkeys and they showed adverse effects consistent with the pharmacologic activity. Based on these studies, the following adverse effects may be anticipated in the FIH study:

- Systemic inflammation, manifested as described in the next 2 bullets below
- Cytokine elevation, including of IL-6, IP-10, MCP-1, IFNβ, and TNF-α, peaking at approximately 8 hours postdose, and which is likely to be markedly lower after 24 hours. The amplitude of cytokine response is not expected to change significantly upon repeated dosing.
- Local injection site irritation including reddening, swelling, and ulceration.
- Gastrointestinal signs, including diarrhea

Overall, considering the promising antitumor activity and limited toxicity of E7766 in nonclinical studies at the doses showing antitumor activity when administered via the intratumoral route, clinical evaluation of E7766 via the intratumoral route is planned in subjects with advanced solid tumors and lymphomas.

8 STUDY OBJECTIVES

8.1 Primary Objectives

The primary objectives of the study are:

Dose Escalation part

- Assess the safety/tolerability profile of E7766 administered intratumorally in subjects with advanced solid tumors or lymphomas
- Determine the MTD and/or recommended Phase 2 dose (RP2D) of E7766 in subjects with advanced solid tumors or lymphomas

Dose Expansion part

- Assess the safety/tolerability profile of E7766 administered intratumorally in cohorts of subjects with selected tumor types
- Assess clinical activity of E7766 based on investigator assessment of objective response rate (ORR), duration of response (DOR), and disease control rate (DCR) according to modified Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 and modified RECIST 1.1 for immune-based therapeutics (iRECIST) for solid tumors, and for lymphoma (if included in Dose Expansion part), lymphoma response according to Lugano and LYmphoma Response to Immunomodulatory Therapy Criteria (LYRIC) criteria, in cohorts of subjects with selected tumor types

8.2 Secondary Objectives

The secondary objectives of the study are:

Dose Escalation part

- Evaluate preliminary clinical activity of E7766 based on investigator assessment of ORR, DOR, and DCR according to modified RECIST 1.1 and iRECIST for solid tumors, and Lugano and LYRIC criteria for lymphoma
- Evaluate the pharmacokinetic (PK) profile of E7766 and any metabolites in plasma, urine, and feces

Dose Escalation and Dose Expansion parts

- Evaluate the PK profile of E7766 and any metabolites in plasma
- Evaluate progression-free survival (PFS) based on investigator assessment and overall survival (OS) in subjects treated with E7766
- Evaluate tumor size changes per investigator assessment in injected lesions and in non-injected lesions

8.3 Exploratory Objectives

The exploratory objectives of the study are:

Dose Escalation and Dose Expansion parts

- Evaluate changes in tumor size assessed by independent imaging review (IIR) using volumetric computed tomography (CT)/magnetic resonance imaging (MRI)
- Evaluate immune pharmacodynamics effects of E7766 in the tumors and in peripheral blood
- Explore PK/pharmacodynamics relationships (safety and efficacy endpoints)
- Explore correlation of baseline tumor and peripheral blood immune phenotypes and of STING genotypes with safety and/or efficacy endpoints
- Evaluate pre-injection changes in size of injected lesion per investigator assessment in addition to the scheduled tumor assessments to characterize the kinetics of response, progression, or immune-induced flare in the injected lesion.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This is an open label, multicenter, Phase 1/1b study to assess the safety and evaluate the clinical activity of E7766 administered intratumorally to subjects with advanced solid tumors

or lymphomas. A Dose Escalation part will enable selection of a dose of E7766 to move forward with as the RP2D in the Dose Expansion part, where clinical activity in selected tumor types or populations will also be evaluated.

Dose escalation will be conducted initially using an improved modified toxicity probability interval (mTPI) design (Guo, et al., 2017; Yan, et al., 2017) to determine the MTD for E7766. Each subject will be assessed for tumor response (injected and non-injected lesions), PK, and pharmacodynamic (blood and tumor factors). The RP2D will be selected based on integrating results of safety (including the MTD), clinical activity, PK, and pharmacodynamics. During the Dose Escalation part, selected dose level cohorts may accrue additional subjects to provide further safety, drug administration-related, biomarker, and/or PK data needed for selection of the RP2D. Intrapatient dose escalation of study drug will be allowed in the study as described in Section 9.1.1.1.

The Dose Expansion part will be initiated when the RP2D and/or MTD is available from the Dose Escalation part. In the Dose Expansion part, separate study arms will evaluate E7766 at the RP2D in selected tumor types and populations to confirm safety and assess clinical activity. The study populations will be decided based on the emerging data from the Dose Escalation part.

The overall study design is shown in Figure 2.

A fixed E7766 dose will be administered for each subject. There will be no adjustments for subject weight. Detailed instructions for intratumoral injection of E7766 are provided in Section 9.4.1.3.

CCI

- Induction cycle (Cycle 1): intratumoral injection on Days 1, 8, 15
- Maintenance cycle (Cycle 2 and after): intratumoral injection on Day 1 of each cycle, once in 3 weeks (Q3W).

In the Dose Escalation part, there should be at least a 7 days interval between initiating treatment of the first and second subject in each new dose escalation cohort.

Systemic E7766 drug levels will be measured after intratumoral injection.

Pharmacodynamics assessments will include evaluation of drug target-mediated immune pathway activation by gene expression profiling, immunohistochemistry or other appropriate methodologies in the injected tumor as well as in non-injected lesions. Pre- and posttreatment tumor biopsies will be required for the injected lesion and, if available, for one pre-specified non-injected lesion. Changes in frequency, differentiation and activation status of intratumoral immune cell populations will be evaluated as well. In addition, the effect of

E7766 on systemic levels of cytokines and immune cell phenotypes reflective of innate and adaptive immune activation will be assessed.

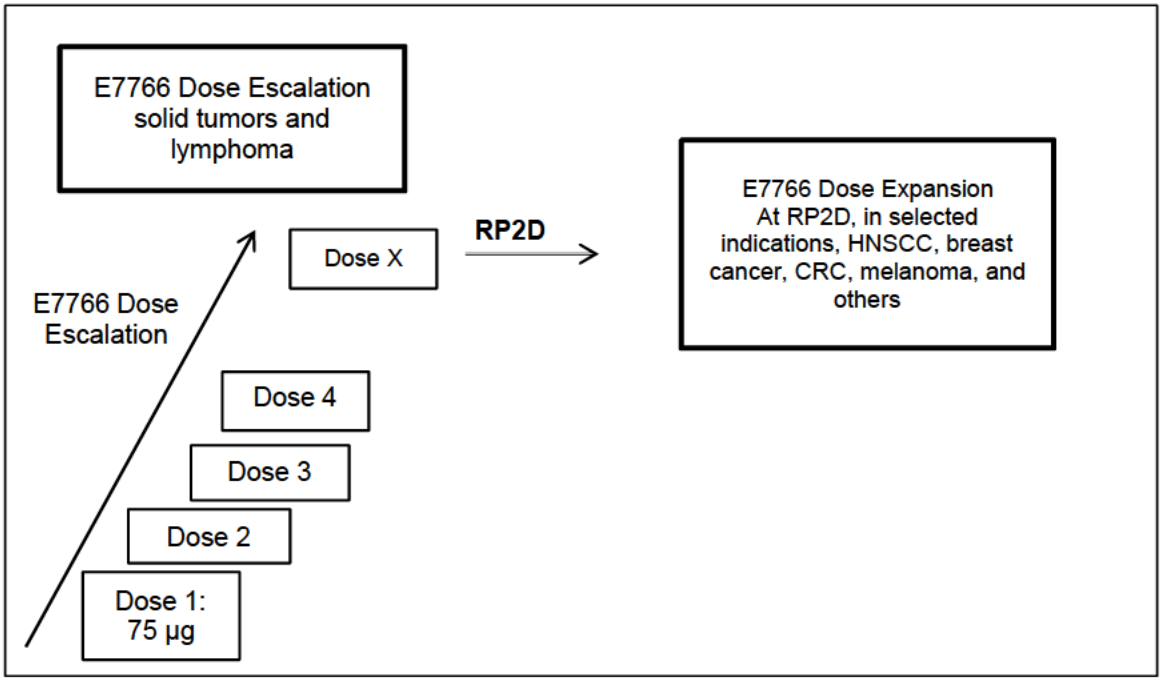

Figure 2 Study Schematic for Dose Escalation and Dose Expansion parts
CRC = colorectal cancer, HNSCC = head and neck squamous cell carcinoma, RP2D = recommended Phase 2 dose.

The end of the study will be the date of data cutoff for the final analysis or the time of last subject/last visit, whichever occurs later.

9.1.1 Dose Escalation

9.1.1.1 Dose Escalation Design

Dose assignment of subjects will be done using the improved mTPI design in order to determine the MTD of E7766. Each subject will be assigned a dose in accordance with the rules of the improved mTPI design based on a target dose-limiting toxicity (DLT) rate of 25% and its equivalence interval (EI) of 20% to 30%.

The dose assignment decision rule is pre-tabulated in (Table 1). Two subjects will be enrolled for each tested dose level, and recruitment to the dose level will be expanded as required per Table 1. Based on the number of subjects with DLTs in each dose level, dose assignment for the next dose will be determined according to the Table 2 after consultation between the investigators and the sponsors. For the lowest dose, extra subjects may be added if a DLT develops in 1 of the 2 subjects, if deemed appropriate. Subjects who are not evaluable for DLT (eg, those subjects who fail to complete at least 2 E7766 injections during

Cycle 1 for reasons other than DLT occurrence) should be replaced within their dose level, if at least 2 subjects in total have not been tested at the dose level. Subject enrollment will be closed when the DLT rate at the lowest dose level greatly exceeds the target DLT rate (25%), or when the RP2D has been determined.

Additional details of the improved mTPI design are presented in Section 9.7.4.1.

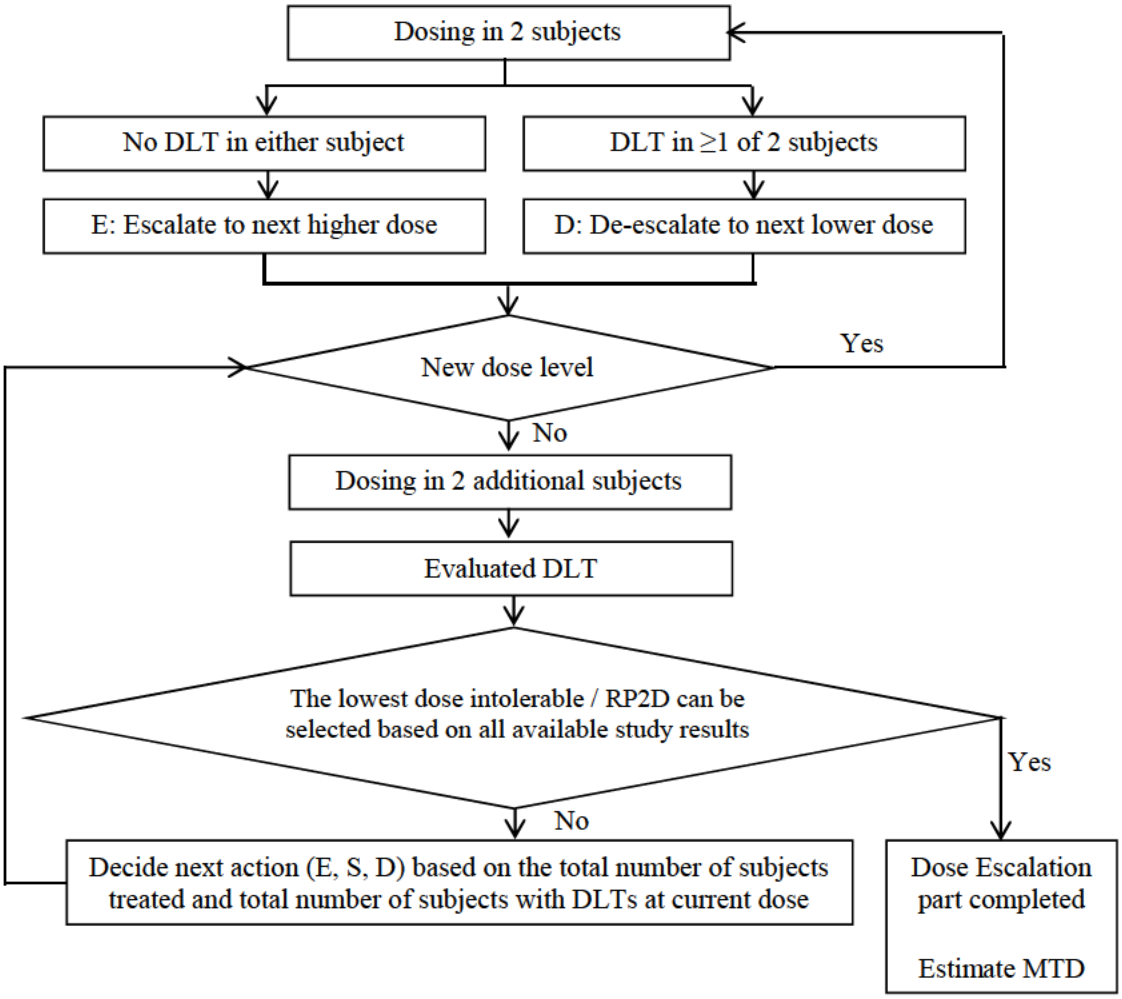

Figure 3 Schematic for Dose Escalation

D = de-escalate to next lower dose, DLT = dose-limiting toxicity, E = escalate to next higher dose, MTD = maximum tolerated dose, RP2D = recommended Phase 2 dose, S = Stay at current dose.

Table 1 Decision Rule for Dose Assignment

		Number of Subjects Treated at Current Dose					
		2	**4**	**6**	**8**	**10**	**12**
Number of Subjects With DLTs	**0**	E	E	E	E	E	E
	1	D[a]	S	E	E	E	E
	2	D, U	D	D	S	S	E
	3		D, U	D	D	D	S
	4		D, U	D, U	D, U	D	D
	5			D, U	D, U	D, U	D
	≥6			D, U	D, U	D, U	D, U

Target DLT rate at MTD = 25% and its equivalence interval = 20% to 30%, Cohort size = 2 subjects.
Display for more than 12 subjects at the current dose is omitted. If the required rules are not available in the table, the decision will follow the rule determined by the improved mTPI design with the same settings above.
E = Escalate to the next higher dose, S = Stay at the current dose, D = De-escalate to the next lower dose, U = Current dose is unacceptably toxic (ie, Do not re-enter the current dose).
DLT = dose-limiting toxicity, MTD = maximum tolerated dose, mTPI = modified toxicity probability interval.
a: Extra subjects may be added for the lowest dose, for example if the investigators and the sponsor determine that more subjects would be required to adequately evaluate that dose level and it is considered safe to do so.

Subjects will be assigned to a dose level in the order of study entry. There should be at least 7 days between initiating treatment of the first and second subject in each new dose escalation. This would provide enough safety margin in terms of safety evaluation for any acute serious toxicities arising from activation of the immune system, which would generally be expected to occur within the first hours or 1 to 3 days of drug exposure. In cohorts where the dose is de-escalated or re-escalated, a delay in administration between the first subject and subsequent subjects in that cohort is not required if the same or a higher dose level has already been investigated in a previous cohort.

The first E7766 dose administered to the subjects will be 75 µg (refer to Section 9.2 for justification of starting dose). The dose of subsequent dose groups will be determined based on the E7766-related AEs that develop in subjects in the prior dose group during the 3 weeks of Cycle 1 (see Table 2). When escalating or de-escalating the dose to the next dose level according to the improved mTPI design, if there is a higher or lower dose level that has been tested previously, subjects should be enrolled to the previously tested dose and Table 2 below shall not apply. In addition, intermediate doses can be further added if necessary based on the safety or PK of the previously tested dose. The addition of new dose levels will be decided based on discussions between the investigators and sponsors during dose escalation meetings.

Table 2 Method for Deciding the Dose of the Next Dose Group

Dose Escalation Steps	E7766-Related Toxicity During Cycle 1
Increase ~75% to 100%	Up to Grade 1
Increase ~30% to 60%	Grade 2 in 1 subject
Increase ~10% to 30%	Grade 2 in 2 or more subjects and/or Grade 3 or higher in 1 or more subject

Intrapatient dose escalation of study drug will be allowed in the study after a minimum of 3 cycles of study therapy at the designated dose and after there is sufficient information to ensure safety at the higher dose. The decision for individual cases, if requested, will be made in agreement between the investigators and the sponsor. Subjects on the intrapatient dose escalation will be identified, but included in the evaluation of tolerability/safety and efficacy at the dose level assigned in Cycle 1, instead of at the higher dose level.

