Clinical Study Protocol

Phase I/IIA Safety and Efficacy Study of IMSA101 in Patients with Advanced Treatment-Refractory Malignancies

IMSA101-101

Drug Development Phase:	Phase I/IIA
Investigational Product:	IMSA101
IND Number	142445
Indication:	Advanced treatment-refractory malignancies
Sponsor:	ImmuneSensor Therapeutics 2110 Research Row #610 Dallas, TX 75235
Protocol Amendment	9
Protocol Date and Version:	13 June 2022 FINAL

Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP) and regulatory requirements as applicable.

PROTOCOL APPROVAL SIGNATURE PAGE

SPONSOR: IMMUNESENSOR THERAPEUTICS

I have reviewed and approved this protocol, including appendices and confirm that it follows current regulations and GCP guidelines.

Approved By (Signature): **Date:**

[redacted]

Vice President,
Clinical Operations and Project Management

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study No. IMSA101-101 and will adhere to the study requirements as presented, including all statements regarding confidentiality. In addition, I will conduct the Study in accordance with current Good Clinical Practices and applicable FDA regulatory requirements:

Name of Principal Investigator:

_____

_____ _____

Signature **Date**

PROTOCOL SYNOPSIS

Sponsor: ImmuneSensor Therapeutics	**Investigational Product:** IMSA101	**Developmental Phase:** Phase I/IIA
Title of Study: Phase I/IIA Safety and Efficacy Study of IMSA101 in Patients with Advanced Treatment-Refractory Malignancies		
Protocol Number: IMSA101-101		
Study Center(s): Approximately 5 sites for Phase I and 20 sites for Phase IIA in the United States (US)		
Indication: Advanced treatment-refractory malignancies		
Study Population: Adult patients with advanced malignancies refractory to or ineligible for standard-of-care therapies		
Study Design: Open-label, dose escalation (Phase I) and dose expansion (Phase IIA) study of patients receiving IMSA101 alone or in combination with an immune checkpoint inhibitor (ICI) (Phase I and II)		

Objectives:

Primary Objective:

- Establish safe recommended Phase II doses (RP2Ds) of IMSA101 administered as monotherapy or in combination with an immune checkpoint inhibitor (ICI)

Secondary Objectives:

- Characterize the safety and tolerability of IMSA101 administered to cancer patients via intratumoral injections as monotherapy or in combination
- Identify and characterize preliminary signals of anti-tumor activity including overall response rate (ORR), duration of treatment response (DOR), time-to-tumor progression (TTP), and progression-free survival time (PFS)
- Characterize the pharmacokinetics (PK) of IMSA101 administered by intratumoral injection as monotherapy

Exploratory Objective:

- Assess the pharmacodynamics (PD) and biologic activity of IMSA101

Methodology:

All Patients:

- Pre-treatment screening radiographic tumor assessments will be collected within 30 days prior to initial dose for all patients. Photographic assessments of skin lesions will be performed as detailed in a separate photography manual.
- Treatment cycles will be 28 days in duration with lesions injected weekly on Day 1 for the first three weeks of Cycle 1 and then every 2 weeks during cycles 2 and beyond.

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- A single pre-defined lesion/lesion site (longest diameter ≥ 10 mm and ≤ 50 mm) shall be injected throughout study duration, if possible. Where the original injection site is considered by the investigator to become inaccessible, a second lesion/lesion site shall be selected as a replacement and this shall be used henceforth so long as it is considered accessible. Subsequent injection sites shall be replaced when they are considered inaccessible.
- Where no remaining accessible lesions are present and where benefit of IMSA101 therapy is, in the opinion of the investigator, being derived by the patient, continued injections of IMSA101 into the vicinity of an inaccessible lesion or, in the case that a lesion can no longer be radiographically visualized, into the last known location of the non-visible lesion shall be allowed.
- Patients will be admitted to the hospital for observation overnight following intratumoral injection with IMSA101 on Day 1 of Cycle 1. Patients will be followed throughout the study for drug tolerability and safety by collection of clinical and laboratory data, including information on adverse events (AEs) using Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria, serious adverse events (SAEs), dose-limiting toxicities (DLTs), concomitant medications, vital signs, and electrocardiograms (ECGs).
- Patients will be assessed for anti-tumor efficacy based on radiographic assessments and if applicable, photographic tumor assessments, and analysis of ORR, DOR, TTP, and PFS using response evaluation criteria in solid tumors (RECIST) v1.1 criteria at screening and at the end (≤ 7 days) of even numbered cycles (Cycle 2, Cycle 4, etc.) after the first dosing.

  RECIST v1.1 criteria do not mention including or excluding lesions that are being biopsied or injected. However, for the purposes of this protocol, the injected and biopsied lesions are to be captured as non-target lesions only (Phase I only), as follows:
  - Injected and biopsied lesion = non-target lesion #1
  - Non-injected and biopsied lesion = non-target lesion #2 (if applicable)
- See Schedule of Assessments and Study Activities (Table 1 and Table 2) for details.

The Phase I dose escalation is detailed in Figure 8 for monotherapy and Figure 9 and Figure 10 for combination therapy.

Phase I Dose Escalation - Monotherapy:

- Each dose escalation cohort will initially recruit at least 3 patients in a standard 3+3 design. To proactively ensure at least 3 patients are considered evaluable, a fourth patient may be enrolled and treated in addition to the initial 3 patients in each cohort (the fourth patient may only be enrolled if they are identified at the time the third patient slot is being filled).

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- Dose escalation design in which administered dose levels will be escalated stepwise in successive cohorts of 3 to 6 (NOTE: 7 if fourth slot is filled and a single DLT is identified among the first 4 patients) patients per dose group until the RP2D or maximum tolerated dose (MTD) level is identified.
- The first patient enrolled in each dose level must complete the first two weeks of Cycle 1 prior to enrolling the second and third (fourth when applicable) patients.
- Dose levels to be evaluated include (although not necessarily limited to) 100 µg (representing 1/60th of the pre-clinical highest non-severely toxic dose [HNSTD] dose), 200 µg, 400 µg, 800 µg, and 1,200 µg.
- IMSA101 will initially be administered by intratumoral injections on Day 1 of Weeks 1, 2, and 3 for Cycle 1 (i.e., weekly dosing 3 out of 4 weeks), and on Day 1 of Weeks 1 and 3 (i.e., bi-weekly dosing) for all cycles thereafter.
- No dose escalation decisions will be made until all patients in a dose level complete the first 28 days of treatment. NOTE: this includes a fourth additional patient when applicable. Dose-escalation/de-escalation decisions will be based on the occurrence of DLTs during Cycle 1 of the evaluated dose level and the recommendation of the Cohort Review Committee (CRC).
- If no DLTs are observed among the initial 3 (4 when applicable) patients of an evaluated dose level, the dose will be escalated for the following 3 patients.
- If a single DLT occurs among the initial 3 (4 when applicable) patients of an evaluated dose level, 3 additional patients will be enrolled at the same dose level.
- If ≥ 2 DLTs occur among the initial 3 (4 when applicable) or 6 (7 when applicable) patients in an evaluated dose level, the dose level shall be considered unacceptably toxic and escalation will be discontinued.
- Subsequent to invalidation of a given cohort (e.g., when ≥ 2/3 [4 when applicable] or ≥ 2/6 [7 when applicable] patients in an evaluated dose level experience a DLT), a new cohort (e.g., dosing Cohort Xa) will be evaluated in which IMSA101 will be administered by intratumoral injection at the same dose level but with the Day 1 dose (priming dose) reduced to the next lower dose level.
- For dosing Cohort Xa, if ≥ 2/3 (4 when applicable) or ≥ 2/6 (7 when applicable) patients experience a DLT, the amended dose level shall be considered unacceptably toxic and the next lower dose (DL-1) level shall be provisionally labeled the MTD.
- If the amended dose level Xa is found to be safe, dose escalation shall proceed with the exception of the priming dose (Cycle 1, dose 1) which shall be held constant and not escalated further.
- No fewer than 6 total patients shall be evaluated at a given dose level prior to confirmation of the dose level as the MTD or RP2D.

Phase I Dose Escalation - Combination Therapy:

- Combination therapy with IMSA101 + ICI includes the following IMSA101 dose levels:
  - 800 μg
  - 1,200 μg
  - 2,400 μg (with an initial "priming" dose of 1,200 μg)
  - 3,600 μg (with an initial "priming" dose of 2,400 μg)
  - 4,800 μg (with an initial "priming dose" of 3,600 μg)
- Combination dosing of IMSA101 shall be evaluated in Phase I upon satisfaction of the following criteria:
  A. A given dose level (combo dose level 1) has been confirmed as safe for monotherapy dosing (i.e., < 2/6 [7 when applicable] patients experience Cycle 1 DLT).
  B. The next higher dose level (combo dose level 2) has been confirmed as safe for monotherapy dosing (i.e., < 2/6 [7 when applicable] patients experience Cycle 1 DLT).
  C. The dose level (combo dose level 1) is found to demonstrate adequate IMSA101 PD activity based on exploratory endpoints.
- Eligible patients for Phase I combination dosing shall meet one of the following criteria:
  - have radiographically-confirmed RECIST stable disease through ≥ 2 consecutive cycles of an approved PD-1/PD-L1-targeted immune checkpoint inhibitor (ICI) administered as monotherapy
  - be clinically stable following a first (unconfirmed) follow-up radiographic scan demonstrating progression of disease on ICI monotherapy
  - have progression through prior ICI therapy administered either as mono or combination therapy
  - have received no prior ICI therapy but otherwise be ineligible for all available standards of care
- Phase I combo patients have experienced no prior Grade ≥ 3 CTCAE adverse events on ICI therapy that were considered by the investigator to be at least possibly ICI drug-related
- Phase I combo patients shall either receive de novo the combination of IMSA101 + an ICI of their investigator's choosing or, in cases where they are already receiving ICI monotherapy, have IMSA101 added to their current therapy such that Day 1 of IMSA101 shall represent Cycle 1, Day 1.
- A radiographic tumor assessment shall have occurred within 30 prior days of adding IMSA101 to current therapy.
- Phase I combination therapy IMSA101 doses of 800 μg and 1,200 μg will be administered by intratumoral injections each week for 3 weeks in Cycle 1 (Days 1, 8, and 15), and for

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Cycle 2 and all other cycles thereafter, every other week on Days 1 and 15. Additional combination therapy IMSA101 doses of 2,400 µg, 3,600 µg, and 4,800 µg require the following priming dose on Day 1 of Cycle 1: 1,200 µg for the 2,400 µg dose group, 2,400 µg for the 3,600 µg dose group, and 3,600 µg for the 4,800 µg group. After Day 1 of Cycle 1, the full dose for these groups will be administered on Day 1 of Weeks 2 and 3 of Cycle 1 (i.e., weekly dosing 3 out of 4 weeks), and on Day 1 of Weeks 1 and 3 for all cycles thereafter (i.e., bi-weekly dosing).