Late immune-related toxicities occurring after Cycle 1 (DLT period) and up to 90 days after last dose of E7766, will also be considered to inform any corrections to the MTD and aid selection of the RP2D.

Escalation of E7766 dose will be achieved based on the concentrations and volumes administered according to the guidance in Table 3.

During the Dose Escalation part, selected dose level cohorts may accrue additional subjects to provide additional safety, drug administration-related, biomarker, and/or PK data needed for selection of the RP2D.

9.1.1.2 Dose-Limiting Toxicities

DLTs are any of the following toxicities occurring during Cycle 1 and assessed by the investigator as related to study drug (any toxicities considered related to any degree to E7766):

- Clinically significant nonhematologic toxicity ≥ Grade 3 (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] v. 5.0), except
  - Grade 3 fatigue <5 days.
  - Asymptomatic Grade 3 or 4 laboratory abnormalities that are corrected within 72 hours.
  - ≥ Grade 3 nausea, vomiting, and diarrhea unless lasting >48 hours despite optimal supportive care.
  - Other AEs that per investigator assessment are not dose limiting nor dose related.
- CTCAE Grade 2 nonhematologic toxicities which, in the opinion of the investigator, require a dose reduction or discontinuation of study drug, or lead to the subject's failure to complete at least 2 out of 3 scheduled injections of E7766 in Cycle 1, or be

considered intolerable for any other reason by the investigator, may be deemed to be dose-limiting if agreed upon by participating investigators and the sponsors.

- Nonhematologic laboratory findings of Grade ≥3 that were ≤ Grade 1 at baseline with the exception of abnormal Grade 3 laboratory values with no clinical significance that resolve within 7 days (this includes electrolyte abnormalities which respond to medical intervention).
- Hematologic toxicity:
  - Grade 4 neutropenia for ≥5 days, or febrile neutropenia.
  - Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with hemorrhage.
- Any other toxicity assessed as related to E7766 treatment, and which in the opinion of the study investigator(s) and the study medical monitor constitutes a DLT.
- A delay of initiating Cycle 2 of 7 days or more due to toxicity.
- Any death not clearly due to the underlying disease or extraneous causes
- For patients with hepatic metastases, AST or ALT >8×upper limit of normal (ULN), or AST or ALT >5×ULN for ≥14 days.
- For patients with normal ALT and AST and total bilirubin (TBIL) value at baseline: AST or ALT >3.0×ULN combined with TBIL >2.0×ULN without evidence of cholestasis (ALP ≤2×ULN), with no alternative etiology (Hy's law)
- For patients with elevated AST or ALT or TBIL value at baseline: [AST or ALT >2×baseline AND >3.0×ULN] OR [AST or ALT >8.0×ULN], whichever is lower, combined with [TBIL >2×baseline AND >2.0×ULN] without evidence of cholestasis (ALP ≤2×ULN)

A subject should have received at least 2 E7766 injections during the DLT period (Cycle 1) to be considered evaluable for a DLT, unless the subject experienced a treatment-related toxicity preventing more than 1 administration of E7766.

If a subject at a given dose level receives fewer than 2 out of the 3 planned E77766 intratumoral injections during the Induction cycle (ie, the DLT period/Cycle 1) because of E7766-related AEs, the subject should be considered as potentially experiencing a DLT by the Study Safety Committee, composed of investigators and representatives of the sponsor.

A subject experiencing a DLT may continue treatment at a reduced dose if the DLT has resolved and in the opinion of the investigator the subject is benefiting from treatment. In case of recurrence of the DLT at a lower dose, E7766 treatment should be discontinued.

9.1.1.3 Selection of the RP2D

The RP2D of E7766 will be selected based on an integrated evaluation of safety, tolerability, clinical activity, PK data, and any available pharmacodynamics data for all dose levels or all available data according to the following guidelines:

- The RP2D must not exceed the MTD, as defined in the Dose Escalation part of the study.
- Consideration will be given to other toxicities including: AEs assessed as related to study drug treatment but not considered dose limiting, late immune-related toxicities (up to 90 days after last dose of the study drug), the nature and frequency of toxicities, and the emergence of any specific category of toxicities.
- Consideration will be given to the tumor response(s) and antitumor activity.
- Pharmacodynamic demonstration of biologic activity, including but not limited to: activation of STING-mediated immune pathways and modulation of innate and adaptive immune response in the tumors and/or in the peripheral blood such as INFβ, CXCL10, and MCP1.

The investigators and sponsors will together conduct the evaluation and the recommended Phase 2 dose/doses and/or any modification to the dosing regimen will be agreed upon jointly.

9.1.2 Dose Expansion

Expansion arms shall be opened in specific tumor types and populations with treatment at the E7766 RP2D.

Safety and clinical activity of E7766 at the RP2D will be tested in separate expansion arms with defined populations potentially including but not limited to melanoma, HNSCC, breast cancer, colorectal cancer, and/or other tumors. About 40 patients will be recruited in each expansion arm.

9.1.3 Study Phases

There will be 4 phases for each subject in the Dose Escalation part and the Dose Expansion, part: a Pretreatment Phase, a Treatment Phase, an Extension Phase, and a Follow-Up Phase.

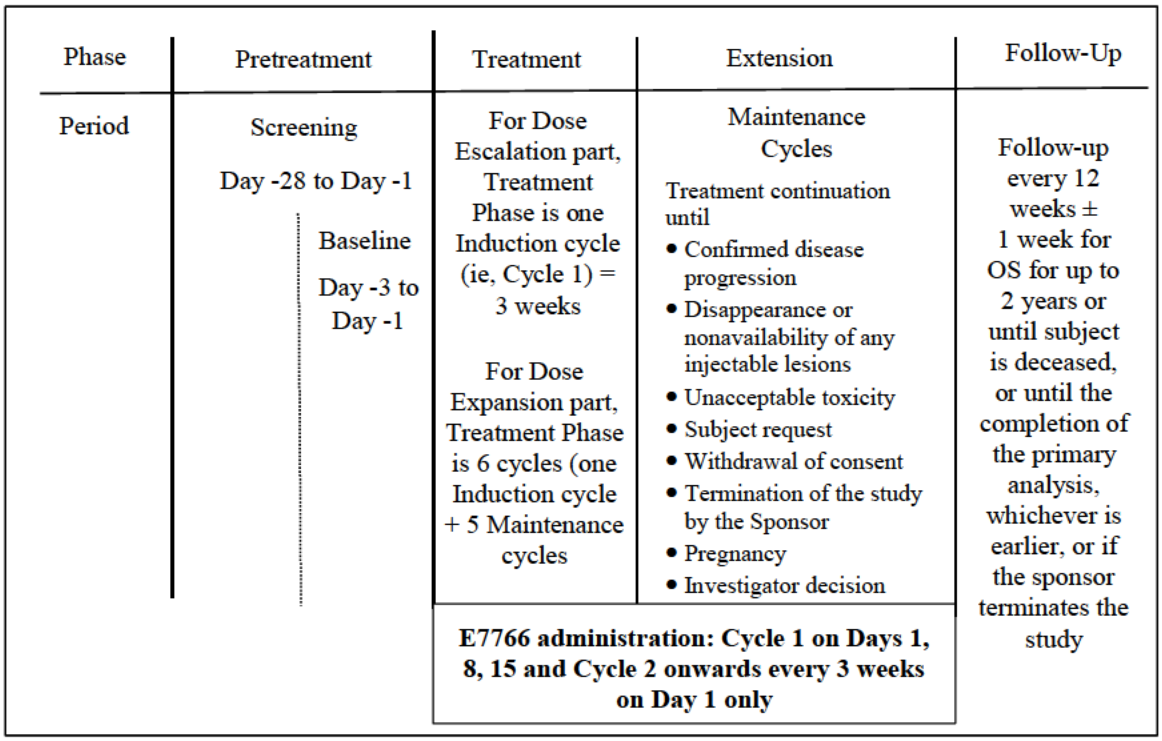

Figure 4 Study Phases

9.1.3.1 Pretreatment Phase

This phase will last no longer than 28 days and includes:

- A Screening Period spanning Day -28 to Day -1 to obtain informed consent and establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3.
- A Baseline Period from Day -3 to Day -1 to establish disease characteristics before treatment

9.1.3.2 Treatment Phase

Subjects whose screening assessments and evaluations are completed and reviewed by the principal investigator and who continue to meet all of the inclusion/exclusion criteria will enter the Treatment Phase.

The Treatment Phase will extend from the start of study drug administration in Cycle 1 and will last for 1 treatment cycle of 21 days in the Dose Escalation part and 6 cycles in the Dose Expansion part. At the end of the Treatment Phase subjects will continue to the Extension Phase.

9.1.3.3 Extension Phase

In the Extension Phase, subjects who are receiving study drug at the end of the Treatment Phase will continue to receive drug treatment at the same dose and according to the Dosing Schedule described in Section 9.4.1.1.

In the **Treatment** and **Extension phases,** subjects will undergo disease assessments every 6 weeks in the case of solid tumors and 12 weeks in the case of lymphomas, and will discontinue study drug at the time of confirmed disease progression (per iRECIST or LYRIC), disappearance or nonavailability of any injectable lesions, development of unacceptable toxicity, subject request, withdrawal of consent, termination of the study program, pregnancy, or investigator decision.

An off-treatment assessment should occur within 30 days after the final dose of study treatment.

Subjects who are continuing to derive clinical benefit in the view of the investigator at the time of study termination by the sponsor, can continue to be treated with E7766 after discussion with the sponsors.

9.1.3.4 Follow-Up Phase

The Follow-Up Phase will begin immediately after the off-treatment assessments have been completed and will continue for up to 2 years or until study subject is deceased, or until the completion of the primary analysis, whichever is earlier, unless the subject withdraws consent or until the sponsor terminates the study.

Subjects who discontinue study treatment before disease progression will continue to undergo disease assessment every 6 weeks in case of solid tumors and 12 weeks in case of lymphomas until documentation of disease progression or start of another anticancer therapy.

Subjects will be followed every 12 weeks (±1 week) for survival, performance status and subsequent anticancer treatments. The sponsor may decide to terminate survival follow-up anytime during the Extension Phase or when all subjects have discontinued study treatment. Survival follow-up will be conducted in person or via phone call.

In the Follow-Up Phase, subjects will be treated by the investigator according to the prevailing local standard of care.

The sponsor may decide to terminate survival follow-up anytime during the Extension Phase or when all subjects have discontinued study treatment.

9.2 Discussion of Study Design, Including Choice of Control Groups

In this FIH study (intratumoral route), E7766 will be studied to assess safety and tolerability, clinical activity, PK, and to explore pharmacodynamics markers to identify potential human-relevant biomarkers of safety and efficacy. The study will identify an MTD and/or a RP2D of E7766. Phase 1b expansion arms in selected tumor types are planned after RP2D has been determined.

E7766 will be tested in sequential escalating dose cohorts (n=2) using the mTPI method. Expanding individual dose levels to generate additional safety, drug administration-related, biomarker, and/or PK information will be allowed.

Starting Dose Determination and Subsequent Dose Escalation and Descalation

Based on the analysis of the nonclinical package and feedback from FDA, the approach selected for determining the Phase 1 FIH E7766 starting dose is the calculation of a pharmacologically active dose (PAD) level. CCI

Design

E7766 will be administered intratumorally on Days 1, 8, and 15 in the first cycle, and then on Day 1 of each subsequent cycle every 3 weeks. Treatment is planned until progressive disease or until other discontinuation criteria have been met.

The escalation steps and doses of subsequent dose groups will be determined based on the E7766-related AEs that develop in subjects in the prior dose group during Cycle 1 as per improved mTPI methodology as outlined in Section 9.7.4.1. In addition, intermediate doses can be further added if necessary based on the safety or PK of the previously tested dose. The addition of new dose levels will be decided based on discussions between the investigators and sponsors.

Translational approach

CCI

[redacted]

9.3 Selection of Study Population

Approximately 35 to 40 subjects will be enrolled in the Dose Escalation part and 80 subjects will be enrolled in the Dose Expansion part. Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. Age ≥ 18 years.
2. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.

3. Life expectancy ≥12 weeks.
4. Subjects with solid tumors or lymphomas, confirmed by available histopathology records or current biopsy, that are advanced, nonresectable, or recurrent and progressing since last antitumor therapy, and for which no alternative standard therapy exists.
5. Subjects must have a minimum of one injectable lesion which is also accessible for biopsy, and if available, one other measurable lesion also accessible for biopsy.

   An injectable lesion is defined as being measureable (defined below) with a maximum of 3.0 cm longest diameter, accessible for injection as judged by the investigator, and has not been subjected to any prior intratumoral treatment or radiotherapy. Lesions selected for injection must not be too close to a major vessel, as judged by the investigator, and not be associated with increased risk of bleeding, eg, subcapsular liver lesions or hypervascular tumors.

   Measurable lesions are:

   a. Solid tumors: At least 1 lesion of ≥1 cm by longest axial diameter or ≥1.5 cm short axis diameter if a nodal lesion, which is serially measurable according to modified RECIST 1.1 using CT/MRI or photography. Lesions that have had external beam radiotherapy or locoregional therapies such as radiofrequency ablation must show evidence of progression to be deemed a target lesion (Appendix 1, Appendix 2).
   b. Lymphoma: At least 1 lymph node with a longest diameter >1.5 cm or an extranodal lesion with a longest diameter >1.0 cm (Appendix 3).
6. Prior anticancer therapy such as chemotherapy, immunotherapy (eg, tumor vaccine, cytokine, checkpoint inhibitors), or investigational drugs, or any vaccine must have been completed at least 4 weeks before study drug administration, and all AEs must have either returned to baseline or stabilized. Subjects with prior immunotherapy known to have experienced severe nontolerable toxicities attributed to drug should be excluded.
7. Prior definitive radiation therapy must have been completed at least 6 weeks and prior palliative radiotherapy at least 2 weeks before study drug administration. Radiopharmaceuticals (eg, strontium, samarium) must be at least 8 weeks before study drug administration.
8. Immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses >10 mg/day prednisone or equivalent) must have been discontinued at least 4 weeks before study drug administration.
9. Subjects with prior Hepatitis B or C are eligible if they have adequate liver function as defined by Inclusion Criterion #13.
10. Left ventricular ejection fraction (LVEF) >50% or within normal limits per institutional practice, on echocardiography or multigated acquisition (MUGA) scan.
11. Adequate renal function defined as serum creatinine <1.5 × ULN (or use SI units or calculated creatinine clearance ≥50 mL/min per the Cockcroft and Gault formula [Appendix 4]).

12. Adequate bone marrow function:
    a. Absolute neutrophil count (ANC) ≥1000/mm^3 (≥1.0 × 10^3/μL)
    b. Platelets ≥75,000/mm^3 (≥75 × 10^9/L)
    c. Hemoglobin ≥9.0 g/dL
13. Adequate liver function defined by:
    a. Adequate blood coagulation function as evidenced by an International Normalized Ratio (INR) ≤1.5
    b. Total bilirubin ≤1.5 × ULN except for unconjugated hyperbilirubinemia or Gilbert's syndrome
    c. Alkaline phosphatase (ALP), ALT, and AST ≤3 × ULN (in the case of liver metastasis ≤5 × ULN) unless there are bone metastases. Subjects with ALP values >3 × ULN and known to have bone metastases can be included.
14. Willing and able to comply with all aspects of the protocol.
15. Provide written informed consent prior to any study-specific screening procedures.

9.3.2 Exclusion Criteria

Subjects with any of the following criteria will be excluded from this study:

1. Other malignancy active within the previous 2 years except for basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the cervix or breast that has completed curative therapy.
2. Subjects with any active autoimmune disease (Appendix 5) or a documented history of autoimmune disease, except for subjects with vitiligo or resolved childhood asthma/atopy.
3. Known human immunodeficiency virus (HIV) infection.
4. Active infection requiring therapy, including known positive tests for Hepatitis B surface antigen or Hepatitis C ribonucleic acid (RNA).
5. Major surgery within 4 weeks before the first dose of study drug.
6. Concurrent medical condition requiring the use of immunosuppressive medications or immunosuppressive doses of systemic medications, such as steroids or absorbed topical steroids (doses >10 mg/day prednisone or equivalent).
7. Brain metastases that are untreated or in the posterior fossa or involve the meninges. Subjects with stable or progressing brain metastases (except in the posterior fossa or involving the meninges) previously treated with brain stereotactic radiotherapy (SRT), whole-brain radiotherapy (WBRT) and/or surgery are allowed as long as the subject is asymptomatic neurologically and does not require immediate local intervention (radiotherapy and/or surgery). In addition, subjects must be off immunosuppressive doses of systemic steroids (>10 mg/day prednisone or equivalent) for at least 4 weeks before study drug administration.
8. Prolongation of corrected QT (QTcF) interval to >450 msec for males and females, when electrolytes balance is normal.

9. Significant cardiovascular impairment: history of congestive heart failure greater than New York Heart Association (NYHA) Class II, uncontrolled arterial hypertension, unstable angina, myocardial infarction, or stroke within 6 months of the first dose of study drug, or cardiac arrhythmia requiring medical treatment (including oral anticoagulation).
10. Subjects on oral anticoagulants including low dose aspirin. To meet eligibility, these subjects can be switched to receive preventive dose of low molecular weight heparin (LMWH). It is recommended that their LMWH treatment is stopped 24 hours before the intratumoral injection and resumed again 24 hours after the injection.
11. Any history of a medical condition or a concomitant medical condition that, in the opinion of the investigator, would compromise the subject's ability to safely complete the study.
12. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
13. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception (total abstinence [if it is their preferred and usual lifestyle], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 180 days after study drug discontinuation. For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide. If currently abstinent, the subject must agree to use a highly effective method as described above if she becomes sexually active during the study period or for 180 days after study drug discontinuation. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 28 days before dosing and must continue to use the same contraceptive during the study and for 180 days after study drug discontinuation.
14. Male subjects who are partners of women of childbearing potential must use a condom and spermicide and their female partners if of childbearing potential must use a highly effective method of contraception (see methods described above in Exclusion Criterion #13) beginning at least 1 menstrual cycle prior to starting study drug(s), throughout the entire study period, and for 180 days after the last dose of study drug, unless the male subjects are totally sexually abstinent or have undergone a successful vasectomy with confirmed azoospermia or unless the female partners have been sterilized surgically or are otherwise proven sterile. No sperm donation is allowed during the study period or for 180 days after study drug discontinuation.

15. Known hypersensitivity to E7766 or any of the excipients or prior therapy with E7766 or any other STING agonist.
16. Use of illegal recreational drugs.
17. Currently enrolled in another clinical study or used any investigational drug or device within 28 days preceding informed consent.

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

The investigator may discontinue treating a subject with study treatment or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study treatment or withdraw from the study at any time for any reason. The reason for discontinuation will be documented. If a subject discontinues study treatment, the subject will enter the Follow-Up Period and complete protocol-specified off-treatment visits, procedures, and survival follow-up unless the subject withdraws consent. The investigator should confirm whether a subject will withdraw from study treatment but agree to continue protocol-specified, off-treatment study visits, procedures, and survival follow-up, or whether the subject will withdraw consent. If a subject withdraws consent, the date will be documented in the source documents.

During the Follow-Up Period, subjects who have discontinued study treatment without progression should have disease assessments every 6 weeks in case of solid tumors and 12 weeks in case of lymphomas from the date of the last assessment until disease progression is documented or another anticancer therapy is initiated.

All subjects will be followed for survival every 12 weeks for up to 2 years, except where a subject withdraws consent or the sponsors choose to halt survival follow-up after completion of the primary study analysis.

9.4 Treatments

9.4.1 Treatments Administered

Subjects enrolled in the study will receive E7766 administered intratumorally.

CCI [redacted]

CCI

9.4.1.1 Dosing Schedules

E7766

A fully equipped and functional crash cart must be available in the unit where a subject is to be administered E7766. CCI

E7766 will be administered in 3-week cycles, with treatment as follows:

- Induction (Cycle 1): Days 1, 8, 15
- Maintenance (Cycle 2 and after): on Day 1 of each cycle, Q3W.

CCI

In the Maintenance treatment portion, ie, Cycle 2 forward, if a scheduled dosing is missed or delayed, this dosing will be administered as soon as allowed under dose interruption/retreatment guidelines. Treatment cycles will be synchronized to the new dosing day, ie, the day of administration of the made-up dosing will be considered Day 1 of the next cycle. This synchronization will include all cycle Day 1 assessments and procedures, but will exclude response assessments as outlined in Section 9.5.1.3.

9.4.1.2 Dose Adjustments

E7766 Dose Adjustments

In the Dose Escalation part, dose adjustments may be allowed at the discretion of the investigator after discussion with the sponsors. Subject may be allowed to continue study drug at a reduced dose, if this is judged to be in their best interest. E7766 dose reductions and interruptions should be carried out as outlined in Table 4.

Guidelines for dose adjustments after Cycle 1

E7766 dose reduction and interruption for subjects who experience therapy-related toxicity (as assessed by the investigator) will be in accordance with the dose modification guidelines described in Table 4.

- Subjects who experience toxicities that could have been qualified as DLTs may, at the discretion of the investigator and after discussion with the sponsors, be allowed to continue study drug at a reduced dose according to these dose modification guidelines, if this is judged to be in their best interest.

For subjects who require dose interruption due to E7766-related toxicity in Cycle 2 or beyond, the treatment may re-start once the toxicity has been resolved to Grade ≤1 or baseline according to the dose reduction and interruption instructions in Table 4.

Table 4 E7766 Dose Reduction and Interruption Instructions

E7766-Related Toxicity[a]	During Therapy	Approximate Dose Adjustment
Grade 1		
All occurrences	Continue E7766 treatment. If CRS, then interrupt E7766 until Grade 0.	Maintain dose level.
Grade 2[b]		
1st occurrence	Interrupt E7766 until resolved to Grade ≤1 or baseline. If CRS, then interrupt E7766 until Grade 0[c].	Maintain dose level. If CRS, consider dose reduction.
2nd occurrence (same toxicity)	Interrupt E7766 until resolved to Grade ≤1 or baseline. If CRS, then interrupt E7766 until Grade 0[c].	Consider reduction by 1 dose level of starting dose, if dose delayed. If CRS, then consider further dose reduction.
3rd occurrence (same toxicity)	Interrupt E7766 until resolved to Grade ≤1 or baseline[c]. If CRS, then discontinue E7766.	Reduce by 1 or 2 dose levels of starting dose, if appropriate.
4th occurrence (same toxicity)	Interrupt E7766 until resolved to Grade ≤1 or baseline[c].	Discuss with sponsors.
Grade 3[b]		
1st occurrence	Interrupt E7766 until resolved to Grade ≤1 or baseline[c]. If CRS, then discontinue E7766.	Reduce by 1 dose level of starting dose

2nd occurrence (same toxicity)	Interrupt E7766 until resolved to Grade ≤1 or baseline[c].	Reduce by 2 dose levels of starting dose
3rd occurrence (same toxicity)	Discontinue E7766 treatment	Not applicable
Grade 4[d]: Discontinue E7766		

For grading, see Common Terminology Criteria for Adverse Events (CTCAE v. 5.0)
a: Excluding alopecia, anemia, lymphocytopenia, and asymptomatic neutropenia. Initiate optimal medical management for nausea, vomiting, diarrhea, and/or fever before any E7766 interruption or dose reduction.
b: Applicable only to those Grade 2 toxicities judged by the subject and physician to be intolerable and to all Grade 3 toxicities.
c: Interruption of E7766 treatment for more than 21 days (due to E7766-related toxicities) will require a discussion with the sponsors before treatment can be resumed.
d: Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

9.4.1.3 Intratumoral Injection

Lesions selected for injection must be at least 1.0 cm for solid tumors, and >1.5 cm for lymphoma in the longest diameter, so as to be measureable by RECIST (solid tumors) or Lugano criteria (lymphoma). The maximum size of any injected lesion is 3.0 cm in the longest diameter for both solid tumors and lymphoma. Lymph nodes for injection must be at least 1.5 cm in the short axis for solid tumors and >1.5 cm in the longest diameter for lymphoma.

Investigators will define which lesions are appropriate for E7766 injection. Preference in the initial dose levels will be given to easier to access lesions. Intratumoral injection approaches for lesions that are proximal to major vessels or those deemed to have a risk of bleeding should be discussed in a multidisciplinary setting with regards to safety of the approach in order to avoid a risk of vascular catastrophe and/or inadvertent risk of intravascular systemic injection. Lesions in the vicinity of major vessels with a high risk of bleeding (eg, the common, internal or external carotid arteries or their branches), or other situations with a risk of vascular catastrophe such as tumor-encased large vessels, subcapsular liver lesions, hypervascular tumors, lesions that have been previously irradiated, lesions with macroscopic intravascular tumor invasion (eg, liver lesions with tumor infiltration into the main portal vein, hepatic vein or vena cava) should be excluded from intratumoral injection. To avoid potential risk of bleeding and systemic exposure, Doppler ultrasound guidance is recommended for intratumoral injections with E7766 to ensure that the injection is not carried out within a vessel (Marabelle, et al., 2018). Lesions selected for injections must not have been subjected to any prior intratumoral therapy.

Local (at site of injection) plus or minus systemic analgesic treatments should be anticipated and are recommended to be initiated at least 30 minutes before undertaking intratumoral injection procedure. Skin analgesia at the site of injection can be administered using topical xylocaine (4%) or other local anaesthetic agents. The options for systemic analgesia are recommended to include the full range of analgesia from paracetamol/acetaminophen to opioids, depending on the precise details of the procedure and the subject's underlying symptoms (Marabelle, et al., 2018).

The same lesion will be injected at each administration. In the event that the injected lesion shrinks and/or is no longer injectable (ie, no longer accessible, not appropriate for injection, or for other reasons), additional lesions may also be considered for injection and the same guidance for injection of these lesions will apply in terms of accessibility, injectability, and follow-up. The sequence of lesion selection for injection should be agreed in advance by the investigator and treating team. If no other injectable lesions are available, treatment will stop.

Additional guidance for direct and ultrasound/CT guided injection will be provided in a separate manual.

9.4.1.4 Management of Cytokine Release Storm

Cytokine release storm (CRS) has been identified as a potential safety risk in immunotherapies, especially drugs that act as agonists for immune activation. Guidance for identification and management is provided in Table 5. IL-6 will be assessed by the site as clinically indicated. For E7766 dose adjustments and interruptions for the management of CRS, refer to Table 4.

Table 5 Management of Cytokine Release Storm and Organ Toxicity

CRS Grade (CTCAE)	Sign/Symptom	Management
Grade 1	Fever or Grade 1 organ toxicity	• Acetaminophen and hypothermia blanket as needed for fever • Ibuprofen if fever is not controlled with above; use with caution or avoid if thrombocytopenic • Assess for infection with blood and urine cultures, and chest x-ray • Consider antibiotics and filgrastim (if neutropenic) • IV fluids as needed • Symptomatic management of constitutional symptoms and organ toxicities • Consider IL-6 antagonist[1] for persistent (greater than 3 days) or refractory fever
Grade 2	Hypotension	• IV fluid bolus of 500 – 1,000 mL normal saline; repeat as necessary to maintain SBP greater than 90 mmHg • Consider IL-6 antagonist[1] for hypotension refractory to fluid boluses • If hypotension persists after two fluid boluses and IL-6 antagonist[1], start vasopressors, transfer patient to ICU, and obtain ECHO • In patients at high-risk for severe CRS[2], if hypotension persists after IL-6 antagonist[1], if there are signs of hypoperfusion[3] or if there is rapid deterioration in the opinion of the clinician, may use dexamethasone 10 mg IV every 6 hours • Manage fever and constitutional symptoms as in Grade 1 CRS
	Hypoxia	• Use supplemental oxygen as needed • Use IL-6 antagonist[1] with or without corticosteroids as in hypotension • Manage fever and constitutional symptoms as in Grade 1 CRS
	Grade 2 organ toxicity	• Manage organ toxicity as per standard guidelines • Use IL-6 antagonist[1] with or without corticosteroids as in hypotension • Manage fever and constitutional symptoms as in Grade 1 CRS
Grade 3	Hypotension	• IV fluid boluses as needed as in Grade 2 CRS • IL-6 antagonist[1] as in Grade 2 if not administered previously • Use vasopressors as needed • Transfer patient to ICU and obtain ECHO if not performed already • Start dexamethasone 10 mg IV every 6 hours; increase to 20 mg IV every 6 hours

		if refractory • Manage fever and constitutional symptoms as in Grade 1 CRS
	Hypoxia	• Use supplemental oxygen including high-flow oxygen delivery and non-invasive positive pressure ventilation • Use IL-6 antagonist[1], corticosteroids as above and supportive care
	Grade 3 organ toxicity or Grade 4 increased transaminases	• Manage organ toxicity as per standard guidelines • Use IL-6 antagonist[1], corticosteroids as above and supportive care • Manage fever and constitutional symptoms as in Grade 1 CRS
Grade 4	Hypotension	• IV fluids, IL-6 antagonist[1], vasopressors, and hemodynamic monitoring as in Grade 3 • High-dose methylprednisolone[1] • Manage fever and constitutional symptoms as in Grade 1
	Hypoxia	• Mechanical ventilation • Use IL-6 antagonist[1], high-dose methylprednisolone[1] and supportive care
	Grade 4 organ toxicity, excluding increased transaminases	• Symptomatic management of organ toxicity as per standard guidelines • Use IL-6 antagonist[1], high-dose methylprednisolone[1] and supportive care

CRS = cytokine release storm, CTCAE = Common Terminology Criteria for Adverse Events, ECHO = echocardiogram, ICU = intensive care unit, IL-6 = interleukin 6, IV = intravenous, SBP = systolic blood pressure.

[1] See Appendix 6 for Interleukin-6 Antagonist and Corticosteroid Dosing Tables.

[2] High risk for CRS includes any of the following:

- High tumor burden
- Early onset CRS (less than 3 days from cell infusion)
- Co-morbidities (a score of 3 or greater using the Hematopoietic Cell Transplantation Comorbidity Index; for solid tumor patients – prior solid tumor will not be counted)

[3] Signs of hypoperfusion include:

- Decreased urine output (less than 0.5 mL/kg/hour)
- Lactate greater than or equal to 4 mmol/L, rising lactate, and/or poor lactate clearance (less than 10%) despite adequate fluid resuscitation.

Source: Adapted from MD Anderson Cancer Center CAR cell therapy toxicity assessment and management protocol (Teachey, et al., 2016; MD Anderson Cancer Center, 2017).

9.4.2 Identity of Investigational Product(s)

9.4.2.1 Chemical Name, Structural Formula of E7766

Standard Text

- Test drug code: E7766
- Generic name: N/A
- Chemical name: (1*R*,3*R*,15*E*,28*R*,29*R*,30*R*,31*R*,34*R*,36*R*,39*S*,41*R*)-29,41-Difluoro-34,39-bis(sulfanyl)-2,33,35,38,40,42-hexaoxa-4,6,9,11,13,18,20,22,25,27-decaaza-34λ^5,39λ^5-diphosphaoctacyclo [28.6.4.1^{3,36}.1^{28,31}.0^{4,8}.0^{7,12}.0^{19,24}.0^{23,27}]dotetraconta-5,7,9,11,15,19,21,23,25-nonaene-34,39-dione diammonia

- Molecular formula: $C_{24}H_{26}F_2N_{10}O_8P_2S_2 \cdot 2NH_3$
- Molecular weight: 780.66 (746.60, Free Acid)

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

E7766 will be labeled in accordance with text that is in full regulatory compliance with each participating country and will be translated into the required language(s) for each of those countries.

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

This is an open-label, single-arm study. All subjects who provide signed informed consent to participate in this study and satisfy all eligibility requirements (see Section 9.3) will be assigned to receive E7766. There is no randomization in this study.

9.4.4 Selection of Doses in the Study

Refer to Section 9.2 for the rationale for FIH dose selection.

9.4.5 Selection and Timing of Dose for Each Subject

Refer to Section 9.4.1.1 for dosing schedule for E7766.

9.4.6 Blinding

This is an open-label study; the treatment will not be blinded.

9.4.7 Prior and Concomitant Therapy

All prior medications (including over-the-counter medications) administered 30 days before the first dose of study drug and any concomitant therapy administered to the subject during the course of the study (starting at the date of informed consent) until 90 days after the final dose of study drug or start day of another anticancer therapy, whichever is earlier. If the subject initiates new anticancer therapy within 30 days, then concomitant medications must be collected for 30 days following the last dose of E7766. Additionally, all diagnostic, therapeutic, or surgical procedures relating to malignancy should be recorded. Any medication that is considered necessary for the subject's health and that is not expected to interfere with the evaluation of or interact with E7766 may be continued during the study.