- Safety evaluations and dose escalation of IMSA101 administered in combination with current ICI therapy shall proceed in a manner consistent with monotherapy escalation, with the exception of allowed de-escalation, and shall proceed independently of monotherapy dose escalation and evaluations.
- De-escalation: If ≥ 2 DLTs occur among the initial 3 (4 when applicable) or 6 (7 when applicable) patients, de-escalation of IMSA101 is allowed for the combination therapy dose levels as follows:
  - 2,400 µg may be de-escalated to 1,800 µg (with a priming dose of 1,200 µg on Day 1 of Cycle 1)
  - 3,600 µg may be de-escalated to 3,000 µg (with a priming dose of 2,400 µg on Day 1 of Cycle 1)
  - 4,800 µg may be de-escalated to 4,200 µg (with a priming dose of 3,600 µg on Day 1 of Cycle 1)

  If ≥ 2 DLTs occur among the initial 3 (4 when applicable) or 6 (7 when applicable) patients at a de-escalated dose level, the dose level shall be considered unacceptably toxic and escalation will be discontinued.
- Administration of combination drug will follow the labeled instructions for the product.
- IMSA101 dose escalation shall proceed such that there will be generated separate RP2Ds for IMSA101 administered alone or in combination with other agents (although it is possible these will be the same).
- No fewer than 6 total patients shall be evaluated at a given dose level prior to confirmation of the dose level as the MTD or RP2D.

<u>Phase IIA Dose Expansion:</u>

- This dose-expansion stage is intended to confirm the tolerability of the RP2D and identify provocative signals of IMSA101 anti-tumor activity.
- It is anticipated that the monotherapy and combination RP2Ds will be evaluated in 3 discrete arms of 20 patients each with a single arm evaluating monotherapy (Arm A) and 2 arms evaluating IMSA101 in combination with immuno-oncology (IO) therapies (Arm B and Arm C).
  - Arm B will be a combination of IMSA101 with PD-1/PD-L1-targeted ICIs. Dosing will be predicated by the combination RP2D identified in Phase I.

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- Arm C will be a combination of IMSA101 with non-PD-1/PD-L1-targeted IO drugs approved by the Food and Drug Administration (FDA).

- Administration of approved drugs to be combined with IMSA101 will follow the labeled instructions for the product.
- Combination arms evaluating IMSA101 combinations shall include a safety run-in of 5-10 patients to be conducted as follows:
  - If ≤ 1 of 5 initial safety evaluable patients experience a DLT during Cycle 1, enrollment shall proceed to Patient 6.
  - If ≤ 3 of 10 initial safety evaluable patients experience a DLT during Cycle 1, enrollment shall proceed to its entirety (20 patients in that arm).
  - If ≥ 2 of 5 or ≥ 4 of 10 patients experience a DLT, dose de-escalation shall occur to the next lower dose level evaluated in Phase I and the run-in shall be repeated at the next lower dose.
- Tumor types and corresponding treatment combinations to be evaluated will be identified prior to Phase IIA commencement with patients enrolled separately into tumor-specific arms of 20 patients each. **This change will be documented in a protocol amendment before it occurs.**
- The need for futility criteria to be evaluated in any of the arms following enrollment of a pre-defined number of patients < 20 shall be determined at a later date depending on tumor types evaluated. **This change will be documented in a protocol amendment before it occurs.**
- For all potential patients, there will be up to a 30-day screening and eligibility assessment period prior to enrollment.

All patients will continue to receive their assigned treatment throughout the study until the occurrence of disease progression, death, or other unacceptable treatment-related toxicity, or until the study is closed by the sponsor.

Inclusion Criteria:

Phase I combination only:

1. Eligible patients will meet one of the following criteria:
   - Have radiographically-confirmed RECIST stable disease through ≥ 2 consecutive cycles of an approved PD-1 or PD-L1 targeted ICI administered as monotherapy
   - Be clinically stable following a first (unconfirmed) follow-up radiographic scan demonstrating progression of disease on ICI monotherapy
   - Have progression through prior ICI therapy administered either as mono or combination therapy
   - Have received no prior ICI therapy but otherwise be ineligible for all available standards of care
2. Have experienced no prior Grade ≥ 3 CTCAE adverse events on ICI therapy that were considered by the investigator to be at least possibly ICI drug-related.

All patients (unless otherwise indicated):

1. Signed informed consent and mental capability to understand the informed consent
2. Male or female patients ≥ 18 years of age
3. Histologically or cytologically documented locally advanced or metastatic solid tumor malignancies refractory to or otherwise ineligible for treatment with standard-of-care agents/regimens, including but not limited to:
   - Malignant melanoma
   - Hormone receptor negative breast cancer
   - Gastro-esophageal cancer
   - Non-small cell lung cancer
   - Head and neck cancer
   - Hepatoma
   - Renal cell carcinoma
4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1
5. Evaluable or measurable disease as follows:
   - 2 or 3 RECIST-evaluable lesions: one that is suitable for injection and biopsied; an optional non-injected second lesion that will be biopsied for abscopal effect (only 1 patient per cohort required to have non-injected lesion that is biopsied; optional for all other patients in that cohort); and one measurable lesion that will be followed for response only.
   - Injectable tumors shall be accessed by intralesional (cutaneous) or percutaneous injection only, including those lesions that are visible, palpable, or detectable by standard radiographic or ultrasound methods. Neither surgical procedures nor endoscopically-guided injections including those to endobronchial, endoluminal, or endosinusoidal spaces shall be allowed. While no anatomic locations are required or

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disallowed, lesions selected for intratumoral injection must, in the opinion of the investigator:

- Not be immediately adjacent to blood vasculature or other physiologic landmarks in such a way that will accrue undue safety risk to the patient
- Have longest diameter ≥ 10 mm and ≤ 50 mm
- Be fully efficacy evaluable per RECIST v1.1 criteria

6. Life expectancy > 3 months (Phase I) and > 6 months (Phase IIA)
7. ECG without evidence of clinically meaningful conduction abnormalities or active ischemia as determined by the investigator
8. Acceptable organ and marrow function as defined below:
   - Absolute neutrophil count > 1,500 cells/μL
   - Platelets > 50,000 cells/μL
   - Total bilirubin ≤ 1.5 times the upper limit of normal (ULN)
   - Aspartate aminotransferase (AST)/alanine transaminase (ALT) ≤ 2.5 times ULN. If liver metastases are present, AST/ALT < 5 times ULN
   - Serum creatinine < 1.5 mg/dL and a measured creatinine clearance ≥ 50 mL/min using the Cockcroft-Gault formula
   - Prothrombin time (PT)/partial thromboplastin time (PTT) ≤ 1.5 times ULN
9. Women of child-bearing potential (defined as a female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea for at least 12 consecutive months with an appropriate clinical profile at the appropriate age, e.g., greater than 45 years) must have a negative serum pregnancy test prior to first dose of study drug
10. Male and female patients with reproductive potential must agree to use two forms of highly effective contraception throughout the study

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Exclusion Criteria:

All patients:

1. Anti-cancer therapy within 4 weeks or < 5 half-lives of the first dose of study drug
2. Failure to recover, to Grade 1 or less, from clinically significant AEs due to prior anti-cancer therapy, as judged by the investigator.
3. Known untreated brain metastases or treated brain metastases that have not been stable (scan showing no worsening of CNS lesion[s] and no requirement of corticosteroids) ≥ 4 weeks prior to study enrollment
4. Baseline prolongation of QT/QTc interval (QTc interval > 470)
5. Uncontrolled intercurrent illness (including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations) that in opinion of the investigator would limit compliance with study requirements
6. Women who are pregnant or breastfeeding
7. Sponsor reserves right to exclude any patient from the study on basis of pre-study medical histories, physical examination findings, clinical laboratory results, prior medications, or other entrance criteria.

Test Product, Dose and Mode of Administration:

Phase I (dose escalation):

Monotherapy: IMSA101 dose levels of (but not necessarily be limited to) up to 100, 200, 400, 800, and 1,200 µg through intratumoral injection as monotherapy.

Combination therapy: IMSA101 in combination with current ICI therapy administered according to the label of that product. IMSA101 combination dose levels through intratumoral injection are as follows:

- 800 and 1,200 µg
- 2,400 µg (with an initial "priming" dose of 1,200 µg)
- 3,600 µg (with an initial "priming" dose of 2,400 µg)
- 4,800 µg (with an initial "priming" dose of 3,600 µg)

1 mL IMSA101 total volume will be given as follows:

Monotherapy: IMSA101 every week for 3 weeks in Cycle 1 (Days 1, 8, and 15) followed by every other week in Cycles 2+ (Days 1 and 15).

Combination therapy:

- IMSA101 dose levels of 800 and 1,200 µg doses every week for 3 weeks in Cycle 1 (Days 1, 8, and 15) followed by every other week in Cycles 2+ (Days 1 and 15).

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- IMSA101 dose levels of 2,400, 3,600, and 4,800 µg: Day 1 of Cycle 1 priming dose of 1,200 µg for the 2,400 µg dose group, 2,400 µg for the 3,600 µg dose group, and 3,600 µg for the 4,800 µg group through intratumoral injection. After Day 1 of Cycle 1, the full dose through intratumoral injections on Day 1 of Weeks 2 and 3 of Cycle 1 (i.e., weekly dosing 3 out of 4 weeks), and on Day 1 of Weeks 1 and 3 for all cycles thereafter (i.e., bi-weekly dosing).

Phase IIA (dose expansion)

Monotherapy: IMSA101 at RP2D dose through intratumoral injection.

Combination therapy: IMSA101 at combination RP2D dose through intratumoral injection in combination with IO therapy administered according to the label of that product.

1 mL IMSA101 total volume will be given every week for 3 weeks in Cycle 1 (Days 1, 8, and 15) followed by every other week in Cycles 2+ (Days 1 and 15).

Number of Patients: Approximately: 115

Phase I: Approximately 45 patients in 5 dose cohorts

Phase IIA: Approximately 70 patients in 3 arms of approximately 20–25 patients each

Estimated Study Duration:

The expected duration of Phase I is approximately 18 months.

The expected duration of Phase IIA is approximately 18 months.