Treatment of complications or AEs, or therapy to ameliorate symptoms (including blood products, blood transfusions, fluid transfusions, antibiotics, and antidiarrheal drugs), may be given at the discretion of the investigator, unless it is expected to interfere with the evaluation of (or to interact with) E7766.

Aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), and LMWH are permissible but should be used with caution. It is recommended that their LMWH treatment is stopped 24 hours before the intratumoral injection and resumed again 24 hours after the injection. Granulocyte colony-stimulating factor (g-CSF) or equivalent may be used in accordance with American Society of Clinical Oncology (ASCO), institutional, or national guidelines. Erythropoietin may be used according to ASCO, institutional, or national guidelines, but the subject should be carefully monitored for increases in red blood cell counts.

9.4.7.1 Drug-Drug Interactions

CCI

[redacted]

9.4.7.2 Prohibited Concomitant Therapies and Drugs

- Other investigational drugs.
- Other antitumor therapies such as chemotherapy, radiotherapy, antitumor interventions (surgical resection), or antitumor immunotherapy. Palliative radiotherapy may be allowed in up to 2 nontarget lesions upon discussion between investigator and sponsors. Patients may continue the use of bisphosphonates or denosumab for bone disease provided the dose is stable before and during the study and they were started at least 2 weeks prior to study drug. Additionally, cases where these drugs may be indicated should be discussed and agreed upon between investigator and sponsors.

- Systemic steroid therapy or any other form of immunosuppressive therapy. Any such therapy should be stopped at least 7 days prior to the first dose of study treatment. The use of physiologic doses of corticosteroids (up to 10 mg/d of prednisone or equivalent) may be approved after consultation with the sponsors.
- CCI

If subjects receive additional antitumor therapies, such as chemotherapy, hormone therapy, radiotherapy (with the exception of palliative radiotherapy as described above), or immunotherapy, this will be judged to represent evidence of disease progression, and study medication will be discontinued. These subjects should complete all off-treatment assessments and continue to be followed for survival in the Follow-Up Phase.

9.4.8 Prohibitions and Restrictions During the Study Period

It is recommended that subjects should avoid prolonged exposure to sunlight, and use sunscreens, umbrellas, and protective long sleeved clothing to minimize sun exposure, pending completion of test to assess E7766's phototoxicity potential.

Physical Activity Restrictions in subjects with Lymphoma (undergoing ^{18}fluorodeoxyglucose [^{18}FDG] -positron emission tomography-CT [PET-CT] assessments):

To minimize uptake of radiotracer into muscle, the subject should avoid strenuous exercise or exposure to cold before undergoing a ^{18}FDG-PET-CT examination for a minimum period of at least 6 hours, but with a target of 24 hours, prior to the examination. Specific instructions will be provided by the imaging core laboratory.

9.4.9 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.10 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsors:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsors and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study

- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator (PI) and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae (CV) of the PI including a copy of the PI's current medical license or medical registration number on the CV
- A signed and dated clinical studies agreement
- A copy of the regulatory authority approval for the country in which the study is being conducted, and the Import License

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs/study supplies (dispensing, inventory, and record keeping) following the sponsors' instructions and adherence to Good Clinical Practice (GCP) guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs/study supplies to be used other than as directed by this protocol. Study drugs/study supplies will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs/study supplies, dispensing of study drugs/study supplies to the subject, collection and reconciliation of unused study drugs/study supplies that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs/study supplies to the sponsor or (where applicable) destruction of reconciled study drugs/study supplies at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs/study supplies, (b) study drugs/study supplies dispensing/return reconciliation log, (c) study drugs/study supplies accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs/study supplies and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, MHRA). As applicable, all unused study drugs/study supplies and empty and partially empty containers from used study drugs/study supplies are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs/study supplies that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's

designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs/study supplies and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs/study supplies to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs/study supplies that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs/study supplies may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs/study supplies are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity.

9.5.1.2 Baseline Assessments

9.5.1.2.1 Medical History and Physical Examinations

Medical and surgical history and current medical conditions will be recorded at the Screening Visit. All medical and surgical history must be noted in the Medical History and Current Medical Conditions case report form (CRF).

Physical examinations (comprehensive or symptom directed) will be performed as designated in the Schedule of Procedures/Assessments (Table 7). A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Event CRF.

Information on history of current malignancy will be collected, including tumor type and prior therapy, with response and duration of response for each therapy.

9.5.1.2.2 OTHER BASELINE ASSESSMENTS

Assessment of prior and concomitant medications, ECOG performance status echocardiogram/MUGA, 12-lead ECG, ECG Holter monitoring, pregnancy test, vital signs, hematology, blood chemistry, and urinalysis will be performed per the Schedule of Procedures/Assessments (Table 7).

9.5.1.3 Efficacy Assessments

The schedule of assessments for efficacy analysis based on tumor imaging is presented in the Schedule of Procedures/Assessments (Table 7) and details are described below.

9.5.1.3.1 SOLID TUMORS

Tumor assessments will be performed according to modified RECIST 1.1, followed by iRECIST, if appropriate. Tumor assessments will follow Eisenhauer, et al. (2009) per a modified RECIST 1.1. The modification allows selection of up to 10 target lesions, with up to 5 per organ (as opposed to a maximum of 5 target lesions, up to 2 per organ in unmodified RECIST 1.1). Investigator-determined response assessments will be performed at each assessment time point.

All tumor assessment scans and photographs will be sent to an imaging core laboratory designated by the sponsor for quality assessment, tumor lesions volumetric assessment, and archival for potential independent efficacy review.

Tumor assessments at Screening:

- **Tumor assessments:** CT scans (with oral and intravenous contrast) of chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to Cycle 1 Day 1. Information from the baseline scans should be used to complete Appendix 1 for identification, categorization, and documentation of all target lesions, injectable lesions, and if available, non-injected biopsy lesion. This should be performed in a joint multidisciplinary team approach comprising of the radiologist, interventional radiologist, and oncologist. Injectable lesions should be prioritized based on ease of accessibility and degree of risk (eg, bleeding) involved with administration of E7766.

  Skin lesions may be considered as target lesions if documented with color photographs with a millimeter ruler in the same plane as the lesion, as nontarget lesions if photographic and measurement documentation is not available, or as new lesions if they meet the minimum size criteria for a measurable lesion.

  MRI scans may be used instead of CT scans for head, neck, abdomen and pelvis; however, chest lesions must be assessed using CT. Chest disease may not be followed

using chest x-ray. The same method of assessment used at Screening must be used at all time points.

Subjects with HNSCC must also have head and neck scans performed. Historical standard of care scans that are performed with scanning parameters consistent with the requirements for the protocol within 28 days prior to dosing are acceptable.

CT scans should be performed with oral and iodinated intravenous contrast and MRI scans with intravenous gadolinium chelate unless there is a medical contraindication to contrast. If iodinated intravenous contrast is contraindicated, chest CT should be performed without intravenous contrast. The method of assessment must be consistent at all time points.

- **Bone scans**: For subjects with triple-negative breast cancer and non-small cell lung carcinoma, or other tumor types where bone metastases are common, bone scans will be performed at Screening. Lesions identified on bone scans must be verified with correlative cross-sectional imaging. Cross sectional imaging will be used to follow response in target and nontarget lesions.
- **Brain MRI:** A brain MRI (pre- and post-gadolinium contrast) must be performed at Screening to assess potential CNS disease and/or metastases. Subjects with protocol-eligible treated bone metastasis (See Exclusion Criterion #7) will be followed up as described below.
- **Biopsy:** A pretreatment biopsy will be obtained during the Screening Period (Day -28 to Day -1) from the lesion selected for injection (mandatory), and from one prespecified non-injected lesion, if available (Appendix 1).

Tumor assessments during study:

- CT scans for head, neck, abdomen and pelvis will be carried out every 6 weeks (± 7 days) counting from Cycle 1 Day 1 during treatment cycles in the Treatment Phase, the Extension Phase, and, if the subject has discontinued treatment without confirmed disease progression, the Follow-Up Phase.

  MRI scans may be used instead of CT scans for head, neck, abdomen and pelvis; however, chest lesions must be assessed using CT. Chest disease may not be followed using chest x-ray. The same method of assessment must be used at all time points as used at Screening
- **Bone scans:** For subjects with triple-negative breast cancer and non-small-cell lung carcinoma, or other tumor types where bone metastases are common, bone scans will be performed every 24 weeks, or sooner if clinically indicated, and at confirmation of response. Lesions identified on bone scans must be verified with correlative cross-sectional imaging. Cross sectional imaging will be used to follow response in target and nontarget lesions.
- **Brain MRI**:

- For subjects with protocol-eligible treated brain metastases (See Exclusion Criterion #7) detected at the Screening MRI brain, a brain scan must be performed at all tumor assessment time points.
- For all subjects, a follow-up brain scan must be performed to confirm a CR within 1 week following response confirmation, or if clinically indicated.

For definitions of target and nontarget lesions at Baseline, assessment of target, nontarget, and new lesions after Baseline, and overall tumor assessment using iRECIST, refer to Appendix 1 and Appendix 2.

Responses should be confirmed no less than 4 weeks following the initial response (generally at the next 6 weekly scheduled tumor assessment visit).

Tumor assessments should initially proceed according to modified RECIST 1.1.

Per iRECIST, disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of progressive disease in clinically stable subjects. Subjects who have unconfirmed progressive disease per iRECIST (iUPD) may continue on treatment at the discretion of the investigator until progression is confirmed by the site, provided they have met the following conditions.

When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules (Appendix 2). This allowance to continue treatment despite initial radiologic progressive disease takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. These data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Subjects who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging should resume at the subsequent scheduled imaging time point, if clinically stable. Subjects who have confirmed disease progression by iRECIST (for solid tumors) or LYRIC (for lymphoma), as assessed by the site, will discontinue study treatment. Exceptions may be discussed with the study medical monitor.

Subjects going off study without disease progression will also undergo tumor assessments every 6 weeks until disease progression is documented or another anticancer therapy is initiated.

9.5.1.3.2 LYMPHOMA

Tumor assessments will be performed based on Lugano (Cheson, et al., 2014) followed by LYRIC criteria (Cheson, et al., 2016) for confirmation of disease progression, if appropriate. Investigator-determined response assessments will be performed at each assessment time point.

Tumor assessments will be carried out during the Pretreatment Phase, at Week 9 (during the 9th week counting from Cycle 1 Day 1), and then every 12 weeks during treatment cycles in both the Treatment Phase and the Extension Phase.

An ^{18}FDG-PET-CT scans (contrast-enhanced diagnostic quality CT) of neck, chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to Cycle 1 Day 1), using the above tumor assessment schedule, and as indicated clinically. While diagnostic quality contrast-enhanced PET-CT is preferred, if contrast-enhanced images are not obtainable, noncontrast PET-CT will be acceptable. Historical standard of care scans that are performed with scanning parameters consistent with the requirements for this protocol within 28 days prior to dosing are acceptable.

Information from the baseline scans should be used to complete Appendix 1 for identification, categorization, and documentation of all target lesions, injectable lesions, and, if available, the non-injected biopsy lesion. This should be performed in a joint multidisciplinary team approach comprising of the radiologist, interventional radiologist, and oncologist.

A pretreatment biopsy will be obtained during the Screening Period (Day -28 to Day -1) from the lesion selected for injection (mandatory), and from one prespecified non-injected lesion, if available (Appendix 1).

Tumor assessments should initially proceed according to Lugano criteria (Appendix 3).

If the investigator believes that, at the time of Lugano progressive disease, a subject is experiencing clinical stability or improvement, they will be considered as having an immune response (IR), and continue to be followed according to LYRIC criteria. The subject must be considered likely to tolerate continued treatment and not at risk of serious complications should further tumor growth occur. For a subject categorized as having IR, repeat imaging is mandatory after an additional 12 weeks (or sooner if clinically indicated) to assess whether they have true progressive disease.

9.5.1.3.3 ALL SUBJECTS

In addition to the individual lesion measurement data that will be collected for all lesions, the specific lesion injected at each time point/dose administration should be recorded. In addition, lesions that are biopsied should be recorded as such (at the time point) to allow evaluation of exploratory efficacy endpoints such as the effect on injected versus non-injected lesions.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Samples of blood, urine, and feces for PK analyses will be collected as described in the Schedule of Procedures/Assessments.

E7766 in plasma, urine, and feces will be determined using validated LC-MS/MS assays. If appropriate, assay of plasma, urine and feces samples for any metabolites of E7766 may be explored. Instructions on PK sample collection, handling, storage, and shipment will be detailed in the study-specified Laboratory Manual to be provided to the site.

Blood, urine, and fecal samples may also be used for exploratory analysis of metabolites.

Blood will also be drawn where possible at the first report of a serious adverse event (SAE) or severe unexpected AE and at its resolution.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ASSESSMENTS

Overview of Biomarker Approach

Pharmacodynamics biomarkers of E7766 include POM biomarkers and Proof of Principle (POP) biomarkers, which will be measured to evaluate modulation of the STING pathway and of both innate and adaptive immune response, respectively, by E7766 treatment in human subjects.

- To measure the STING pathway modulation, expression of a panel of STING pathway genes by E7766 will be examined as part of immune gene profiling in the tumor biopsies and in the blood.
- To measure the innate and adaptive immune response, immune gene profiling will be performed for the available tumor biopsies and for the blood. Immune cytokines and immune cell phenotyping may be analyzed in the blood as well.

Results from the pharmacodynamics biomarker studies may be used to aid the selection for the RP2D and to monitor drug biological activity. Blood and tumor tissue samples will be collected from study subjects at protocol-specified time points as indicated in the Schedule of Procedures/Assessments (Table 7). It is worthy to note that when new research results

emerge, the parameters and methods for the pharmacodynamics biomarker analysis may change.

Instructions for the processing, storage, and shipping of samples will be provided in the Laboratory Manual.

Biomarker sample collection:

Mandatory paired pre- and on-treatment tumor biopsies will be obtained from injected and, if available, from one non-injected lesion, with appropriate subject consent, to examine the potential intratumoral STING pathway modulation and antitumor immune response enhancement upon E7766 treatment at both local and systemic levels. These markers may include a panel of E7766-regulated STING pathway genes, including IFNβ1, type I IFN genes, TNFα, and IL6, and immune activation genes such as granzyme B, perforin, and IFNy. Immune cell infiltration and T-cell repertoire may also be investigated. Mandatory on-treatment tumor biopsy will be performed on Day 1 of Cycle 2, on the day of drug administration. Subjects should have the biopsy with the same image-guided procedure as E7766 injection. The biopsy will be performed after the E7766 administration. In the event that E7766 administration is delayed, the biopsy time will be moved as well, to coincide with drug administration.

In the event that a subject is required to have additional tumor biopsy(s) for medically indicated reasons while on study, formalin-fixed paraffin-embedded (FFPE) tissue will be requested for shipment for exploratory biomarker analysis.

Blood biomarkers:

Blood biomarker samples from study subjects may be analyzed for immune cytokine expression monitoring by ELISA, multiplex bead-based immunoassay, or other assays/methods and new technology. Whole blood (peripheral blood mononuclear cell [PBMC]) may be subjected to immune gene expression profiling and flow cytometric analysis as well. Blood biomarker samples will be collected both prior to the first administration and during the treatment process.

Archival Tumor:

Archived, fixed tumor tissue will be collected (if available). These tissues may be used for assessment of mutations and other genetic alterations or immune cell infiltration status and their relationship with tumor response to E7766.

Pharmacogenetic (PG) Assessment:

Whole blood DNA and RNA samples will be collected for STING genotype and gene expression analyses, respectively. The DNA samples may be utilized also for PG analysis. The role of DNA sequence variability on the absorption, distribution, metabolism, and

elimination (ADME) of E7766 may be evaluated in this study. Variation in E7766 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or pharmacodynamics data.

General

Data obtained will be used for research, to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. The DNA will not be used to determine or predict risks for diseases that an individual subject does not currently have. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to E7766 or cancers, and for potential diagnostic development.

Archived tumor tissue samples and blood samples for pharmacodynamics, PG, and other biomarker assessments will be collected from all consented study subjects, except where prohibited by regional or local laws.

Samples may be used for biomarker discovery and/or validation to identify blood or tumor biomarkers that may be useful to predict treatment response (efficacy, pharmacodynamics), PK, and/or safety-related outcomes. Samples may also be used for potential diagnostic development. In addition, biomarkers identified in other clinical studies may also be assessed in samples collected from subjects enrolled in this study. The decision to perform exploratory biomarker analysis may be based on the clinical outcome of the study and/or the signals observed in other clinical studies.

Further details are provided in Appendix 8.