Study Endpoints:

Primary Endpoint:

- MTD/RP2D of IMSA101 administered by intratumoral injection alone or in combination with approved ICI therapy

Secondary (Safety) Endpoints:

- Safety of IMSA101 as determined by incidence of treatment-emergent adverse events (TEAEs), laboratory abnormalities, and other safety using CTCAE v5.0 criteria
- Incidence of DLTs in patients administered IMSA101 by intratumoral injection

Secondary (Efficacy) Endpoints including:

- RECIST-based objective response rate (ORR)
- Duration of response (DOR)
- Time to RECIST-based tumor progression (TTP)
- Progression-free survival time (PFS)

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PK Endpoints (Phase I monotherapy only):

- PK parameters of IMSA101 administered by intratumoral injection

Exploratory PD Endpoints (Phase I only):

- Blood levels of cytokines (pre-dose, 2h, 4h, 6h, 24 h post-dosing Cycle 1 Day 1 and Cycle 2 Day 15): IL6 and IP10, IFNγ, TNFα, IL-10, IL-1β, IFN-β, MCP-1 (CCL2)
- Blood (pre-dose on Day 1 of Cycles 1, 2, and 3): Flow cytometry of Cryopreserved PBMCs CD3, CD4, CD8, CD45, CD69, CD19, CD56, FOXP3, PD-1, PD-L1, CD141, CD86, HLA-DR, CD14, CD16, CD11c
- Tumor Biopsy for injected tumor and non-injected tumor, if applicable (non-injected tumor biopsy required in at least 1 patient per cohort) (pre-dose on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 15): Multiplexed Immunofluorescence (mIF) including antibodies to CD45, CD4, CD8, CD11c, CD56(NK), FOXP3, DAPI, PD-1, and PD-L1

An aliquot of tumor sample for injected and non-injected tumor is to be stored for later RNA isolation and sequencing when the analysis is warranted based on clinical or immunological responses.

Criteria for Evaluation:

MTD/RP2D:

- Definition of Maximum Tolerated Dose (MTD): The MTD is defined as the highest dose level of IMSA101 at which no more than 1 out of 6 (7 when applicable) patients experiences a DLT during the first cycle (28 days) of therapy.
- Definition of Recommended Phase 2 Dose (RP2D): The RP2D is defined as the dose (either at MTD or below MTD) that is selected for evaluation in the Phase IIA component of the study.
- The MTD/RP2D of IMSA101 will be determined by the sponsor and the CRC.

Safety:

- Safety assessments will include evaluation of TEAEs, DLTs, vital signs, 12-lead ECG, physical examination, and laboratory safety assessments. Toxicities will be graded using CTCAE v5.0. Patients will be observed for 1 hour in the clinic following intratumoral injections. In addition, following intratumoral injection on Day 1 of Cycle 1, patients will be admitted to the hospital for observation overnight.
- Safety data will be listed by study site, patient number, and cycle. All TEAEs will be summarized by study phase and assigned dose. In addition, all SAEs, including deaths will be listed separately and summarized.
- Grade 3 and 4 laboratory data will be summarized by study phase and assigned dose.
- For patients who experience a DLT, data on AEs leading to treatment/study discontinuation will be listed.

Dose Limiting Toxicity (DLT): DLT will be defined as the occurrence of any of the following events that is considered at least possibly related to IMSA101 in the first 28 days (first cycle) of treatment. The severity of AEs will be graded according to CTCAE v5.0.

Hematologic AEs

- ≥ Grade 4 neutropenia lasting for > 7 days
- Febrile neutropenia (defined as ANC < 1000/mm^3 with a single temperature of 38.3ºC (101°F) or a sustained temperature of 38ºC (100.4°F) for > 1 hour)
- ≥ Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with Grade ≥ 2 bleeding
- ≥ Grade 4 anemia

Non-hematologic AEs:

- Elevation of ALT or AST by ≥ 3X ULN with concurrent elevation of serum total bilirubin ≥ 2X ULN
- Any ≥ Grade 3 non-hematologic AE of any duration will be considered a DLT with the following exceptions:
  - Nausea/vomiting/diarrhea:
    - To be considered a DLT, ≥ Grade 3 nausea/vomiting/diarrhea must be refractory to supportive care and last > 3 days.

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- ≥ Grade 3 nausea/vomiting/diarrhea that lasts ≤ 3 days is not a DLT.

- Fatigue:
  - To be considered a DLT, ≥ Grade 3 fatigue must last > 7 days.
  - ≥ Grade 3 fatigue that lasts ≤ 7 days is not a DLT.

Efficacy:

Tumor Assessments

- All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation.
- Screening and subsequent tumor assessments must include CT scans (with IV contrast unless contraindicated and oral contrast as appropriate per institutional standards) or MRI of the chest, abdomen, and pelvis. Photographic assessments of skin lesions will be performed through a photography vendor as detailed in a separate photography manual.
- If a CT scan for tumor assessment is performed in a positron emission tomography (PET)/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast CT scan.
- Brain imaging (either MRI or contrast-enhanced CT) is required at screening for all patients displaying clinical signs of possible CNS involvement.
- Further investigations such as bone scans should also be performed if there is any clinical suspicion of disease at any site that may not be demonstrated by the minimum schedule of assessments listed above.
- The same radiographic procedures used to assess disease sites at screening should be used throughout the study (e.g., the same contrast protocol for CT scans). Assessments should be performed by the same evaluator if possible to ensure internal consistency across visits.
- All findings will be assessed for response according to RECIST v1.1 criteria at the end (≤ 7 days) of every even numbered cycle (Cycle 2, Cycle 4, etc.).

Pharmacokinetics (Phase I monotherapy only):

Blood samples for PK will be collected at multiple time points. Plasma concentrations at each time point will be listed and summarized by each dose level. Plasma concentrations versus time profiles (with concentrations on both a log and linear scale) will be plotted for each patient; similar summary plots will be constructed for each dose level. PK parameters will be calculated by visit.

Pharmacodynamics (Phase I only):

Blood and tumor samples to be collected at multiple time points for exploratory assessment of several biomarkers.

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Statistical Methods:

Phase IIA statistics will be mainly descriptive and informed by the ultimate selection of tumor types to be evaluated. Statistical methods including pre-defined criteria for signal detection and drug differentiation from standard-of-care benchmarks as well as stage progression and futility assessment will be included in the final statistical analysis plan (SAP).

Table 1 Phase I Schedule of Assessments and Study Activities

Procedures	Screening Days –30 to 1	Cycle 1 [14]			≥ Cycle 2 [14]			EOT[14]	EOS [15]
Study Day		**Day 1**	**Day 8**	**Day15**	**Day 1**	**Day 15**	**End of Even Cycles**		
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical history [1]	X								
Concomitant medications	X	X[16]	X	X	X	X		X	
Demographic data	X								
Height	X								
Vital signs, weight	X	X[16]	X	X	X	X		X	
Physical examination [2]	X							X	
Neurologic examination	X	X[16]	X	X	X	X		X	
ECOG Performance Status	X	X[16]	X	X	X	X		X	
ECG [3]	X	X	X	X				X	
Hematology [4]	X		X	X	X	X		X	
Coagulation [4]	X								
Chemistry [4]	X		X	X	X	X		X	
Urinalysis [4]	X								
Pregnancy test [5]	X							X	
PK blood samples [6]		X				C2D15			
PD blood samples [7]		X			C2, C3	C2D15			
PD tissue samples [7]		X		X		C2D15			
Disease assessment using RECIST [8]	X						X	X	
Drug administration [9]		X	X[17]	X[17]	X	X			
Patient Observation[10]		X	X	X	X	X			
Hospital admission[11]		X							
Assessment for AEs [12]		X	X	X	X	X		X	X
Archival Tumor Tissue [13]	X								

AE: adverse event; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOS: end of study; EOT: end of treatment; PD: pharmacodynamics; PK: pharmacokinetics; RECIST: response evaluation criteria in solid tumors.

[1] Full medical history at screening.

[2] Full physical examinations will be done at screening and EOT visit only; all other endpoints will employ assessment of AEs and captured in AE and disease assessment CRFs.

[3] ECGs will be performed at screening, 30 to 60 minutes post-dose on C1D1, C1D8, C1D15, and at EOT and at any other visit where the investigator believes the assessment is indicated.

[4] Laboratory analyses will be performed by local lab and include hematology, coagulation, chemistry, and urinalysis. Screening labs must be performed ≤ 72 hours prior to Cycle 1 Day 1. Refer to Section 6.6 for details.

[5] If the patient is a woman of childbearing potential, a serum pregnancy test must be performed during screening and at EOT.

[6] PK plasma samples will be collected from Phase I monotherapy patients only at pre-dose, 10, 20, and 30 minutes after treatment, and 1, 2, and 4 hours after treatment on Cycle 1, Day 1. If concentrations of IMSA101 are detectable at any timepoint in Cycle 1, samples will be collected on Cycle 2, Day 15 pre-dose, 10, 20, and 30 minutes after treatment and 1, 2, and 4 hour after treatment. Additional time points (6 and 24 hours after treatment) will also be collected, if any concentrations of IMSA101 are detected at the Cycle 1, 4 hour measurement. The following time windows for plasma PK sample collection are allowed: ≤ 24 hours for the pre-dose sample, ± 5 minutes for the 10-, 20-, and 30-minute post-dose samples, ± 10 minutes for the 1-hour post-dose sample, ±15 minutes for the 2-, 4-, and 6-hour post-dose samples, and ± 2 hours for the 24-hour post-dose sample. For detailed instructions, refer to laboratory manual.

[7] PD blood samples outlined in Section 2.4.5 will be collected on both blood and tumor tissue for all Phase I patients in Cycles 1, 2, and 3. The allowable time windows for PD sample collections are described in Section 6.8.1. Core biopsies should be obtained; if not appropriate, biopsies via fine needle aspirate (FNA) or excision are permitted. See laboratory manual for detailed instructions.

[8] All findings will be assessed for response according to RECIST v1.1 criteria (Appendix 13.2). RECIST v1.1 criteria do not mention including or excluding lesions that are being biopsied or injected. However, for the purposes of this protocol, the injected and biopsied lesions are to be captured as non-target lesions only (Phase I only), as follows: injected and biopsied lesion = non-target lesion #1; non-injected and biopsied lesion = non-target lesion #2 (if applicable). Disease assessments will include radiographic assessments and if applicable, photographic assessments of skin lesions, prior to the end (≤ 7 days) of every even numbered treatment cycle (Cycle 2, Cycle 4, etc.), and EOT. Photographic assessments of skin lesions will be performed through a photography vendor at the same time points as the radiographic assessments. Detailed instructions for photography will be included in a separate photography manual. In certain circumstances, a patient experiencing RECIST progression of disease may be allowed to continue therapy on study where there is agreement between the investigator and sponsor that the patient is deriving clinical benefit.