Exploratory Imaging Biomarkers

Tumor volume (3-dimensional size as opposed to measuring a single diameter) changes (per independent imaging review) as assessed using all CT/MRI scans will also be explored as a continuous variable.

Time course changes in pre-injection sizes of injected lesions per investigator assessment will be evaluated. The assessment should be performed using the same modality of radiological guidance that will be used for the E7766 injection (for example, USG, CT, or MRI, or for superficial lesions, photography, calipers, or ruler).

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs, including all CTCAE v 5.0 grades (for both increasing and decreasing severity), and SAEs; regular monitoring of hematology, blood chemistry, and urine values; periodic measurement of vital signs, ECHO/MUGA scans, safety ECGs; and physical examinations. The effects of E7766 on cardiac repolarization will be evaluated via continuous Holter/ECG monitoring.

9.5.1.5.1 ADVERSE EVENTS

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E7766.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE).
- Any new disease or exacerbation of an existing disease.
- Any new disease or exacerbation of an existing disease. However, worsening of the primary disease should be captured under efficacy assessments as disease progression rather than as an AE.
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug.
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline).
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs, regardless of relationship to study drug or procedure, should be recorded beginning from the time the subject signs the study ICF through the last visit and for 90 days after the subject's last dose or start day of another anticancer therapy, whichever is earlier. If the subject initiates new anticancer therapy within 30 days, then AEs must be collected for 30 days following the last dose of E7766. SAEs will be collected for 90 days after the last dose or start day of another anticancer therapy, whichever is earlier. If the subject initiates new anticancer therapy within 30 days, then SAEs must be collected for 30 days following the last dose of E7766. All AEs should be recorded in the Adverse Event CRF.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

Abnormal ECG (QTcF) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTcF interval is more than 450 ms and there is an increase of more than 60 ms from baseline. Any ECG abnormality that the investigator considers as an AE should be reported as such.

All AEs must be followed for 90 days after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Subjects with onset of an AE or deterioration of a preexisting AE will be followed until resolution to baseline, start of a new anticancer treatment, or death.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to CTCAE v 5.0. Investigators will report CTCAE grades for all AEs (for both increasing and decreasing severity).

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated With Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 6. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 7) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 6 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Chloride, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin, International Normalized Ratio (INR)
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, calcium, cholesterol, globulin, glucose, lactate dehydrogenase, phosphorus, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, RBCs, specific gravity, WBCs

RBC = red blood cell, WBC = white blood cell.

All hematology, blood chemistry (including pregnancy test, as applicable), and urinalysis samples are to be obtained prior to study drug administration and results reviewed prior to administration/dispensing of study drug at the beginning of each treatment cycle. Refer to Table 4 for the management of clinically significant laboratory abnormalities.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the CRF Completion Guidelines). In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic blood pressure [BP] [mmHg], pulse [beats per minute], respiratory rate [per minute], body temperature [in centigrade]), height, and weight (kg) will be obtained at the visits designated in the Schedule of Procedures/ Assessments (Table 7) by a validated method. Blood pressure and pulse will be measured

after the subject has been sitting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

For subjects with an elevated BP (≥140/90 mmHg), confirmation should be obtained by performing 3 measurements (at least 5 minutes apart) to yield a mean value. Systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg should be confirmed by repeat measurements after 1 hour.

9.5.1.5.5 PHYSICAL EXAMINATIONS

Comprehensive or system-directed physical examination will be performed as designated in the Schedule of Procedures/Assessments (Table 7). Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Event CRF.

A comprehensive physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, skin, and a complete neurological examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. A symptom-directed physical examination will be performed on Day 1 of all treatment cycles and at any time during the study, as clinically indicated.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in the Schedule of Procedures /Assessments (Table 7). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Event CRF.

Additionally, QTc intervals will be evaluated in the Dose Escalation part only, unless a signal indicates the need for continued monitoring in the Dose Expansion part.

The effects of E7766 on cardiac repolarization will be evaluated via 24-hour, 12-lead continuous Holter/ECG monitoring during Baseline, Cycle 1 Day 1, Cycle 1 Day 14, and Cycle 1 Day 15 in the Dose Escalation part of the study only. Additionally, cardiodynamic evaluation, including concentration-QTc (C-QTc) analysis will be performed in the Dose Escalation part only, unless a signal indicates the need for continued monitoring in the Dose Expansion part. For this purpose, replicate 12-lead ECGs will be extracted from 24-hour

continuous recordings (Holters) by a central ECG laboratory at time points, as detailed in the Schedule of Procedures/Assessments (Table 7). QT intervals will be measured from Lead II and will be corrected for QTc using Fridericia's correction factors (QTcF). The primary QTc parameter will be QTcF. Secondary parameters (heart rate, PR interval and QRS) and treatment-emergent T wave abnormalities and U-waves will be evaluated. Potential effects of E7766 will be evaluated as change-from predose baseline heart rate, PR interval, QRS, and QTcF by postdosing time point. For purposes of QT assessment, concentration-QTc analysis will be performed of the relationship between E7766 plasma levels and ΔQTcF.

9.5.1.5.7 ECHO/MUGA

A MUGA scan (using technetium-99m-pertechnetate) or an ECHO to assess LVEF will be performed as indicated in Schedule of Procedures/Assessments (Table 7). MUGA and ECHO scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual subject at Baseline should be repeated for all subsequent LVEF assessments for that subject. The LVEF as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.

9.5.1.5.8 PREGNANCY TEST

A serum β-hCG test will be performed for premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months at Screening. A 6-mL sample of blood will be taken at designated time points as specified in the Schedule of Procedures/ Assessments (Table 7). Subsequent to the serum pregnancy test at Screening, a urine or serum pregnancy test can be performed at subsequent time points as specified in the Schedule of Procedures/Assessments (Table 7).

9.5.1.5.9 ASSESSMENT OF CYTOKINES

In preclinical studies, intratumorally or subcutaneously administered E7766 upregulated expression of certain cytokines in the blood, suggesting a possibility of inducing CRS in patients who will receive E7766 treatment.

In case a CRS-like symptoms occur, tocilizumab (anti-IL6R) and other treatment as per standard practice at the study sites may be given to the subjects according to the recent successful outcome in the CART clinical study (Teachey, et al., 2016; MD Anderson Cancer Center, 2017) (Table 5).

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 7 presents the schedule of procedures and assessments for the E7766-G000-101 study.

Table 7 Schedule of Procedures/Assessments in Study E7766-G000-101 for Dose Escalation and Dose Expansion parts

	Phase	PRETREATMENT[a]		TREATMENT[b]						EXTENSION			Off-Treatment[b]	FOLLOW-UP PHASE
	Period	Screening	Baseline	Cycle 1 (Induction Cycle)						Cycle 2		Cycle 3 and beyond	Within 30 days	
	Visit	1	2	3	3	4	5	5	5	6	7	8, 9, etc	98	100
	Day	-28 to -1	-3 to -1	1	2	8	14	15	16	1	15	1		
CRF	Procedures/Assessments													
S	Informed consent	X												
S	Inclusion/exclusion criteria	X												
S	Medical history and demography	X												
N	Admit to clinic[c]		X[c]				X							
N	Discharge from clinic[c]				X[c]				X					
S	Physical examination[d] and vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	
S	Echocardiogram/MUGA[e]	X											X	
S	Pregnancy test[f]	X	X	X						X		X	X	
S	ECOG performance status	X		X									X	
S	12-lead ECGs[g]	X	X	X						X		X	X	
S	ECG Holter monitoring[h]		X	X	X		X	X	X					
S	Hematology/blood chemistry[i]	X	X	X	X	X		X		X		X	X	
S	Urinalysis[j]	X	X	X		X		X		X		X	X	
S	PK blood samples[k]			X	X	X		X	X	X		X		
N	PK urine and feces[l]		X	X	X			X	X					
N	PG whole blood	X												
N	PD whole blood for cell profiling[m]			X				X				X	X	

	Phase	PRETREATMENT[a]		TREATMENT[b]						EXTENSION			Off-Treatment[b]	FOLLOW-UP PHASE
	Period	Screening	Baseline	Cycle 1 (Induction Cycle)						Cycle 2		Cycle 3 and beyond	Within 30 days	
	Visit	1	2	3	3	4	5	5	5	6	7	8, 9, etc	98	100
	Day	-28 to -1	-3 to -1	1	2	8	14	15	16	1	15	1		
CRF	Procedures/Assessments													
N	PD whole blood for RNA [n]		X	X	X			X	X	X		X	X	
N	PD whole blood for ctDNA[o]	X		X				X		X	X	X	X	
N	PD whole blood for cytokines[p]		X	X	X			X	X	X		X	X	
N	Paired tumor biopsy[q]	X	X							X				
S	Archival tumor block or slides[r]	X												
N	Solid tumor assessments: CT or MRI[s]	X									X			X[s]
N	Lymphoma tumor assessments[t]	X									X			X[t]
N	Brain MRI[u]	X									X			
S	Bone scan[v]	X									X		X	
S	Adverse events [w]	X	X	X	X	X	X	X	X	X	X	X	X	X
S	Prior and concomitant medications[w]	X	X	X	X	X	X	X	X	X	X	X	X	X
N	Administration of E7766[x]			X		X		X		X		X		
N	Pre-injection lesion size assessment[y]			X		X		X		X		X		
S	Survival status[z]													X

For the CRF: N = nonstandard assessment (study-specific), N/A = not applicable, S = standard assessment.

β-hCG = beta-human chorionic gonadotropin, BP = blood pressure, C = cycle, CR = complete response, CRF = case report form, CT = computed tomography, D = day, DNA = deoxyribonucleic acid, ECOG = Eastern Cooperative Oncology Group, FDG-PET = fluorodeoxyglucose-positron emission tomography, h = hour, HNSCC = head and neck squamous cell carcinoma, HR = heart rate, IV = intravenous, LYRIC = LYmphoma Response to Immunomodulatory Therapy Criteria, MRI = magnetic resonance imaging, MUGA = multigated acquisition, NSCLC = non-small cell lung cancer, PK = pharmacokinetic, PD = pharmacodynamics, RECIST = Response Evaluation Criteria in Solid Tumors, RNA = ribonucleic acid, RR = respiratory rate, SAE = serious adverse event, TNBC = triple-negative breast cancer, USG = ultrasonography.

a. The Pretreatment Phase (Screening Period) extends from Day -28 to Day -1, except for signing of the informed consent form, which may be up to 8 weeks

	Phase	PRETREATMENT[a]		TREATMENT[b]						EXTENSION			Off-Treatment[b]	FOLLOW-UP PHASE
	Period	Screening	Baseline	Cycle 1 (Induction Cycle)						Cycle 2		Cycle 3 and beyond	Within 30 days	
	Visit	1	2	3	3	4	5	5	5	6	7	8, 9, etc	98	100
	Day	-28 to -1	-3 to -1	1	2	8	14	15	16	1	15	1		
CRF	Procedures/Assessments													

before the first dose of study drug is administered. The baseline assessments may be performed from Day -3 to Day -1 (before the first dose of E7766). Screening assessments may be used as baseline assessments if performed within 72 hours of administration of the first dose of study medication.

b. The Treatment Phase consists of 1 cycle (Cycle 1 [induction cycle]) in the Dose Escalation part and 6 cycles in the Dose Expansion part (ie, Cycle 1 [induction cycle] + 5 maintenance cycles [ie, Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6]). The off-treatment assessments should occur within 30 days after the final dose of study treatment.

c. In the Dose Escalation part, subjects will be admitted at Baseline and on Cycle 1 Day 14 to the study clinic. In the Dose Escalation part, on Day 1 of Cycle 1 (ie, after the first dose only), subjects will remain at the study clinic for at least 30 hours after E7766 administration for monitoring of safety and can be discharged on Cycle 1 Day 2 if there are no safety concerns.

d. A comprehensive physical examination will be performed at Screening and at the Off-Treatment Visit. A symptom-directed physical examination will be performed on Day 1 of all treatment cycles and at any time during the study, as clinically indicated. Vital signs include BP, HR, RR, and body temperature, as well as weight and height. BP, HR, and RR will be collected after the subject has been sitting for 5 minutes. Height will be measured at the Screening Visit only. On all dosing days, vital signs should be measured prior to dosing. On Day 1 of Cycle 1, vital signs should be obtained postdose within 2 hours of dosing, and subsequently every 4 hours or as clinically indicated for 30 hours postdose. On the other dosing days, vital signs should be assessed postdose within 2 hours of dosing. Vital signs will also be assessed at the Off-Treatment Visit.

e. Echocardiograms or MUGA will be performed at Screening, during the Off-Treatment Visit (window of ±1 week), and if clinically indicated. MUGA scans and echocardiograms will be performed locally in accordance with the institution's standard practice.

f. A serum pregnancy test (β-hCG) will be performed at Screening for all premenopausal women and postmenopausal women who have been amenorrheic for less than 12 months. A urine or serum pregnancy test will be performed at Baseline, before the first dose of E7766 on Cycle 1 Day 1, on Day 1 of all subsequent cycles before E7766 dosing, and at the Off-Treatment Visit.

g. 12-Lead ECGs will be collected locally at the following time points: Screening (single) and Baseline (single unless abnormalities are observed or if clinically indicated, then in triplicate at 2-minute intervals); Day 1 of all Cycles (before and after [within 1 to 2 hours after E7766 injection]); and at Off-Treatment Visit. In case of any alteration, or if clinically necessary, an echocardiogram and/or cardiac enzymes should be performed.

h. Continuous time matched Holter-ECGs to be collected on the day prior to first and third administration of E7766 in Cycle 1, ie, Day -1 and Day 14; and on Cycle 1 Day 1 and Day 15. Replicate 12-lead ECGs will be extracted from the recordings at predose, at end of E7766 administration, and at 0.25, 0.5, 1, 1.5,

	Phase	PRETREATMENT[a]		TREATMENT[b]						EXTENSION			Off-Treatment[b]	FOLLOW-UP PHASE
	Period	Screening	Baseline	Cycle 1 (Induction Cycle)						Cycle 2		Cycle 3 and beyond	Within 30 days	
	Visit	1	2	3	3	4	5	5	5	6	7	8, 9, etc	98	100
	Day	-28 to -1	-3 to -1	1	2	8	14	15	16	1	15	1		
CRF	Procedures/Assessments													

2, 3, 4, 5, 6, 8, 10, 12, and 24 hours after the start of E7766 administration on both days. Subjects must be recumbent for a period of approximately 10 minutes before each time point. If possible, subjects will be encouraged to eat the same or similar food at the same time on all days that the Holter ECGs are conducted. Holter monitoring will be done only during the Dose Escalation part of the study.

i. Hematology and blood chemistry samples will be obtained before drug administration. Screening assessments may be used as baseline assessments if performed within 72 hours of the first dose of study medication. On Cycle 1 Day 1 before drug administration and at 6 hours and 24 hours posttreatment; on Cycle 1 Days 8 and 15 before drug administration, and from Cycle 2 onwards, Day 1 only predose, and at the Off-treatment Visit.

j. Urine samples will be obtained Screening, Baseline, and before all drug administration (either formal urinalysis or urine dipstick for protein and glucose are acceptable) and at the Off-Treatment visit.

k. During Dose Escalation part, blood samples for PK analysis will be collected on Day 1 and Day 15 of Cycle 1 at predose, and postdose at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours. During Dose Escalation part, on Day 8 of Cycle 1, and Day 1 of Cycle 2, Cycle 3, Cycle 4, Cycle 5 and Cycle 6, PK blood samples will be collected at predose and a sample postdose between 0.25 and 2 hours. During Dose Expansion part, on Day 1 and Day 15 of Cycle 1, and Day 1 of Cycle 2 PK blood samples will be collected at predose and a sample postdose between 0.25 and 2 hours. To the extent possible, blood samples will be collected from the arm contralateral to the injection site. Blood PK samples may also be used for pharmacodynamic analysis.

l. Urine collection for PK: all urine excreted over the 24-hour period starting with the administration of E7766 will be collected on Cycle 1 Day 1 and Day 15. The collection intervals are: 0 – 4 h, 4 – 8 h, 8 – 12 h, and 12 – 24 h. Urine samples for PK will only be taken during the Dose Escalation part of the study. Feces collection for PK: all feces excreted over the 24-hour period starting with the administration of E7766 will be collected. If a fecal sample is not obtained in the first 24-hour period, then the subject should remain in the clinic until the first available fecal sample is obtained. Time of collection will be recorded as well as the mass of each sample. Each sample will be kept separate. Fecal samples for PK will be taken only during the Dose Escalation part of the study at Cycle 1 Day 1. A predose feces sample should be also collected during the Baseline Pretreatment Phase prior to dose administration.