[9] IMSA101 monotherapy doses of 100, 200, 400, 800, or 1,200 µg will be administered by intratumoral injection on Day 1 of Weeks 1, 2, and 3 for Cycle 1 (i.e., weekly dosing 3 out of 4 weeks), and on Day 1 of Weeks 1 and 3 (i.e., bi-weekly dosing) for all cycles thereafter. IMSA101 combination therapy doses of 800 and 1,200 µg will be administered by intratumoral injection on Day 1 of Weeks 1, 2, and 3 for Cycle 1 (i.e., weekly dosing 3 out of 4 weeks), and on Day 1 of Weeks 1 and 3 (i.e., bi-weekly dosing) for all cycles thereafter, and IMSA101 doses of 2,400, 3,600, or 4,800 µg will be administered by intratumoral injections on Day 1 of Cycle 1 with a priming dose of 1,200 µg for the 2,400 µg dose group, 2,400 µg for the 3,600 µg dose group, and 3,600 µg for the 4,800 µg group and after Day 1 of Cycle 1, the full dose for these groups will be administered by intratumoral injections on Day 1 of Weeks 2 and 3 of Cycle 1 (i.e., weekly dosing 3 out of 4 weeks), and on Days 1 and 15 for all cycles thereafter (i.e., bi weekly dosing). For combo therapy patients, the partner drug will be administered as per product label. Where no remaining accessible lesions are present and where benefit of IMSA101 therapy is, in the

opinion of the investigator, being derived by the patient, continued injections of IMSA101 into the vicinity of an inaccessible lesion shall be allowed. In the case that a lesion can no longer be radiographically visualized, continued injections into the last known location of the non-visible lesion shall be allowed.

[10] Patients will be observed in the clinic for 1 hour after each intratumoral injection.

[11] Patients will be admitted to the hospital for observation overnight following intratumoral injection with IMSA101 on Day 1 of Cycle 1 and will be released from the hospital when clinically indicated.

[12] AE reporting begins at the time of study drug administration and continues until 30 days after the last dose.

[13] Collect archival tumor specimens if available.

[14] A +/- 3 day visit window is allowed for each visit except for Cycle 1, Day 1 and the End of Even Cycle disease assessment.

[15] Patients should be followed for safety after the EOT visit and return to clinic 30 days after the last dose for final assessment of interval changes and AEs.

[16] Cycle 1 Day 1 assessments must be performed within 72 hours prior to Cycle 1 Day 1.

[17] For Cycle 1 Day 8 and Cycle 1 Day 15, IMSA101 doses should be administered no less than 4 days apart.

Table 2 Phase IIA Schedule of Assessments and Study Activities

Procedures	Screening Days –30 to 1	Cycle 1 [11]			≥ Cycle 2 [11]			EOT[11]	EOS[12]
Study Day		**Day 1**	**Day 8**	**Day15**	**Day 1**	**Day 15**	**End of Even Cycles**		
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical history [1]	X								
Concomitant medications	X	X[13]	X	X	X	X		X	
Demographic data	X								
Height	X								
Vital signs, weight	X	X[13]	X	X	X	X		X	
Physical examination [2]	X							X	
Neurologic examination	X	X[13]	X	X	X	X		X	
ECOG Performance Status	X	X[13]	X	X	X	X		X	
ECG [3]	X	X	X	X				X	
Hematology [4]	X		X	X	X	X		X	
Coagulation [4]	X								
Chemistry [4]	X		X	X	X	X		X	
Urinalysis [4]	X								
Pregnancy test [5]	X							X	
Disease assessment using RECIST [6]	X						X	X	
Drug administration [7]		X	X[14]	X[14]	X	X			
Patient Observation[8]		X	X	X	X	X			
Hospital admission [9]		X							
Assessment for AEs [10]		X	X	X	X	X		X	X

AE: adverse event; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOS: end of study; EOT: end of treatment; RECIST: response evaluation criteria in solid tumors.

1 Full medical history at screening.

2 Full physical examinations will be done at screening and EOT visit only; all other endpoints will employ assessment of AEs and captured in AE and disease assessment CRFs.

[3] ECGs will be performed at screening, 30 to 60 minutes post-dose on C1D1, C1D8, C1D15, and at EOT and at any other visit where the investigator believes the assessment is indicated.

[4] Laboratory analyses will be performed by local lab and include hematology, coagulation, chemistry, and urinalysis. Screening labs must be performed ≤ 72 hours prior to Cycle 1, Day 1. Refer to Section 6.6 for details.

[5] If the patient is a woman of childbearing potential, a serum pregnancy test must be performed during screening and at EOT.

[6] Disease assessments will include radiographic assessments and if applicable, photographic assessments of skin lesions, prior to the end (≤ 7 days) of every even numbered treatment cycle (Cycle 2, Cycle 4, etc.), and EOT. Photographic assessments of skin lesions will be performed through a photography vendor at the same time points as the radiographic assessments. Detailed instructions for photography will be included in a separate photography manual. In certain circumstances a patient experiencing RECIST progression of disease may be allowed to continue therapy on study where there is agreement between the investigator and sponsor that the patient is deriving clinical benefit.

[7] IMSA101 will be administered by intratumoral injection on Day 1 of Weeks 1, 2, and 3 for Cycle 1 (i.e., weekly dosing 3 out of 4 weeks), and on Day 1 of Weeks 1 and 3 (i.e., bi-weekly dosing) for all cycles thereafter. For combo therapy patients, the partner drug will be administered as per product label. (See Figure 11). Where no remaining accessible lesions are present and where benefit of IMSA101 therapy is, in the opinion of the Investigator, being derived by the patient, continued injections of IMSA101 into the vicinity of an inaccessible lesion shall be allowed. In the case that a lesion can no longer be radiographically visualized, continued injections into the last known location of the non-visible lesion shall be allowed.

[8] Patients will be observed in the clinic for 1 hour after each intratumoral injection.

[9] Patients will be admitted to the hospital for observation overnight following intratumoral injection with IMSA101 on Day 1 of Cycle 1 and will be released from the hospital when clinically indicated.

[10] AE reporting begins at the time of study drug administration and continues until 30 days after the last dose.

[11] A +/- 3 day visit window is allowed for each visit except for Cycle 1, Day 1 and the End of Even Cycle disease assessment.

[12] Patients should be followed for safety after the EOT visit and return to clinic 30 days after the last dose for final assessment of interval changes and AEs.

[13] Cycle 1 Day 1 assessments must be performed within 72 hours prior to Cycle 1 Day 1.

[14] For Cycle 1 Day 8 and Cycle 1 Day 15, IMSA101 doses should be administered no less than 4 days apart.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine transaminase
AMP	adenosine monophosphate
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
ATP	adenosine triphosphate
$AUC_{0\text{-}inf}$	area under the plasma concentration-time curve from time zero to infinity
$AUC_{0\text{-}t}$	area under the plasma concentration-time curve from time zero to time t
CD	cluster of differentiation
CFR	Code of Federal Regulations
cGAMP	cyclic-GMP-AMP
cGAS	cyclic GMP-AMP synthase
CI	confidence interval
CK	creatine kinase
CRC	Cohort Review Committee
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA4	cytotoxic T-lymphocyte-associated protein 4
DC	Dendritic cells
DL	dose level
DLT	dose limiting toxicity
DOR	duration of treatment response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOS	End of Study
EOT	End of Treatment
F	bioavailability
F_{rel}	relative bioavailability
FDA	Food and Drug Administration
FIH	first-in-human
FNA	fine needle aspirate

Abbreviation	Definition
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	guanosine monophosphate
hERG	human ether-a-go-go related gene
HIPAA	Health Insurance Portability and Accountability Act
HNSTD	highest non-severely toxic dose
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICB	immune checkpoint blockade
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICI	immune checkpoint inhibitor
IEC	Institutional Ethics Committee
IFN	interferon
IHC	immunohistochemistry
IO	immuno-oncology
INR	international normalization ratio
IL	interleukin
IP-10	IFNγ-inducible protein 10
IR	Interventional Radiology
IRB	Institutional Review Board
IV	intravenous
MABEL	minimum anticipated biological effects level
MCP-1	monocyte chemoattractant protein 1
MedDRA®	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NHP	non-human primate
ORR	overall response rate
PBMCs	peripheral blood mononuclear cells
PD	pharmacodynamics
PD-1	programmed cell death-1
PD-L1	programmed death-ligand 1
PDF	portable document format

Abbreviation	Definition
PFS	progression-free survival time
PK	pharmacokinetic
PT	prothrombin time
PTT	partial thromboplastin time
QTc	corrected QT interval
REB	research ethics board
RECIST	response evaluation criteria in solid tumors
RP2D	recommended Phase II dose
SAEs	serious adverse events
SAP	statistical analysis plan
SEM	standard error of the mean
SmPC	Summary of Product Characteristics
STING	stimulator of interferon genes
TEAE	treatment-emergent adverse event
TILs	tumor infiltrating leukocytes
TNFα	tumor necrosis factor α
TTP	time-to-tumor progression
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
WBC	white blood cell

1 INTRODUCTION

1.1 BACKGROUND

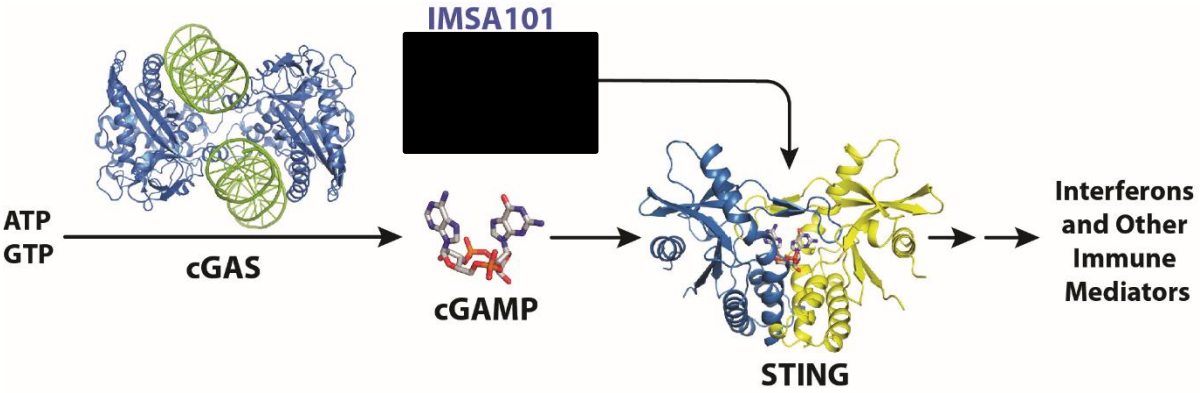
The treatment of advanced solid tumor malignancies as well as many hematologic malignancies continues to be defined by high unmet medical need. In most settings, treatment with cytotoxic chemotherapy and targeted kinase inhibitors leads to the emergence of drug-resistant tumor clones and subsequent tumor progression and metastasis.

In recent years, notable success has been achieved through alternate approaches oriented around activation of immune-mediated tumor destruction. The immune system plays a pivotal role in defending humans and animals against cancer. The anti-tumor effect is controlled by positive factors that activate anti-tumor immunity and negative factors that inhibit the immune system. Negative factors that inhibit anti-tumor immunity include immune checkpoint proteins, such as cytotoxic T-lymphocyte-associated protein 4 (CTLA4), programmed cell death-1 (PD1), and programmed death-ligand 1 (PDL1). Immuno-oncology (IO) approaches, including antibodies against these checkpoint proteins, have shown remarkable efficacy in several types of human cancers.

However, existing cancer immunotherapy through immune checkpoint blockade (ICB) is effective for only a small fraction (on average 20-30%) of cancer patients. The patients who are refractory to ICB often have tumors that are not inflamed, or so-called “cold” tumor cells, i.e., they lack tumor-infiltrating leukocytes (TILs), such as cluster of differentiation 8 (CD8) T cells or the tumor microenvironment suppresses the functions of the TILs. A major thrust of ongoing cancer drug development research remains focused on transforming “cold” tumor cells into “hot” tumor cells in order to achieve better tumor control across a wider array of patients.

The innate immune system, which is the first line of defense against pathogens and cancer cells, is important for turning the non-inflamed tumors (“cold”) into an inflamed (“hot”) microenvironment. A recently discovered innate immunity pathway, the Cyclic GMP-AMP Synthase (cGAS)- Stimulator of Interferon Genes (STING) pathway, plays a critical role in anti-tumor immunity (Figure 1). cGAS is a DNA sensing enzyme that activates the type-I interferon pathway. Upon binding DNA, cGAS is activated to synthesize 2’3’ cyclic-GMP-AMP (2’3’-cGAMP), which then functions as a secondary messenger that binds to and activates the adaptor protein STING. STING then activates a signal transduction cascade leading to the production of type-I interferons, cytokines and other immune mediators.

Figure 1 The cGAS-cGAMP-STING Pathway



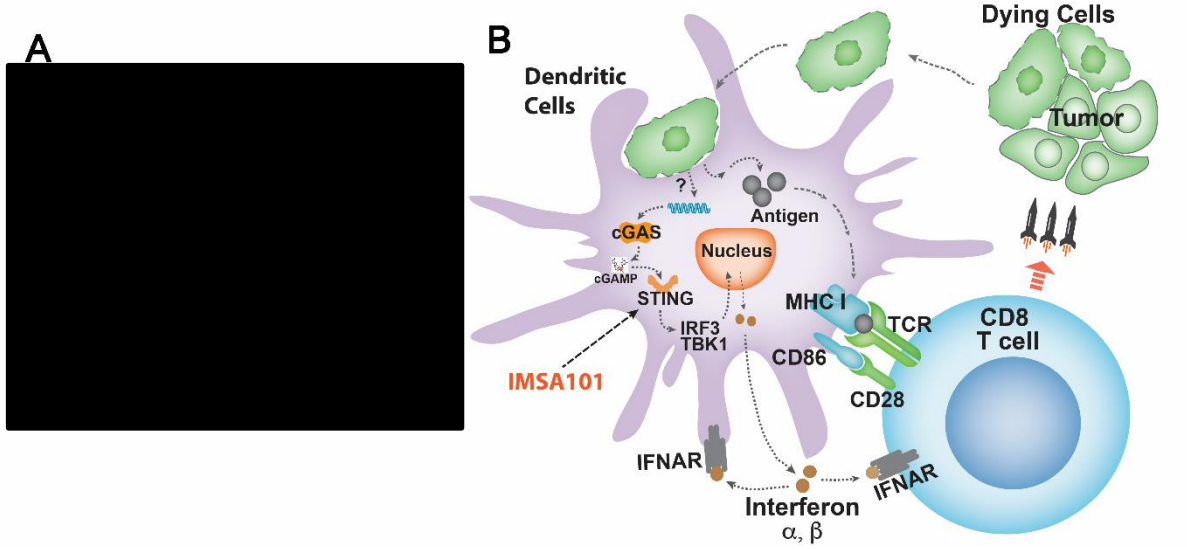
Cytosolic DNA binds to and activates the enzyme cGAS, which then catalyzes the synthesis of cyclic GMP-AMP (cGAMP). cGAMP functions as a second messenger that binds to and activates the endoplasmic reticulum membrane protein STING, which in turn leads to the production of type-I interferons and other immune stimulatory molecules. IMSA101 is an analogue of cGAMP and directly stimulates STING.

When dying tumor cells are taken up and processed by dendritic cells (DCs), DNA from these tumor cells becomes a danger signal that triggers the cGAS–cGAMP-STING pathway to promote maturation of DCs and presentation of tumor antigens to T cells. Interferon and cytokines produced by DCs and other innate immune cells cooperatively stimulate T cell infiltration and function, leading to cytotoxic killing of tumor cells (Figure 2B) (Chen, 2016). There is mounting evidence that the cGAS pathway is essential for generating anti-tumor immunity (Bose, 2017: Wang 2017).

As expected, surviving tumor cells develop mechanisms to antagonize host immunity. For example, high expression of immune checkpoint molecules such as PDL1 on their cell surface bind PD1 on T cells to inhibit the latter's function. PDL1 inhibitor therapy can reverse the inhibition of anti-tumor immunity and restore T cell function. However, in patients with very low anti-tumor immunity, the PDL1 inhibitor will have little benefit. Instead, a positive signal is needed to boost intrinsic immunity. Toward this end, the administration of cGAMP directly stimulates STING and jump-starts antitumor immunity. This activity has demonstrated encouraging therapeutic efficacy in several mouse syngeneic tumor models (Li, 2016: Wang 2017).

Figure 2 The Chemical Structure and Mechanism of IMSA101

A) Chemical structure of IMSA101. **B)** Mechanism of IMSA101 anti-tumor immunity through cGAS-STING pathway. Modified from (Chen, 2016).



1.2 STUDY DRUG

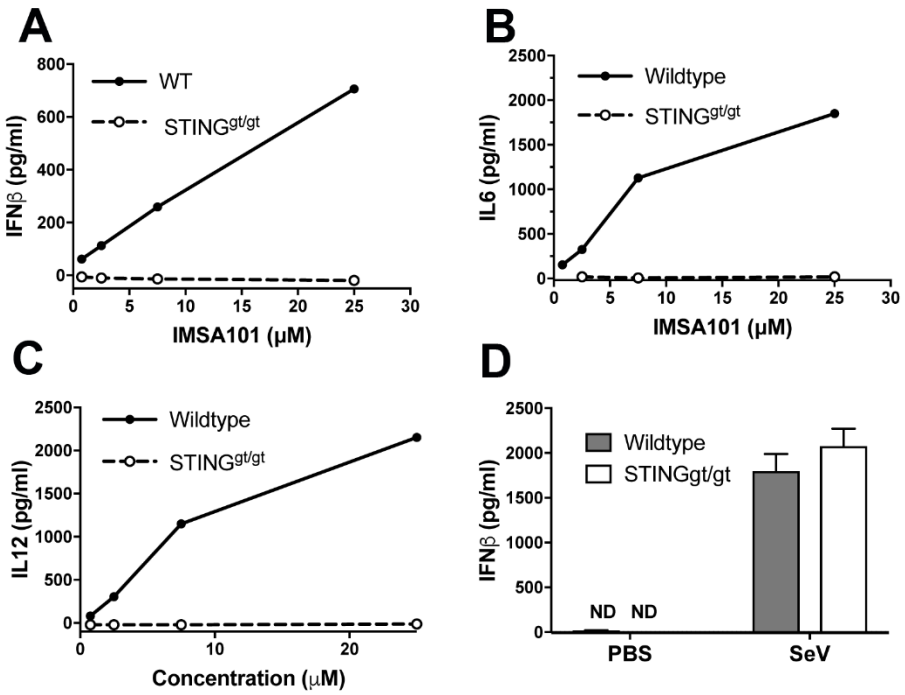
IMSA101 is a small molecule analogue of cGAMP. It contains a [redacted] Figure 2A [redacted].

The drug product (IMSA101 for Injection) is a sterile and nonpyrogenic solution containing 10 mg of IMSA101 in 1.0 mL [redacted], which is used for intratumoral injection.

1.3 NONCLINICAL PHARMACOLOGY STUDIES

In *ex vivo* cell culture experiments using human and mouse cells, IMSA101 induced production of IFNβ, IL6, and IL12 in a dose-dependent manner in wild-type cells, but not in STING$^{gt/gt}$ cells (Figure 3A, B, and C). As a control, IFNβ production in response to Sendai virus, which activates the retinoic acid inducible gene I (RIG-I) dependent RNA-sensing pathway, was not affected (Figure 3D).