m. Whole blood for cell profiling will be obtained in the Dose Escalation as well as Dose Expansion part, 1 predose and 1 postdose sample between 2 to 8 hours (specific time point to be detailed in the laboratory manual) will be collected on C1D1, C1D15, C4D1. One sample will be collected at the Off-treatment Visit.

n. During Dose Escalation, blood samples for PD RNA analysis will be collected at Baseline and on C1D1, C1D15 at predose, and postdose at 1, 2, 4, 6, 8, 10, and 24 hours. On C2D1 and C4D1, 1 predose and 1 postdose sample between 2 to 8 hours (specific time point to be detailed in the laboratory manual) will

	Phase	PRETREATMENT[a]		TREATMENT[b]						EXTENSION			Off-Treatment[b]	FOLLOW-UP PHASE
	Period	Screening	Baseline	Cycle 1 (Induction Cycle)						Cycle 2		Cycle 3 and beyond	Within 30 days	
	Visit	1	2	3	3	4	5	5	5	6	7	8, 9, etc	98	100
	Day	-28 to -1	-3 to -1	1	2	8	14	15	16	1	15	1		
CRF	Procedures/Assessments													

be collected. In the Expansion part, blood samples for PD RNA analysis will be collected at Baseline, and on C1D1, C1D15, at predose, and postdose between 0 to 4 hours, and between 4 to 8 hours (specific time point to be detailed in the laboratory manual); and on C2D1, C4D1 at predose and one sample postdose between 2 to 8 hours (specific time point to be detailed in the laboratory manual). One sample will be collected at Off-Treatment visit.

o. Whole blood for ctDNA will be obtained in the Dose Escalation and Dose Expansion part during Screening, and predose on C1D1, C1D15, C2D1, C2D15, C4D1, Day 1 of every other subsequent cycle (ie, C6D1, C8D1, C10D1, etc), and during the Off-Treatment visit.

p. During Dose Escalation part, a single blood sample for PD cytokine analysis will be collected at Baseline, followed by a timecourse at C1D1 and C1D15 at predose, and postdose at 1, 2, 4, 6, 8, 10, 24 hours. On C2D1 and C4D1, 1 predose and 1 postdose sample between 2 to 8 hours (specific time point to be detailed in the laboratory manual) will be collected. In the Expansion part, blood samples for PD cytokines analysis will be collected at Baseline, and on C1D1, C1D15, at predose, and postdose between 0 to 4 hours, and between 4 to 8 hours (specific time point to be detailed in the laboratory manual); and on C2D1, C4D1 at predose and one sample postdose between 2 to 8 hours (specific time point to be detailed in the laboratory manual). One sample will be collected at the Off-Treatment visit.

q. Subjects must have accessible tumors for repeat biopsy. A pretreatment biopsy will be obtained during the Screening Period (Day -28 to Day -1) from the lesion selected for injection, and if available, from one non-injected lesion selected for biopsy. On-treatment biopsy will occur on Cycle 2 Day 1 on the day of drug administration. Two mandatory paired biopsies will be taken, pre- and postdose from the injected lesion and, where available, two paired biopsies from the non-injected lesion. Biopsies should be taken at the same time as the image-guided E7766 injection, with the biopsy occurring after E7766 administration.

r. Archival formalin-fixed paraffin-embedded (FFPE) tumor tissue will be collected if available.

s. Solid tumor assessments will be performed based on modified RECIST 1.1 followed by modified RECIST 1.1 for immune-based therapeutics (iRECIST), if appropriate. Tumor assessments will be carried out during the Pretreatment Phase and then every 6 weeks (±7 days, counting from Cycle 1 Day 1) during treatment cycles in both the Treatment Phase and the Extension Phase. CT scans (with oral and intravenous contrast) of chest, abdomen, and pelvis and of other known sites of disease will be obtained at Screening (within 28 days prior to Cycle 1 Day 1), and subsequently using the tumor assessment schedule above, and as indicated clinically. Skin lesions may be considered as target lesions if color photographs are available and measurement documented; else can be considered only as nontarget lesions (ie, without photographic or measurement documentation).

Subjects with HNSCC must also have head and neck scans performed. Historical standard of care scans that are performed with scanning parameters

	Phase	PRETREATMENT[a]		TREATMENT[b]						EXTENSION			Off-Treatment[b]	FOLLOW-UP PHASE
	Period	Screening	Baseline	Cycle 1 (Induction Cycle)						Cycle 2		Cycle 3 and beyond	Within 30 days	
	Visit	1	2	3	3	4	5	5	5	6	7	8, 9, etc	98	100
	Day	-28 to -1	-3 to -1	1	2	8	14	15	16	1	15	1		
CRF	Procedures/Assessments													

consistent with the requirements for this protocol within 28 days prior to dosing are acceptable.

MRI scans may be used instead of CT scans for head, neck, abdomen and pelvis; however, chest lesions must be assessed using CT. Chest disease may not be followed using chest x-ray. CT scans should be performed with oral and iodinated IV contrast and MRI scans with IV gadolinium chelate unless there is a medical contraindication to contrast. If iodinated IV contrast is contraindicated, a chest CT should be performed without IV contrast. The method of assessment must be consistent at all time points.

In the Follow-Up Phase, subjects going off study without disease progression will also undergo tumor assessments every 6 weeks (±7 days) until disease progression is documented or another anticancer therapy is initiated.

t. Lymphoma tumor assessments will be performed based on Lugano followed by LYRIC criteria, if appropriate, at Pretreatment, Week 9, and then every 12 weeks during treatment cycles. ^{18}FDG-PET-CT scans of neck, chest, abdomen and pelvis and of other know sites of disease will be obtained at Screening, Week 9 and then every 12 weeks during treatment cycles.

   In the Follow-Up Phase, subjects going off study without disease progression will also undergo tumor assessments every 12 weeks until disease progression is documented or another anticancer therapy is initiated.

u. A brain MRI (pre- and post-gadolinium contrast) must be performed at Screening. For patients with eligible brain metastases a brain scan must be performed at all tumor assessment time points. For all subjects, a follow-up brain scan must be performed to confirm a CR within 1 week following response confirmation, or if clinically indicated.

v. For subjects with TNBC and NSCLC, or other tumor types where bone metastases are common, bone scans will be performed at Screening, every 24 weeks, or sooner if clinically indicated, and at confirmation of response. Lesions identified on bone scans must be verified with correlative cross-sectional imaging.

w. Adverse events and prior and concomitant medications information will be collected at every study visit and until 90 days of last dose of study drug or start day of another anticancer therapy, whichever is earlier. If the subject initiates new anticancer therapy within 30 days, then adverse events/concomitant medications will be collected for 30 days following the last dose of E7766.

x. E7766 will be administered by intratumoral injection in 3-week cycles with an induction period in Cycle 1 (Days 1, 8, and 15) and a maintenance period Cycle 2 and thereafter on Day 1 of each cycle. A window period of ±1 day is allowed from Cycle 3 onwards.

y. Assessment of the size of the injected lesion will be performed on dosing days prior to E7766 injection. The assessment should be performed using the same modality of radiological guidance that will be used for the E7766 injection (for example, USG, CT, or MRI, or for superficial lesions, photography, calipers,

	Phase	PRETREATMENT[a]		TREATMENT[b]						EXTENSION			Off-Treatment[b]	FOLLOW-UP PHASE
	Period	Screening	Baseline	Cycle 1 (Induction Cycle)						Cycle 2		Cycle 3 and beyond	Within 30 days	
	Visit	1	2	3	3	4	5	5	5	6	7	8, 9, etc	98	100
	Day	-28 to -1	-3 to -1	1	2	8	14	15	16	1	15	1		
CRF	Procedures/Assessments													

or ruler). The lesion measurement is recommended to be based on the long axis diameter of the lesion, but measurement should be consistent throughout the study.

z. Subjects who discontinue study will be followed for survival (in person visit or phone call is acceptable). Survival follow-up will be conducted on all subjects approximately every 12 weeks (±1 week), unless they withdraw consent.

9.5.2.2 Description of Procedures/Assessments Schedule

Refer to Schedule of Procedures/Assessments in Table 7 and footnotes therein for description of procedures.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of oncology studies.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event.

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

Serious adverse events, regardless of causality assessment, must be collected through the last visit and for 90 days after the subject's last dose or start day of another anticancer therapy, whichever is earlier. If the subject initiates new anticancer therapy within 30 days, then SAEs will be collected for 30 days following the last dose of E7766. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsors or third party vendor acting on behalf of the sponsors to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in a female subject (or partner of a male subject) in which the estimated date of conception is either before the last visit or within 30 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 30 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of Serious Adverse Events [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study. A subject who becomes pregnant may remain in the study if the investigator judges that the potential benefit to the subject outweighs any potential risk to the subject or the fetus and the subject gives informed consent for the further participation.

9.5.4.3 Reporting of Events Associated With Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

Not applicable.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established

guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All suspected unexpected serious adverse reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Table 7).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, progression of disease, withdrawal of consent, pregnancy, study terminated by the sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the Subject Disposition CRF.

In the Dose Escalation part only, subjects who are not evaluable for DLT (eg, those subjects who fail to complete at least 2 E7766 injections during Cycle 1 for reasons other than DLT occurrence) should be replaced within their dose level, if at least 2 subjects in total have not been tested at the dose level.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits may be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the data cutoff date for the clinical study report (CSR) or the study is completed and the database is locked and released. Statistical analyses will be performed using SAS software or other validated statistical software as required. Details of the statistical analyses will be included in a separate statistical analysis plan (SAP).

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINTS

- Safety-related endpoints, including DLT
- ORR according to modified RECIST 1.1 and iRECIST, or Lugano and LYRIC, defined as the proportion of subjects achieving a best overall response of confirmed partial or complete response (PR + CR). Subjects who do not have a tumor response assessment for any reason will be considered nonresponders and will be included in the denominator when calculating the response rate (Dose Expansion part only)
- DOR according to modified RECIST 1.1 and iRECIST, or Lugano and LYRIC, defined as the time from the date of first documented PR or CR until the first documentation of confirmed disease progression or death, whichever occurs first (Dose Expansion part only)
- DCR according to modified RECIST 1.1 and iRECIST, or Lugano and LYRIC, defined as the proportion of subjects achieving PR or CR or stable disease (SD) (Dose Expansion part only).

9.7.1.1.2 SECONDARY ENDPOINTS

- ORR, DOR, and DCR according to iRECIST and modified RECIST 1.1, or Lugano and LYRIC (Dose Escalation part only)
- PK profile in plasma, urine, and feces (Dose Escalation part) and plasma only (in Dose Expansion part)
- PFS, defined as the time from the date of first dose to the date of the first documentation of confirmed disease progression or death, whichever occurs first
- OS, defined as the time from the date of first dose to the date of death from any cause
- Change in tumor size in injected lesions and in distant non-injected lesions

9.7.1.1.3 EXPLORATORY ENDPOINTS

- Changes in tumor size assessed by IIR using volumetric CT/MRI
- Immune pharmacodynamics effects of E7766 in the tumors and in the peripheral blood
- PK/pharmacodynamics relationships (safety and efficacy endpoints)
- Baseline immune phenotypes and its relationship with the response to E7766
- STING genotypes and its relationship with the response to E7766
- Changes in pre-injection size of injected lesion per investigator assessment

9.7.1.2 Definitions of Analysis Sets

DLT Analysis Set is the group of subjects in the Dose Escalation part who have completed Cycle 1, without incurring certain major protocol deviation (for instance those related to dosing or others identified before database lock), with at least 2 E7766 injections during

Cycle 1, and are evaluable for DLT, or subjects who have experienced DLT during Cycle 1. This will be the analysis set to evaluate tolerability.

Full Analysis Set is the group of subjects who received at least 1 dose of study drug. This will be the primary analysis set for efficacy evaluations, as well as for demographic and baseline characteristics.

Safety Analysis Set is the same group as Full Analysis Set. This will be the analysis set for all safety evaluations except DLT results.

Efficacy Analysis Set is the group of subjects who received at least 1 dose of study drug and had a baseline tumor assessment.

Pharmacokinetic (PK) Analysis Set is the group of subjects who have received at least 1 dose of study drug and have at least 1 evaluable plasma concentration.

Pharmacodynamic Analysis Set is the group of subjects who have received at least 1 dose of study drug and have evaluable pharmacodynamics data.

Pharmacokinetic/Pharmacodynamic Analysis Set is the group of subjects in the Safety Analysis Set that also have evaluable serum PK and pharmacodynamics pretreatment assessment and at least one posttreatment assessment.

9.7.1.3 Subject Disposition

The number (percentage) of enrolled and treated subjects will be summarized as well as subjects who completed the study or discontinued from the study, with reasons for discontinuation. The number (percentage) of subjects who completed the study treatment/discontinued from the study treatment and reasons for discontinuation will also be summarized. The summary will be presented for each dose level/arm, total of each part, and overall.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Full Analysis Set will be summarized for each dose level/arm, total of each part, and overall using descriptive statistics. Continuous demographic and baseline variables including age, weight, and height will be summarized and presented as N, mean, standard deviation, median, Q1, Q3, minimum, and maximum values. For categorical variables such as sex, age group, race, ethnicity, geographic region, ECOG PS, and NYHA cardiac disease classification, the number and percentage of subjects will be used.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The number

(percentage) of subjects who took prior and concomitant medications will be summarized on the Full Analysis Set by Anatomical Therapeutic Chemical (ATC) class (ie, Anatomical class, Pharmacological class), and WHO DD preferred term. Prior medications will be defined as medications that were stopped before the first dose of study drug. Concomitant medications will be defined as medications that were (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to 90 days after the subject's last dose, or start day of another anticancer therapy, whichever is earlier. If the subject initiates new anticancer therapy within 30 days, then medications given concomitantly will be recorded for 30 days following the last dose of E7766. The summary will be presented for each dose level/arm, total of each part, and overall as appropriate. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

Evaluations of clinical activity will be performed primarily on the Full Analysis Set. A summary of clinical activity on the Efficacy Analysis Set will also be provided as needed. The ORR, DOR, DCR, PFS (as assessed by the investigator), and OS will be listed and descriptively summarized as appropriate. If applicable, a waterfall plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions at postbaseline nadir (ie, maximum tumor shrinkage). The summary will be presented for each dose level/arm, total of each part, and overall as appropriate.

The analysis using the tumor assessment by lesions, such as injected lesions and non-injected lesions, will be conducted separately for the selected efficacy endpoints, if appropriate.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

Dose Escalation part:

There will be no primary efficacy analysis since the primary objective of the Dose Escalation part is to assess the safety/tolerability and to determine the MTD and/or RP2D. Thus, the efficacy analyses are described in the subsequent sections according to the study endpoints.

Dose Expansion part:

- **ORR** will be calculated with exact 95% confidence interval (CI) using the Clopper and Pearson method. A summary of best overall response will also be presented.
- **DOR** will be summarized using Kaplan-Meier estimates as appropriate. Median, Q1, Q3, and their 95% CIs will be presented and Kaplan-Meier estimates will be plotted over time. The DOR will be based on subjects achieving a best overall response of confirmed PR + CR.
- **DCR** will be calculated with exact 95% CI using the Clopper and Pearson method.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

- **ORR, DOR,** and **DCR** for the Dose Escalation part will be evaluated using same methodology for primary analysis in the Dose Expansion part.
- **PFS** will be summarized using Kaplan-Meier estimates. Median, Q1, Q3, and their 95% CIs will be presented and Kaplan-Meier estimates will be plotted over time. Subjects without progression of disease or death will be censored at the time of the last tumor assessment.
- **OS** will be summarized using Kaplan-Meier estimates. Median, Q1, Q3, and their 95% CIs will be presented and Kaplan-Meier estimates will be plotted over time. Subjects who are lost to follow-up or withdrew consent will be censored at the last known alive date, or the data cutoff date, whichever occurs first. Subjects who remained alive will be censored at the time of data cutoff.
- Change in tumor size in injected lesions and in distant non-injected lesions will be presented using plots, such as waterfall plots/spider plots, if appropriate.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

- Changes in tumor size assessed by IIR using volumetric CT/MRI will be provided.
- Time course changes in pre-injection sizes of injected lesions per investigator assessment will be presented by injected lesion/subject, if appropriate.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Plasma concentrations of E7766 will be tabulated and summarized by dose level, day, and protocol-specified time. Urine and fecal recovery (as µg as well as percentage of dose) of E7766 will be tabulated and summarized by dose level, day, and protocol-specified collection interval. E7766 PK parameters will be derived from plasma concentrations by noncompartmental analysis using actual times. Minimally, the following PK parameters will be calculated: maximum drug concentration (C_{max}), time to reach maximum concentration following drug administration (t_{max}), area under the concentration × time curve (AUC); and if data permit, terminal elimination half-life ($t_{½}$), apparent body clearance (CL/F), apparent volume of distribution (Vd/F), renal clearance (CLr), accumulation ratio (R), and fraction excreted (fe) in urine and feces. Exploratory characterization/identification of metabolites in urine and plasma will be attempted after administration of E7766. The results will be presented in a separate report. PK analyses may be supported by modeling. Details of the PK analyses will be provided in a separate analysis plan.

Analysis variable(s): Plasma concentrations of E7766

Analysis set: The Safety Analysis Set will be used for individual plasma concentration listings. The Pharmacokinetic Analysis Set will be used for all other analyses such as the summaries of plasma concentrations.

Analysis methods: Summary statistics of plasma concentrations will be obtained by visit. E7766 concentration data will be used to build PK models to explain the observed concentration data using population approach. Additionally, the models may be used to explore the relationship between PK and select demographic variables. The relationship between PK and pharmacodynamics parameters and efficacy/AE endpoints will also be investigated through population PK/ pharmacodynamics modeling. For population PK and PK/ pharmacodynamics analysis, the details will be described in the separately prepared analysis plan and its report, and the results will not be included in the clinical study report.

9.7.1.7.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The effect of E7766 treatment on blood and/or tissue biomarkers, and/or immune cell subsets will be summarized using descriptive statistics. Pharmacodynamic, PG, and other biomarker analyses will be performed and reported separately. Details of these analyses may be described in a separate analysis plan and reported separately.

9.7.1.8 Tolerability/Safety Analyses

Evaluation of DLTs will be performed on the DLT Analysis Set. The number and percentage of subjects with DLT will be calculated.

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented for each dose level/arm, total of each part, and overall as appropriate, will be summarized on an "as treated" basis using descriptive statistics (eg, n, mean, standard deviation, median, Q1, Q3, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, 12-lead ECG results, ECOG performance status, and ECHO/MUGA scans. Study Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

9.7.1.8.1 EXTENT OF EXPOSURE

The number of cycles/days on treatment, quantity of study drug administered, and the number of subjects requiring dose reductions and treatment interruption will be summarized.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 21.1 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment (on or after the first dose of study drug up to 90 days after the subject's last dose) or start day of another anticancer therapy, whichever is earlier; or in case subject has initiated new anticancer therapy within 30 days, then AEs occurring for 30 days following the last dose of E7766, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by highest CTCAE grade.

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by highest CTCAE grade.

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to death will be provided.

The number (percentage) of subjects with treatment-emergent serious adverse events (SAEs) will be summarized by MedDRA SOC and PT. A subject data listing of all SAEs will be provided.

The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value, including off treatment assessment) will be summarized by visit using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects) and change from baseline values to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory parameters will be categorized according to CTCAE v5.0, and shifts from baseline CTCAE grades to worst postbaseline grades will be assessed. Number and percentage of subjects with postbaseline results of CTCAE grades 3 or 4 will also be presented.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight) and changes from baseline will be presented by visit.

9.7.1.8.5 ELECTROCARDIOGRAMS

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit.

For Dose Escalation part only, shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to worst postbaseline category.

In addition, the number (percentage) of subjects with at least 1 postbaseline abnormal ECG result in QTc Fridericia (QTcF) during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTcF interval prolongation:

- QTcF interval >450 ms
- QTcF interval >480 ms
- QTcF interval >500 ms

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 ms
- QTcF interval increases from baseline >60 ms

9.7.1.8.6 OTHER SAFETY ANALYSES

Descriptive summary statistics for LVEF assessed on echocardiograms or MUGA scans and changes from baseline will be calculated.

Shift table for ECOG-PS will present change from baseline classification to worst postbaseline classification.

9.7.2 Determination of Sample Size

It is anticipated that selection of the RP2D will be based on integrated evaluation of safety, tolerability, clinical benefit, PK, and pharmacodynamics data. The total number of subjects for the Dose Escalation part will depend on the observed data including safety profile, which will determine the number of subjects per dose level, as well as the number of dose levels tested before the RP2D is established. Therefore, a formal statistical calculation of sample size is not applicable. The anticipated sample size for E7766 in the Dose Escalation part will be approximately 35 subjects, assuming approximately 10 dose levels and at least 2 subjects per dose level will be tested to achieve the MTD and then approximately 4 subjects for the selected 1 to 3 dose levels may be additionally enrolled for the RP2D selection.

The total number of subjects for the Dose Expansion part will depend on the number of arms by the disease-specific indications, and the number of subjects per arm. The anticipated sample size for the Dose Expansion part will be approximately 80 subjects, assuming 2 arms, and a maximum of 40 subjects per arm will be enrolled.

9.7.3 Interim Analysis

No formal interim analyses are planned. Interim monitoring using a snapshot of the database will be conducted to determine the MTD and/or RP2D, or to confirm safety and detect efficacy signals in subjects with selected disease indications before the analysis for CSR. Database locks are not required to perform these interim evaluations.

The data cutoff date for the CSR will be done after 6 months after the last subject in, and may be conducted before the last subject discontinues study treatment in this study.

9.7.4 Other Statistical/Analytical Issues

9.7.4.1 Improved Modified Toxicity Probability Interval Design in Dose Escalation Part

The improved mTPI design, which uses a Bayesian statistical framework and a beta-binomial hierarchical model, will be employed to determine the MTD and/or RP2D of E7766.

Decision rules for dose assignment will be based on the improved mTPI design with the target DLT rate of 25% and its equivalence interval (EI) of 20% to 30%, and a set of equal-width intervals as EI below/above EI (ie, below EI: 0% to 10%, 10% to 20%; above

EI: 30% to 40%, ... , 90% to 100%). The posterior probabilities of each interval will be calculated with non-informative beta prior distribution Beta (1, 1). The location of the interval with the largest posterior probability—below EI, EI, or above EI—guides the decision for the next dose level to be assigned, ie, Dose Escalation (E), Staying at the current dose (S), or dose De-escalation (D), respectively. This dose assignment rule minimizes the posterior expected penalty in the Bayes' rule under a decision-theoretic framework with the equal prior expected penalties for E, S, and D. The entire dose assignment decision rule can be pre-tabulated as presented in Table 1.

The subject enrollment will be closed when the lowest dose has a >95% posterior probability of being above the target DLT rate of 25% (ie, an unacceptable DLT rate beyond the target DLT rate) or when the RP2D has been determined.

The MTD is defined as the dose with the smallest difference between the target DLT rate of 25% and an estimate of DLT rate at each dose among all the tested doses with a ≤95% posterior probability of being above the target DLT rate of 25%. The isotonically transformed posterior mean under the beta posterior distribution with non-informative beta prior distribution Beta (0.005, 0.005) will be used to determine the estimate of DLT rates at each dose. The pooled adjacent violators algorithm (PAVA) will be used to maintain monotonically the increase of DLT rate with increasing dose level. Late immune-related toxicities occurring after Cycle 1 (DLT period) and up to 90 days after last dose of E7766, will also be used to inform corrections to the MTD and aid selection of the RP2D.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the study medical monitor (or appropriate study team member) and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required, the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan

to retain study documents, as directed by the sponsor, for 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 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor) or, when approval is given by the sponsor, will destroy supplies and containers at the site.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

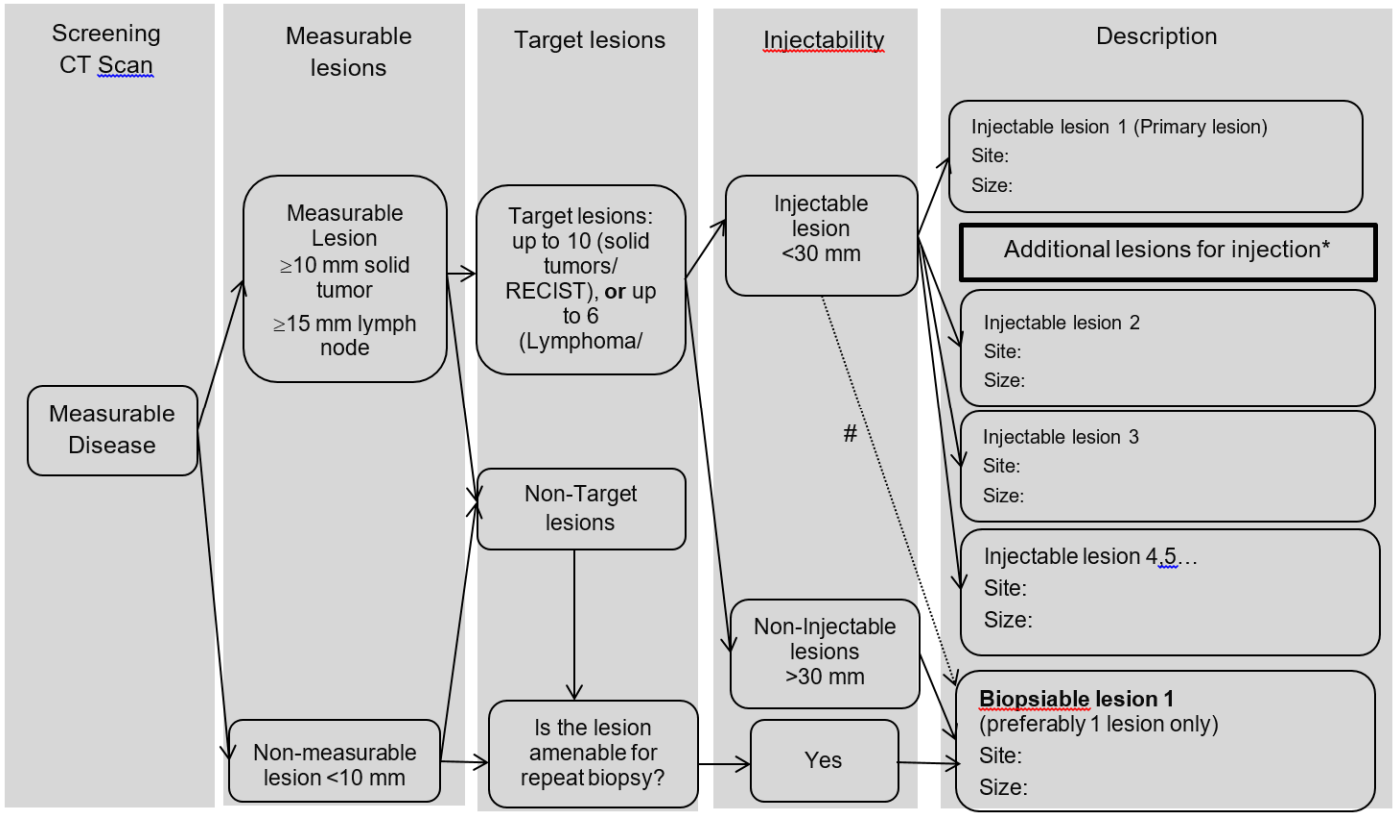
The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Identification and Documentation of Injectable and Biopsiable Lesions at Screening CT Scan



#: An injectable lesion can also be the biopsiable lesion if it has not been injected and there are other lesions available to be targeted for injecting with E7766.

*At Screening, the investigator can identify more than 1 lesion for injection. The sequence of lesion selection for injection should be agreed in advance by the investigator based on ease of accessibility and degree of risk (eg, bleeding) involved. In case additional lesions are required for injection, additional forms can be filled during the study as required.

Lesion Assessment for Injection and Biopsy	
Site Number:_____ **Subject ID:**_____ **Date of Visit:**_____ **Visit ID:**_____ **Investigator:**_____	
_____ **Signature**	_____ **Date (MM/DD/YYYY)**
_____ **Print Name and Title**	

Appendix Table 1: Target and Nontarget Lesion Definitions by LDi (Long Axis Diameter) and SDi (Short Axis Diameter) for Solid Tumors and Lymphoma

	Solid Tumor: Modified RECIST 1.1/iRECIST	**Lymphoma: Lugano/LYRIC**
Maximum number of target lesions	Up to 10 total Nodal/Extranodal Sites / max 5 per organ[a]	Up to 6 Nodal/Extranodal Sites
Target: Lymph Node	15 mm SDi	15 mm LDi
Target: non-Lymph Node	10 mm LDi	10 mm LDi
Non-Target: Lymph Node	10 mm SDi (pathological)	10 mm LDi (pathological)
Non-Target : non-Lymph Node	NA	NA

NOTE: An injectable lesion can also be selected as the lesion for biopsy if it has not been injected previously and there are other lesions available to be targeted for injecting with E7766.
iRECIST = modified RECIST 1.1 for immune-based therapeutics, LYRIC = LYmphoma Response to Immunomodulatory Therapy Criteria, RECIST 1.1 = Response Evaluation Criteria in Solid Tumours version 1.1.
a: Lymph nodes are considered 1 organ system.

Appendix 2 Description of the iRECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to modified RECIST 1.1 Progression

Until radiographic disease progression based on modified RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at modified RECIST 1.1 Progression

For participants who show evidence of radiological PD by modified RECIST 1.1 as determined by the Investigator, the Investigator will decide whether to continue a participant on study treatment until repeat imaging is obtained (using iRECIST for participant management (Appendix Table 2). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study treatment, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective independent imaging review (IIR) and exploratory analysis of tumor volume

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
  - Note: The iRECIST publication uses the terminology "sum of measurements," but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of nontarget lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease per iRECIST) and iCPD (confirmed progressive disease per iRECIST). For purposes of iRECIST assessment, the first visit showing progression according to modified RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and nontarget lesions identified at baseline by modified RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or nonmeasurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the iUPD at the previous visit show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of
  - ≥5 mm, compared to any prior iUPD time point
  - For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any ofthese:
    - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
    - Visible growth of new nontarget lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by modified RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by modified RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which the initial iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset." This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (ie, achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions

  - If nontarget lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified nontarget lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated.

Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication (Seymour, et al., 2017).

Appendix Table 2: Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by modified RECIST 1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment.
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required.	Discontinue treatment.	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment.
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

iCPD = confirmed progressive disease per iRECIST, iCR = complete response per iRECIST, iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics, iSD = stable disease per iRECIST, iUPD = unconfirmed progressive disease per iRECIST, PD = progressive disease, RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.

Appendix 3 Description of the Lugano and LYRIC Assessment of Response in Lymphoma

The Lugano criteria is based on a combination of metabolic and radiographic responses to characterize several components of lymphoma involvement including: nodal disease, extranodal disease, bone marrow disease, spleen and liver involvement, and clinical assessment. The standard assessment for tumor burden is CT for non-FDG avid lymphoma, and PET-CT for FDG-avid lymphoma. Standard definitions associated with the Lugano assessment are summarized in Appendix Table 3.

Responses should be determined on the basis of radiographic and clinical evidence of disease. Assessment of PET-CT should follow the recommendations for initial evaluation, staging, and response assessment for Hodgkin and non-Hodgkin's lymphoma; the Lugano classification described by Cheson (2014) is presented in the Revised Criteria for Response in Appendix Table 4.

In the context of immunotherapy, once PD is indicated by the Lugano criteria, the time point must then be confirmed as a true progression rather than an immune response by the LYRIC described by Cheson (2016). If the LYmphoma Response to Immunomodulatory Therapy Criteria (LYRIC) response does not qualify as true progression, it is called an Indeterminate Response (IR), which requires follow-up imaging as presented in Appendix Table 5.