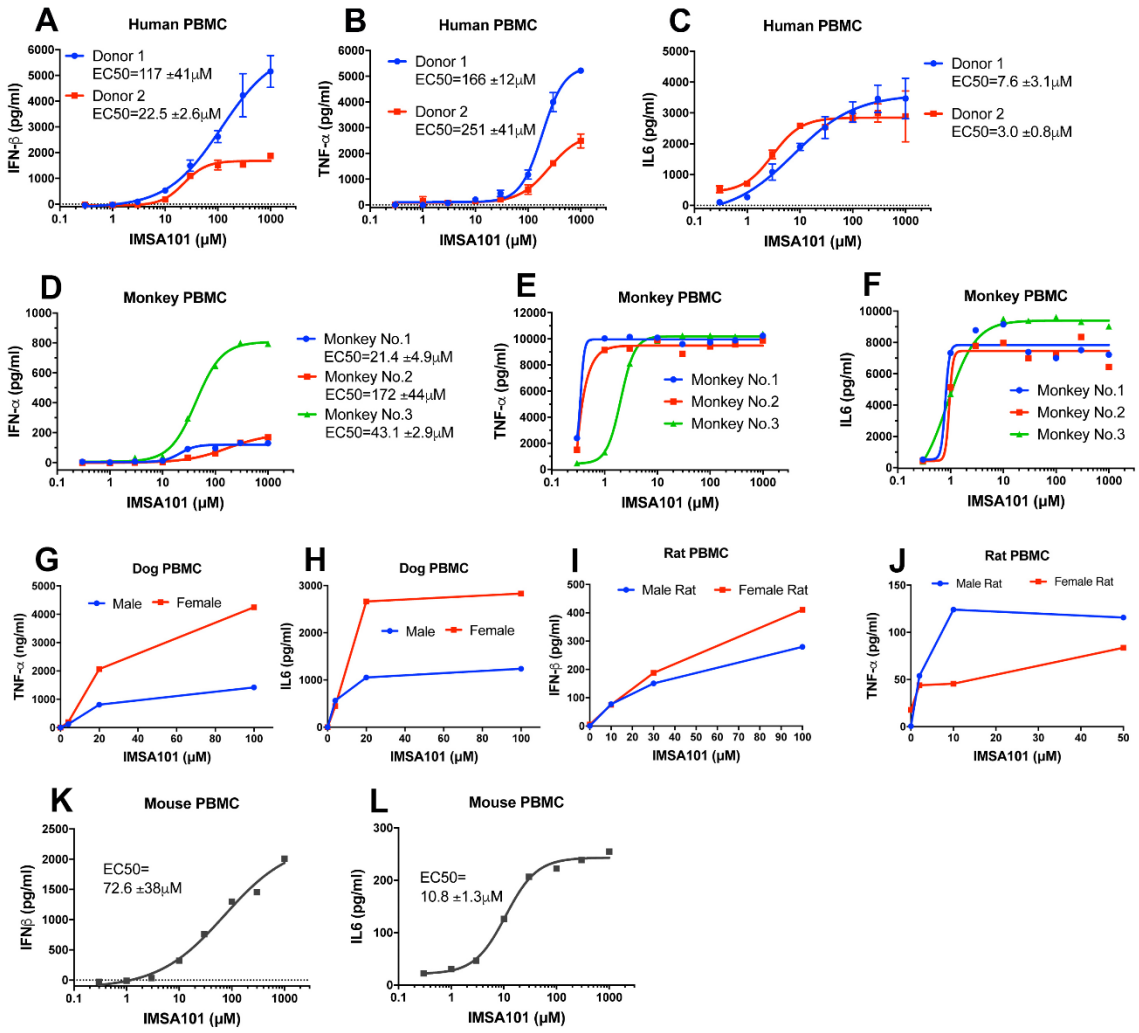
Figure 3 **IMSA101-induced Cytokine Production in Wild-Type and STING-deficient Mouse Dendritic Cells**



A, **B**, and **C)** Cytokine production by dendritic cells (DC) derived from either wild-type or STING$^{gt/gt}$ mice after stimulation with different concentrations of IMSA101 as indicated. **D)** IFNβ production by DC derived from wild-type and STING$^{gt/gt}$ mice after infection with Sendai virus. PBS: phosphate-buffered saline; SeV: Sendai virus; WT: Wild type.

IMSA101 also stimulated IFN and IL6 production in peripheral blood mononuclear cells (PBMCs) from mouse, rat, dog, monkey and human with similar potency (Figure 4).

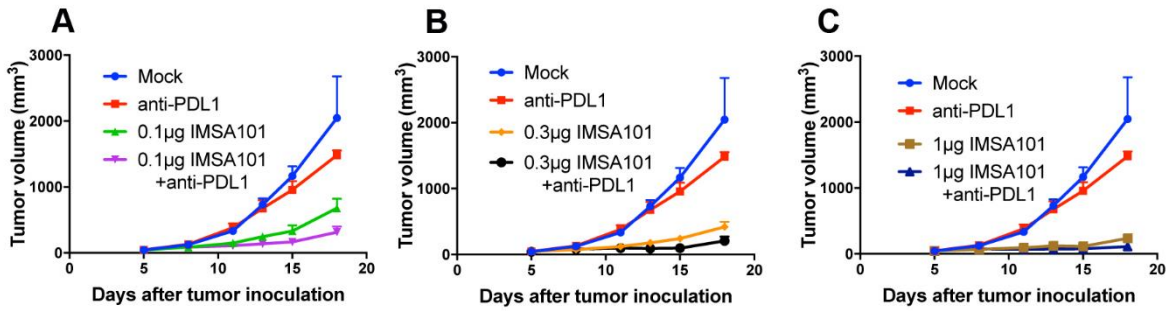
Figure 4 Cytokine Production Induced by IMSA101 in PBMCs



PBMCs from human **(A**, **B**, **C)**, monkey **(D**, **E**, **F)**, dog **(G**, **H)**, rat **(I**, **J)**, and mouse **(K**, **L)**. PBMC: peripheral blood mononuclear cell. Data are representative of at least 2 experiments for PBMC from each species.

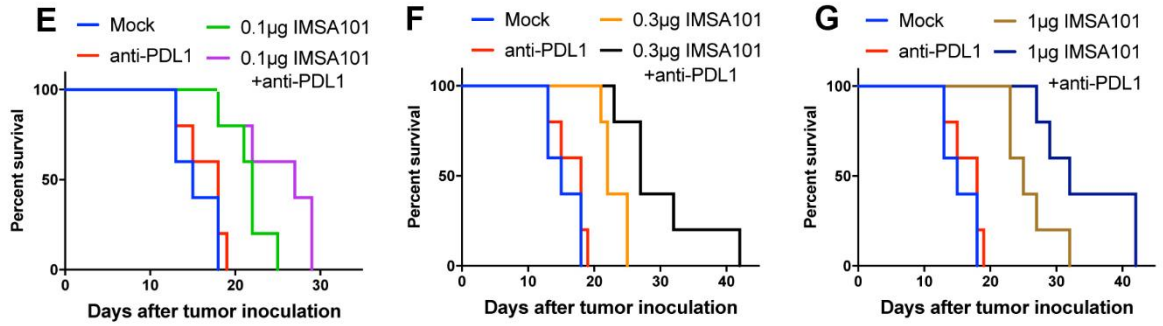
When delivered intratumorally in mice bearing tumors, IMSA101 was highly effective in inhibiting tumor growth in several syngeneic tumor models, including B16F10 (melanoma), MC38 (colon), 4T1 (breast), LL2 (lung) and AG104 (fibrosarcoma). Note that several of these tumors such as B16F10, 4T1, LL2 and AG104 are known to be refractory to antibodies against PD1, PDL1, or CTLA4. In the B16F10 tumor model, twice weekly injection of IMSA101 for two weeks was efficacious in a dose-dependent manner in the range from 0.1 μg to 10 μg (0.005-0.5 mg/kg) (Figure 5). The combination with anti-PDL1 antibody showed improved efficacy at each dose level (Figure 5). Tumor growth was almost completely suppressed at the dose of 0.05 mg/kg (1 μg/mouse) of IMSA101 when combined with anti-PDL1 antibody (Figure 5C).

Figure 5 Effect of Intratumoral Administration of IMSA101 on B16 Melanoma



D

	anti-PDL1	0.1μg IMSA101	0.1μg IMSA101 +anti-PDL1	0.3μg IMSA101	0.3μg IMSA101 +anti-PDL1	1μg IMSA101	1μg IMSA101 +anti-PDL1
Mock	0.166	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
anti-PDL1		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001



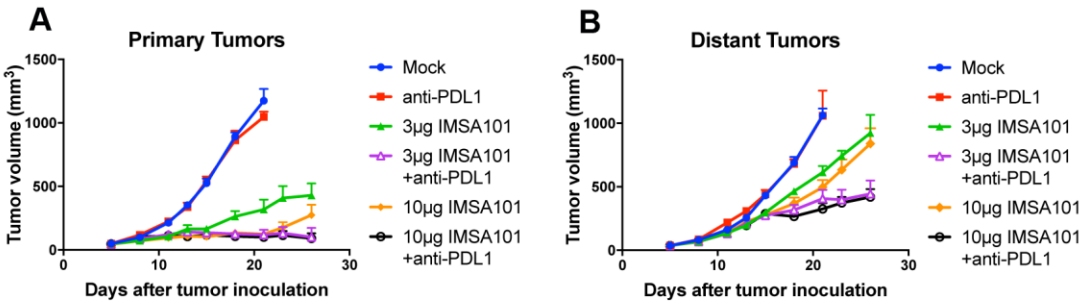
H

	anti-PDL1	0.1μg IMSA101	0.1μg IMSA101 +anti-PDL1	0.3μg IMSA101	0.3μg IMSA101 +anti-PDL1	1μg IMSA101	1μg IMSA101 +anti-PDL1
Mock	0.3474	0.0079	0.0079	0.0025	0.0025	0.0025	0.0025
anti-PDL1		0.0112	0.0112	0.0021	0.0021	0.0021	0.0021

A, B, C) Tumor growth in mice with indicated treatments. **D)** Statistics on tumor growth curves. Numbers indicate *p* values between each comparison groups obtained using two-way ANOVA. **E, F, G)** Survival of mice with indicated treatments. **H)** Statistics on survival curves. Numbers indicate *p* values between each comparison groups obtained using log rank (Mantel Cox) test. ANOVA: analysis of variance; PD1: Programmed Death-Ligand 1.

An abscopal effect, which is an immune-mediated phenomenon wherein direct treatment of a primary tumor can lead to a response in a distant tumor, of IMSA101 was demonstrated in two studies using the B16 melanoma model. In one study, there was a decrease in the sizes of non-injected tumors and prolonged survival following the intratumoral administration of IMSA101 (Figure 6). In another study, intratumoral administration of IMSA101 reduced lung metastases (Figure 7).