Appendix Table 3: Standard Definitions and Assessments Lugano Lexicon

1. Baseline Assessments	
Lugano Measurement Terminology	Radiographic Measurement: Measureable lesions are characterized by the following radiographic parameters to describe lesion size by CT or MRI: • **LDi:** longest transverse diameter of a lesion • **SDi:** shortest axis perpendicular to the LDi • **PPD:** cross product of the LDi and perpendicular diameter • **SPD:** sum of the product of the perpendicular diameters for multiple lesions FDG-PET Measurement: Measureable FDG-avid lesions are characterized by the FDG-PET 5-point scale (5-PS) (recommended by visual inspection of SUV images): • **Score 1:** No uptake above background • **Score 2:** Uptake ≤ mediastinum • **Score 3:** Uptake > mediastinum, but ≤ liver • **Score 4:** Uptake moderately > liver at any site • **Score 5:** Uptake markedly higher than liver at any site and/or new lesions
Measurable (Target) Lesions	Measurable lesions must be accurately measured in at least one dimension with a minimum size of: • >10 mm in the longest diameter (LDi) by CT or MRI scan (or no less than double the slice thickness) for non-nodal lesions and >15 mm in LDi for nodal

	lesions • Identify up to 6 lesions including nodal masses or other lymphomatous disease including extranodal disease measureable in 2 diameters (LDi and SDi) • Likely to be reproducible across all time points • Representative of tumor burden a. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. b. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, and lungs), gastrointestinal (GI) involvement, cutaneous lesions, or those noted on palpation. • For FDG-avid lesions, the target lesion should correlate with a co-registered FDG-PET lesion. • Product of perpendicular diameters (PPD) is used to characterize the size each lesion, PPD = LDi × SDi • Sum of product diameters (SPD) of all target lesions including nodal and non-nodal are reported as baseline SPD which is used for assessing tumor response at follow-up time points.
Bone Marrow Involvement	• Bone marrow biopsy no longer indicated for the routine staging of HL and most DLBC. FDG-PET imaging should be used instead. Involvement determined by FDG avid disease in marrow. • For other lymphoma subtypes 2.5 cm unilateral bone marrow biopsy is recommended, along with immunohistochemistry and flow cytometry at screening/baseline
Spleen Involvement	• Splenomegaly is characterized by a >13 cm vertical length, as measured from cranial to caudal aspects by CT.
Nonmeasurable (Nontarget) Lesions	Nontarget lesions will include: • Measurable lesions not selected as target lesions. Up to 10 nontarget lesions can be recorded at baseline. • All other disease not selected as target lesions consistent with lymphoma • Abnormal nodes, extranodal sites, assessable sites* (*Cutaneous, gastrointestinal, bone lesions, pleural or pericardial effusions, ascites) • For FDG-avid lesions, the nontarget lesion should correlate with a co-registered FDG-PET lesion. Nontarget lesions should be reported as present at baseline
$SPD_{baseline}$	Sum of product diameters at baseline = sum of the perpendicular product diameters, PPD = LDi × SDi, of each nodal and nonnodal target lesion. $SPD = \Sigma_n (PPD_n)$ where the subscript n denotes each target lesion.
Clinical Assessment	Comprehensive history including • Absence/presence of fevers to >101 °F (38.3 °C) • Chills, drenching night sweats, or unexplained weight loss >10% of body mass over 6 months, and history of malignancy. • Fatigue, pruritus, and alcohol-induced pain in patients with HL should also be noted.* (*These factors rarely direct treatment, their recurrence may herald disease

	relapse.)
2. Time Point Assessments After Baseline	
Target Lesion Measurements	Radiographic measurement: Locate image that optimizes the LDi of the nodal and non-nodal target lesions. There is no need to go to an identical slice from baseline. Measure the respective LDi and SDi for all target lesions and calculate time point sum of product diameters ($SPD_{timepoint}$). Special consideration for target lesions: • If target lesion is too small to measure, a default value of 5 mm LDi and 5mm SDi should be entered on the eCRF. • When no longer visible, enter 0 x 0 mm. • For a node >5 mm × 5 mm, but smaller than normal, use actual measurement for calculation. • If target lesion is between 5 to 10 mm, actual diameter should be entered on the eCRF. • If target lesion splits into 2 or more lesion then the LDi and SDi and PPD of the split lesions will be added to the SPD and entered in place of that lesion. • If 2 target lesion merged to form one lesion than the LDi and SDi of one should be entered as "0 x 0 mm" while the other lesion should have the LDi and SDi and PPD of the merged lesion FDG-PET metabolic measurement: Locate each target lesion that is co-registered with CT imaging (maximum of 6) and use 5 point scale with an additional parameters to describe nonlymphoma-related FDG-uptake and nonevaluable lesions: • **Score 1:** No uptake above background • **Score 2:** Uptake ≤ mediastinum • **Score 3:** Uptake > mediastinum, but ≤ liver • **Score 4:** Uptake moderately > liver at any site • **Score 5:** Uptake markedly higher than liver at any site and/or new lesions • **X :** Area of new uptake unlikely to be related to lymphoma • **NE :** Not evaluable
Nontarget Lesion Assessment	Nontarget lesions are evaluated by radiographic assessment qualitatively as present, regressed, absent, not evaluable (NE), or unequivocal progression.
Definition of New Lesion	Any lesion which was not recorded at baseline. There is no minimum size criteria to identify a new lesion and clinical judgment must be used by the investigator. • May include a lesion in an anatomical location that was not scanned at baseline (ie, brain) • Should be unequivocal and not due to differences in scanning technique "x"

5-PS = 5-point scale, CT = computed tomography, DLBC = diffuse large B-cell lymphoma, eCRF = electronic case report form, FDG-PET = ^{18}fluorodeoxyglucose-positron emission tomography, HL= Hodgkin's lymphoma, MRI = magnetic resonance imaging, SUV = standardized uptake value.

Appendix Table 4: Lugano Criteria for Response

Response	Site	PET-CT–Based Response	CT-Based Response
Complete		**Complete metabolic response**	**Complete radiologic response (all of the following)**
	Lymph nodes and extralymphatic sites	Score 1, 2, or 3[a] with or without a residual mass on the 5-PS[b] It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.	Target nodes/nodal masses must regress to ≤1.5 cm in LDi. No extralymphatic sites of disease.
	Nonmeasured lesion	Not applicable	Absent
	Organ enlargement	Not applicable	Regress to normal
	New lesions	None	None
	Bone marrow	No evidence of FDG-avid disease in marrow. If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy.	If the bone marrow was involved by lymphoma prior to treatment, the infiltrate must have cleared on repeat bone marrow biopsy.
Partial		**Partial metabolic response**	**Partial remission (all of the following)**
	Nonmeasured lesion	Not applicable	Absent/normal, regressed, but no increase.
	Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal (>13cm).
	New lesions	None	None
	Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptakecompatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an intervalscan.	Not applicable
No Response or Stable Disease		**No metabolic response**	**Stable disease**
	Lymph nodes and extralymphatic sites	Score 4 or 5[b] with no significant change in FDG uptake from baseline at interim or end of treatment.	<50% decrease from baseline in SPD for up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met.
	Nonmeasured lesion	Not applicable	No increase consistent with progression.
	Organ enlargement	Not applicable	No increase consistent with progression.

Appendix Table 4: Lugano Criteria for Response

Response	Site	PET-CT–Based Response	CT-Based Response
	New lesions	None	None
	Bone marrow	No change from baseline	Not applicable
Progressive Disease		**Progressive metabolic disease**	**Progressive disease (requires at least 1 of the following)**
	Individual target nodes/nodal lesions	Score 4 or 5[b] with an increase in intensity of uptake from baseline	An individual node/lesion must be abnormal with: • LDi >1.5 cm AND • Increase by ≥50% from PPD nadir AND • An increase in LDi or SDi from nadir • 0.5 cm for lesions ≤2 cm • 1.0 cm for lesions >2 cm
	Extranodal lesions	*and/or* New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment.	An individual node/lesion must be abnormal with: • LDi >1.5 cm AND • Increase by ≥50% from PPD nadir AND • An increase in LDi or SDi from nadir • 0.5 cm for lesions ≤2 cm • 1.0 cm for lesions >2 cm
	Nonmeasured lesion		New or clear progression of preexisting
	Organ enlargement		In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, 15 cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly.
	New lesions	*and/or* New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	Regrowth of previously resolved lesions. A new node > 1.5 cm in any axis. A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma.

Appendix Table 4: Lugano Criteria for Response

Response	Site	PET-CT–Based Response	CT-Based Response
			Assessable disease of any size unequivocally attributable to lymphoma.
	Bone marrow	*and/or* New or recurrent FDG-avid foci.	New or recurrent involvement

5-PS = 5-point scale, CR = complete response, CT = computed tomography, FDG = fluorodeoxyglucose, GI = gastrointestinal, LDi = longest transverse diameter of a lesion, MRI = magnetic resonance imaging, PET = positron emission tomography, PPD = cross product of the LDi and perpendicular diameter, PR = partial response, SDi = shortest axis perpendicular to the LDi, SPD = sum of the product of the perpendicular diameters for multiple lesions.

a A score of 3 in many patients indicates a good prognosis with standard treatment, especially if scored at the time of an interim scan. However, in studies involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment).

b PET 5-PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Source: Cheson, et al., 2014.

Appendix Table 5: LYRIC PD Confirmation for Immunotherapy in Lymphoma[a]

LYRIC Measurement Terminology	Indeterminate Response (IR): This modification retains the core concepts of immunotherapy response criteria, incorporating them into lymphoma-specific response criteria. Responses that are potentially due to immune reactions and characterized as IR (as described below) require additional follow-up scanning to confirm disease progression.
LYRIC PD and IR definitions	PD is the same as Lugano with the following exceptions that will qualify as IR: • IR(1): ≥50% increase in SPD in first 12 weeks. • IR(2): <50% increase in SPD with a. New lesions(s), or b. ≥50% increase in PPD of a lesion or set of lesions (including non-TL) at any time during treatment. • IR(3): Increase in FDG uptake without a concomitant increase in lesion size meeting criteria for PD.
LYRIC follow-up after IR for PD confirmation	In patients categorized as having any of the above types of IR, it is mandatory to obtain a repeat imaging after an additional 12 weeks (or earlier if clinically indicated). At that time, response should be re-evaluated, and the patient should be considered to have true PD if the SPD of target lesion has increased further, with the considerations below: • In the case of IR (1), the comparison should be between the first IR and the current overall tumor burden, with an increase of ≥10% constituting PD. In addition there should be an increase of ≥5 mm for at least 1 lesions ≤2 cm, and 10 mm for lesions >2 cm (consistent with Lugano). • In the case of IR(2), the new or growing (including non-TL) lesion(s) (unless biopsy proven benign) should be added to the target lesion(s) up to a total of no more than 6 lesions. If the SPD of the newly defined set of target lesions has increased ≥50% from their nadir value (which may precede IR) this patient would be considered PD. • In the case of IR(3): Since inflammatory response may result in an increase in the standardized uptake value of a lesion, the patient will not be considered to have progressive disease unless there is evidence of progressive disease by an increase in lesion size or the development of a new lesions.
Note on LYRIC PD time point assignment	If a patient is evaluated as IR and then "true" PD at a subsequent time point (without an intervening objective response between IR and PD), the IR assessment should subsequently be corrected to PD for reporting purposes to the date of the prior designation of IR. We recognize that these lesions may remain stable during the time of observation, but, even if this is the case, the initial designation of IR should be changed to PD.

a FDG = fluorodeoxyglucose, IR = Indeterminate Response, LYRIC = LYmphoma Response to Immunomodulatory Therapy Criteria, PD = progressive disease, PPD = product of perpendicular diameters, SPD = sum of product diameters, TL = target lesion.
Source: Cheson, et al. 2016.

Appendix 4 Cockcroft–Gault Calculation of Creatinine Clearance

Subjects must have adequate renal function as evidenced by serum creatinine ≤1.8 mg/dL or calculated creatinine clearance ≥50 mL/min per the Cockcroft–Gault formula as defined below.

Cockcroft–Gault Calculation for Creatinine Clearance

Male	$\frac{(140 - \text{age}) \times \text{weight (kg)} \times 1.23}{\text{serum creatinine (μmol/L)}} = \text{XX mL/min}$
Female	$\frac{(140 - \text{age}) \times \text{weight (kg)} \times 1.23 \times 0.85}{\text{serum creatinine (μmol/L)}} = \text{XX mL/min}$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

Appendix 5 Autoimmune-Related Diseases

Diseases that may be autoimmune related include but are not limited to the following:

Acute disseminated encephalomyelitis
Addison's disease
Alopecia universalis
Ankylosing spondylitis
Antiphospholipid antibody syndrome
Aplastic anemia
Asthma
Autoimmune hemolytic anemia
Autoimmune hepatitis
Autoimmune hypoparathyroidism
Autoimmune hypophysitis
Autoimmune myocarditis
Autoimmune oophoritis
Autoimmune orchitis
Autoimmune thrombocytopenic purpura
Behcet's disease
Bullous pemphigold
Celiac disease
Chronic fatigue syndrome
Chronic inflammatory demyelinating polyneuropathy
Chung-Strauss syndrome
Crohn's disease
Dermatomyositis
Diabetes mellitus type 1
Dysautonomia
Eczema
Epidermolysis bullosa acquista
Gestational pemphigoid
Giant cell arteritis
Goodpasture's syndrome
Graves' disease
Guillain-Barré syndrome
Hashimoto's disease
IgA nephropathy
Inflammatory bowel disease
Interstitial cystitis
Kawasaki's disease
Lambert-Eaton myasthenia syndrome
Lupus erythematosus
Lyme disease - chronic
Meniere's syndrome
Mooren's ulcer
Morphea
Multiple sclerosis
Myasthenia gravis
Neuromyotonia
Opsoclonus myoclonus syndrome
Optic neuritis
Ord's thyroiditis
Pemphigus
Pernicious anemia
Polyarteritis nodusa
Polyarthritis
Polyglandular autoimmune syndrome
Primary biliary cirrhosis
Psoriasis
Reiter's syndrome
Rheumatoid arthritis
Sarcoidosis
Scleroderma
Sjögren's syndrome
Stiff-Person syndrome
Takayasu's arteritis
Ulcerative colitis
Vitiligo
Vogt-Kovanagi-Harada disease
Vulvodynia
Wegener's granulomatosis

Appendix 6 Interleukin-6 (IL-6) Antagonist and Corticosteroid Dosing Tables

IL-6 Antagonist Dosing

Drug	Recommended Dose for CRS and/or CRES	Maximum Dose	Mechanism of Action	Comments
Tocilizumab[1]	8 mg/kg IV for up to three doses in a 24-hour period (Maximum 4 doses total)	Maximum 800 mg per dose	IL-6 receptor antagonist	First line agent Doses can be given 8 hours apart
Siltuximab[2]	11 mg/kg IV once	No more than 1 dose in a 3-week period	Binds to both soluble and membrane bound IL-6 Neutralizes IL-6	Consider in patients who fail to respond to 1-2 doses of tocilizumab Requires chemotherapy consent

[1]Formulary restricted for use in CRS/CRES and for use in hemophagocytic lymphohistiocytosis (HLH)
[2]Formulary restricted for use in CRS/CRES

Corticosteroid Dosing

Drug	Recommended Dose for CRS and/or CRES	Comments
Dexamethasone	10 to 20 mg IV either as a one-time dose or every 6 hours	Frequency of dosing depends on severity of symptoms and response
Methylprednisolone	1 mg/kg IV every 12 hours	May be used in place of dexamethasone for CRES
High-dose Methylprednisolone	500 mg IV every 12 hours for 3 days, followed by • 250 mg IV every 12 hours for 2 days, then • 125 mg IV every 12 hours for 2 days, then • 60 mg IV every 12 hours until CRS or CRES improvement to Grade 1 and then taper over 2 weeks	For patients with improvement to Grade 1 within one week or less, the corticosteroids can be stopped without tapering

CRES = CAR-related encephalopathy syndrome, CRS = cytokine release storm.

Appendix 7 CCI [redacted]

Appendix 8 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Objective

Subjects enrolled in this clinical study will have biologic samples collected for pharmacodynamic , pharmacogenomic (PG), and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PG samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential adverse events related to study treatment, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or noncoding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetics or therapeutic response.

Collection of the pharmacodynamic, PG, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for pharmacodynamic, PG, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection, Handling and Shipment

This information will be included in the laboratory manual.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single coded (subject ID) (according to the ICH E18 draft guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

Samples will be single coded (subject ID). No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample.

At the end of the analysis, results may be presented in the clinical study report (or may be presented in the separately prepared report) which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the pharmacodynamic, PG, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients.

If at any time, pharmacodynamic, PG, and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments (CLIA)-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in CLIA-approved laboratories.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E7766-G000-101

Study Protocol Title: An Open-Label, Multicenter Phase 1/1b Study of **In**tratumorally Administered **STI**NG Agonist E7766 in Subjects With **A**dvanced Solid Tumors or **L**ymphomas – **INSTAL-101**

Investigational Product Name: E7766

IND Number: 137834

EudraCT Number: 2019-000160-17

SIGNATURES

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10 Dec 2019

Date

Oncology Business Group,
Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E7766-G000-101
Study Protocol Title:	An Open-Label, Multicenter Phase 1/1b Study of **In**tratumorally Administered **ST**ING Agonist E7766 in Subjects With **A**dvanced Solid Tumors or **L**ymphomas – **INSTAL-101**
Investigational Product Name:	E7766
IND Number:	137834
EudraCT Number:	2019-000160-17

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date