Figure 6 Abscopal Effect of IMSA101 on AG104A Fibrosarcoma

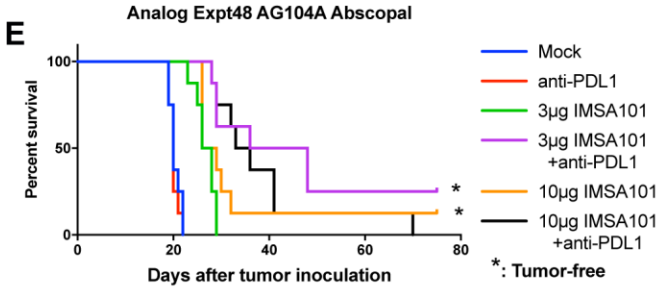


C. *p* values, primary tumors

	anti-PDL1	3μg IMSA101	3μg IMSA101 +anti-PDL1	10μg IMSA101	10μg IMSA101 +anti-PDL1
Mock	0.623	<0.0001	<0.0001	<0.0001	<0.0001
anti-PDL1		<0.0001	<0.0001	<0.0001	<0.0001

D. *p* values, distant tumors

	anti-PDL1	3μg IMSA101	3μg IMSA101 +anti-PDL1	10μg IMSA101	10μg IMSA101 +anti-PDL1
Mock	0.9859	<0.0001	<0.0001	<0.0001	<0.0001
anti-PDL1		<0.0001	<0.0001	<0.0001	<0.0001

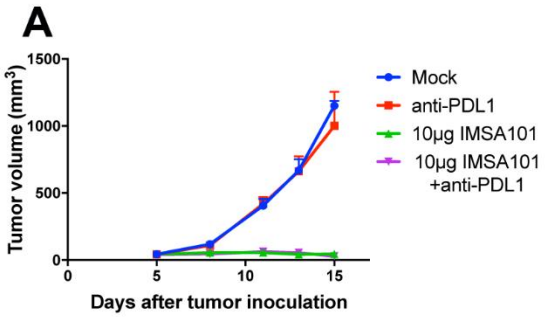


F *p* values, Survial

	anti-PDL1	3μg IMSA101	3μg IMSA101 +anti-PDL1	10μg IMSA101	10μg IMSA101 +anti-PDL1
Mock	0.6167	<0.0001	<0.0001	<0.0001	<0.0001
anti-PDL1		<0.0001	<0.0001	<0.0001	<0.0001

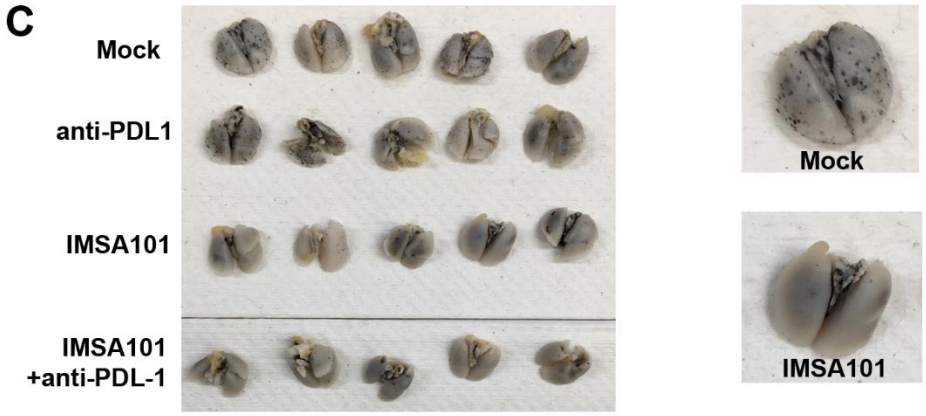
C3B6F1 mice (N=8) bearing AG104A tumors on both left and right flanks were treated intratumorally on the right flank (primary) with IMSA101 on Days 5, 8, 11, and 15. Tumors on the left flank (distant) were not treated. **A)** Primary tumor growth over time. Data are shown as mean ± SEM. **B)** Distant tumor growth over time. Data are shown as mean ± SEM. **C)** Statistical analysis of tumor growth data in A), *P* values between comparison groups were obtained using a two-way ANOVA. **D)** Statistical analysis of tumor growth data in B), *P* values between comparison groups were obtained using a two-way ANOVA. **E)** Survival over time. **F)** Statistical analysis of survival data in E). *P* values between comparison groups were obtained using log rank (Mantel Cox) test. ANOVA: analysis of variance; PDL1: Programmed Death-Ligand 1; SEM: standard error of the mean.

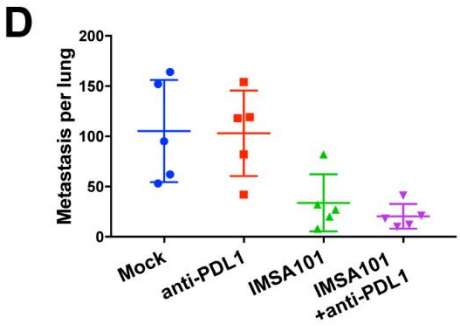
Figure 7 IMSA101 Suppresses Melanoma Metastasis



B

	anti-PDL1	IMSA101	IMSA101 +anti-PDL1
Mock	0.8694	<0.0001	<0.0001
anti-PDL1		<0.0001	<0.0001
IMSA101			0.1148





E

	anti-PDL1	IMSA101	IMSA101 +anti-PDL1
Mock	0.94	0.0254	0.0067
anti-PDL1		0.0165	0.0031
IMSA101			0.36

Mice were dose at Days 5, 8, and 11. **A)** Growth curves of primary tumors over time. Data are shown as mean ± SEM of 5 mice. **B)** Statistical analysis of tumor growth data in A), *P* values between comparison groups were obtained using two-way ANOVA. **C)** Images showing lung metastasis in all groups. Right two panels show magnified images of lungs representing selected treatment groups. **D)** Quantification of lung metastasis in C), each symbol represents one mouse. **E)** Statistical analysis of lung metastasis in D). *P* values between comparison groups were obtained using unpaired *t*-test. ANOVA: analysis of variance; PDL1: Programmed Death-Ligand 1; SEM: standard error of the mean.

1.3.1 Pharmacokinetics and Product Metabolism in Animals

The evaluations of the pharmacokinetics (PK), including the absorption, protein binding, and metabolic stability of IMSA101 in species that were used in the pharmacology and toxicology studies (mouse, rat, and monkey) were conducted. These studies are described in detail in the Investigator Brochure, v 1.0, 2019.

In summary, the PK parameters of IMSA101 were estimated following administration by intravenous, subcutaneous, or intratumoral routes in mice at doses of 0.1 or 0.5 mg/kg. IMSA101 concentrations in plasma were measured using a qualified LC-MS/MS method. The calculated, dose corrected area-under-the curves (AUC_{0-t}) were similar by each route. When administered at the dose of 0.5 mg/kg, the area-under-the-curve (AUC_{0-inf}) of the intravenous dose was 494 ng·hr/mL as compared to the AUC_{0-inf} of 597 ng·hr/mL of the subcutaneous dose. The calculated bioavailability (F) of the subcutaneous dose was 1.21. The area-under-the-curve (AUC_{0-inf}) of the intratumoral dose was 360 ng·hr/mL as compared to the AUC_{0-inf} of 312 ng·hr/mL of the subcutaneous dose. The calculated relative bioavailability (F_{rel}) of the intratumoral dose was 1.12. The calculated half-life was approximately 10-15 minutes. IMSA101 showed maximal absorption at the first sampling point of 15 minutes following administration.

The observed comparability of the subcutaneous and intratumoral dose routes provided a rationale for using the subcutaneous route of administration in the toxicology studies to approximate the intratumoral route that will be used in the clinical studies.

1.3.2 Pharmacodynamic Drug Interactions

No pharmacodynamics drug interactions were evaluated.

1.3.3 Toxicology Studies

The toxicological evaluations of IMSA101 included studies in the rat and cynomolgus monkey (non-human primate [NHP]) and should be relevant to assessing potential human risk, as the STING pathway, the target of IMSA101, is conserved across species.

The non-good laboratory practice (GLP) studies in the rat and NHP covered a broad range of doses and regimens. The objective of these studies was to evaluate the effects of IMSA101 following multiple ascending doses, single doses, and multiple doses. The results of the studies provided guidance to the design of the subsequent GLP studies in the rat and NHP.

The general findings in these studies were related to the mechanism of action (MOA) of IMSA101 and can be categorized as inflammatory responses characterized by dose-related increases in STING pathway factors including Type 1 Interferons (IFNs) and proinflammatory cytokines. The findings were similar in the rat and NHP. The most consistent dose related findings were increases in IFNα, TNFα, and IL6 in the rat and monkey; IL-8 in the rat; IL-1ra, IFNγ-inducible Protein 10 (IP-10), and Monocyte Chemoattractant Protein 1 (MCP-1) in the monkey. The cytokine levels showed increases in the first 3-6 hours with return to baseline in most cases by 6-24 hours. The innate immune response is characterized by a self-regulating/modulation of the production of these factors. At low doses, the findings would be

characterized as pharmacological changes related to the MOA of IMSA101. With increasing doses, the changes could be characterized as "exaggerated" pharmacology, which is expected changes related to the MOA of IMSA101, but greater than the responses needed to affect a therapeutic response. At the highest dose levels, the IMSA101 pharmacology and exaggerated pharmacology resulted in toxicity. Mortality was seen in the GLP rat study in the high doses group at 10 and 30 mg/kg. Test article-related increased incidence or severity of minimal or slight white matter vacuolation in the brain (within the cerebellum) was noted in animals administered ≥1 mg/kg IMSA101 and necropsied at a scheduled or unscheduled interval. The observations were not dose-dependent. In recovery animals, white matter vacuolation was minimal in severity and the incidence was similar between control and high dose groups. There were no abnormal clinical observations that correlated to the brain lesions. Mortality was also seen at the 3.0 mg/kg dose level in the non-GLP NHP study. The deaths were attributed to pulmonary edema consistent with an IMSA101 mediated inflammatory response that was well beyond exaggerated pharmacology and caused the severe toxicity.

The other common findings across species and across the dose ranges/regimens were dose-related findings including a range of macroscopic, hematological, clinical chemistry, and microscopic findings. At the low doses, these changes were consistent with a desired therapeutic effect; at the highest doses, there were severe toxicities and mortality. In studies with recovery animals, there was either full recovery or a trend to recovery in the parameters showing dose-related changes.

The toxicokinetic findings showed no sex related differences, dose proportionality, and no accumulation in the multiple dose studies.

Moribundity and death were seen at the mid and high dose levels in the GLP rat study. Although there was no clear cause of death, the finding was consistent with a dose-related inflammatory response, due to exaggerated pharmacology of the MOA of IMSA101. The 3000 to 10000-fold safety margins at the 10 and 30 mg/kg dose levels in the GLP rat study should reduce safety concerns related to the deaths seen in that study.

The highest non-severely toxic dose (HNSTD) of IMSA101 was determined as 0.3 mg/kg in the monkey GLP study. The first-in-human (FIH) dose was calculated from this dose as 100 µg. Using the minimum anticipated biological effects level (MABEL) based on mouse data, FIH dose at 100 µg was estimated.

1.3.4 Safety Studies

Two safety pharmacology studies were conducted with IMSA101 including an *in vitro* human ether-à-go-go-related gene (hERG) channel assay and *in vivo* study to evaluate cardiovascular function in monkeys. Both studies demonstrate that IMSA101 does not affect cardiovascular function in *in vitro* system and monkeys.

Table 3 Safety Pharmacology Studies

Organ/ Systems Evaluated	Species/ Strain	Method of Admin.	Doses (mg/kg)	No. per Group	Noteworthy Findings	GLP Compliance	Study Number
Blood pressure, ECG	*Macaca fasicularis*	SC	0.03, 0.30, 0.60, 0.10/1.0[a]	10 per sex	No dose related effect	Yes	8370304
In vitro hERG	Human	*In vitro* incubation	0.1, 1.0, 10.0 and 100.0 µM	3 per dose level	Low potential for hERG activation	Yes	170520. DPW

ECG: electrocardiogram; GLP: good laboratory practice; hERG: human ether-à-go-go-related gene; SC: subcutaneous

[a] Administration of 0.1 mg/kg of IMSA101 on Day 1. Administration of 1.0 mg/kg of IMSA101 beginning on Day 8 and weekly thereafter.

To evaluate the potential effect of IMSA101 on the cardiovascular system, safety pharmacology endpoints of blood pressure and electrocardiogram were evaluated in the good laboratory practice (GLP) monkey study (Covance study 8370304). There are no dose-related findings noted (Table 3).

The *in vitro* effects of IMSA101 on the hERG potassium channel current (a surrogate for IKr, the rapidly activating, delayed rectifier cardiac potassium current) expressed in mammalian cells was evaluated at ambient temperature using the QPatch HT® (Sophion Bioscience A/S, Denmark), an automatic parallel patch clamp system (Effects of Two Test Articles on Ion Channels Expressed in Mammalian Cells, hERG assay, Study No. 170520.DPW). IMSA101 was evaluated at 0.1, 1.0, 10.0 and 100.0 µM, with each concentration tested in three cells (n = 3). The duration of exposure to each concentration was at least 3 minutes. On average, no more than 8.7% of hERG current was inhibited at concentrations up to 100 µM; therefore, the IC_{50} values for IMSA101 was greater than 100 µM, indicating a low potential for hERG activation.

1.4 CLINICAL EXPERIENCE

IMSA101 has not been tested clinically.

Clinical trials of similar STING agonists are in progress. These include MIW815 from Novartis/Aduro Biotech (Aduro Biotech Inc. 2016) and MK-1454 from Merck (Merck Sharp & Dohme Corp. 2017). Early results of these studies demonstrate agonism of the STING pathway by cyclic dinucleotides similar to IMSA101. The dose-related findings are consistent with the findings seen in preclinical studies and related to the MOA of a CDN STING agonist.

1.5 SUMMARY OF KNOWN RISKS AND BENEFITS

Anticipated risks based on findings from pre-clinical studies are listed below.

Consistent with the MOA of a STING agonist, the following IMSA101-related findings in these studies were noted:

Dose-proportional Findings:

- Minimal to mildly increases in body temperature

Altered Hematology Parameters:

- Minimal to mildly variable, mild-minimal decreases in platelets, mean corpuscular volume, MCH, and hemoglobin
- Minimal to mildly variable, mild-minimal increases in absolute monocyte count, large unstained cells, eosinophils, white blood cells, RBC, hematocrits, and reticulocytes
- Increases and decreases in basophils and absolute lymphocyte count

Clinical Chemistries:

- Minimal to mildly increased in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, creatine kinase (CK), inorganic phosphorus, urea nitrogen, and fibrinogen
- Minimal to mildly lower creatinine, total calcium, potassium, globulin, total protein, CK, glucose, cholesterol, triglyceride, and sodium
- Minimal to mildly prolonged activated partial thromboplastin time, prothrombin time
- Increases in IL-8, TNFα, IL-6, IFNα, MCP-1, IP-10, IL-1ra

The following drug-related events were reported in ongoing clinical trials evaluating other STING agonists being studied in clinical trials:

Novartis/Aduro Biotech (MIW815) (Aduro Biotech Inc. 2016):

- Headache
- Injection site pain
- Fever
- Elevated lipase

Merck (MK-1454) (Merck Sharp & Dohme Corp. 2017):

- Vomiting
- Fever
- Injection site pain
- Headache
- Chills
- Fatigue
- Myalgia

- Tumor pain
- Diarrhea

Based on pre-clinical findings with IMSA101 and toxicity events reported in clinical trials evaluating other STING agonists, the following risks may reasonably be anticipated in clinical trials evaluating IMSA101:

- Body temperature increases (fever)
- Chills
- Alterations in serum chemistries
- Altered serum hematology parameters
- Headache
- Injection site pain
- Vomiting
- Fatigue
- Myalgia
- Diarrhea

IMSA101 Combinations:

Some patients in this study will be treated with a combination of IMSA101 and an immune checkpoint inhibitor (ICI) targeting either programmed cell death receptor-1 (PD-1) or programmed cell death-ligand 1 (PD-L1). Multiple drugs against PD-1 and PD-L1 are in development and have shown great promise across multiple cancer types. Nivolumab and pembrolizumab, both of which target PD-1, and atezolizumab, avelumab, and durvalumab, all of which target PD-L1, have been approved in various cancer types including melanoma, renal cell carcinoma, non-small cell and small cell lung cancer, head and neck cancer, urothelial cancer, Hodgkin lymphoma, Merkel cell carcinoma, as well as other solid tumors which demonstrate a high level of mutations (also known as microsatellite instability-high or mismatch repair deficient tumors). ICIs are associated with a variety of side effects termed immune-related adverse events. Believed to arise from general immunologic enhancement, these side effects can include skin, gastrointestinal, liver, endocrine/hormonal, and other less common inflammatory events. Although extremely rare, fulminant and even fatal side effects can occur with immune checkpoint inhibitors and prompt recognition and management is essential. These immune related adverse events are generally managed through interruption of the checkpoint inhibitor and temporary immunosuppression with corticosteroids and other drugs. The prescribing information and specific risks associated with particular ICIs selected by investigators will be discussed by investigators with their patients and referenced during informed consent.

1.6 RATIONALE FOR THE STUDY

Cancer progression is frequently associated with genetic changes and abnormalities - including mutations in Wnt, p53, AKT, and signal transducer and activator of transcription 3 (STAT3) – which suppress transcription of critical cytokines, leading, in turn, to immunosuppressive tumor microenvironments. It is hypothesized here that administration of the cGAMP analog IMSA101 (either as monotherapy or in combination) can bypass immunosuppressive factors through the direct stimulation of dendritic cells (DCs). Preliminary mouse experiments suggest that IMSA101-mediated stimulation can super-activate residual DCs through the increased expression and secretion of CD86, interferon β, and cross-present antigens to CD8+ T cells. This approach is designed, in effect, to transform “cold” IO non-responding tumor cells into “hot” IO sensitive cells, addressing unmet medical need and achieving clinical benefit through intensified immuno-modulation of malignant cells.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 PRIMARY OBJECTIVE

- Establish safe recommended Phase II doses (RP2Ds) of IMSA101 administered as monotherapy or in combination with an ICI

2.2 SECONDARY OBJECTIVES

- Characterize the safety and tolerability of IMSA101 administered to cancer patients via intratumoral injections as monotherapy or in combination
- Identify and characterize preliminary signals of anti-tumor activity including overall response rate (ORR), duration of treatment response (DOR), time-to-tumor progression (TTP), and progression-free survival time (PFS)
- Characterize the PK of IMSA101 administered by intratumoral injection as monotherapy

2.3 EXPLORATORY OBJECTIVES

- Assess the PD and biologic activity of IMSA101

2.4 STUDY ENDPOINTS

2.4.1 Primary Endpoint

- Maximum tolerated dose (MTD)/RP2D of IMSA101 administered by intratumoral injection alone or in combination with approved ICI therapy

2.4.2 Secondary (Safety) Endpoints

- Safety of IMSA101 as determined by incidence of treatment-emergent AEs (TEAEs), laboratory abnormalities, and other safety using Common Terminology Criteria for Adverse Events (CTCAE) v5.0 criteria
- Incidence of dose limiting toxicities (DLTs) in patients administered IMSA101 by intratumoral injection

2.4.3 Secondary (Efficacy) Endpoints

Secondary efficacy endpoints may include:

- Response evaluation criteria in solid tumors (RECIST)-based objective response rate (ORR)
- Duration of response (DOR)
- Time to RECIST-based tumor progression (TTP)
- Progression-free survival time (PFS)

2.4.4 Pharmacokinetic Endpoints (Phase I Monotherapy only)

- PK parameters of IMSA101 administered by intratumoral injection:

  Cycle 1 Day 1:
  Pre-Dose, 10 min, 20 min, 30 min, 1 h, 2 h, 4 h post-dose

  Cycle 2 Day 15 (if any detectable signal noted in Cycle 1):
  Pre-Dose, 10 min, 20 min, 30 min, 1 h, 2 h, 4 h post-dose**.** Additionally**,** 6 h, 24 h post-dose if previous 4 h post-dose measurement was found detectable in Cycle 1

2.4.5 Exploratory Pharmacodynamic Endpoints (Phase I only)

- Blood levels of cytokines (pre-dose, 2h, 4h, 6h, 24 h post-dosing Cycle 1 Day 1 and Cycle 2 Day 15): IL6 and IP10, IFNγ, TNFα, IL-10, IL-1β, IFN-β, MCP-1 (CCL2)
- Blood (pre-dose on Day 1 of Cycles 1, 2, and 3): Flow cytometry of Cryopreserved PBMCs CD3, CD4, CD8, CD45, CD69, CD19, CD56, FOXP3, PD-1, PD-L1, CD141, CD86, HLA-DR, CD14, CD16, CD11c
- Tumor Biopsy for injected tumor and non-injected tumor, if applicable (non-injected tumor biopsy required in at least 1 patient per cohort) (pre-dose on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 15:) Multiplexed Immunofluorescence (mIF) including antibodies to CD45, CD4, CD8, CD11c, CD56(NK), FOXP3, DAPI, PD-1, and PD-L1

An aliquot of tumor sample for injected and non-injected tumor is to be stored for later RNA isolation and sequencing when the analysis is warranted based on clinical or immunological responses.

3 STUDY DESIGN

3.1 STUDY DESIGN OVERVIEW

This is an open-label, dose escalation (Phase I), and dose expansion (Phase IIA) study designed to evaluate safety and efficacy of IMSA101 alone or in combination with an ICI (Phase I and II). Therefore, the study will be conducted in 2 phases. The dose of IMSA101 in Phase IIA will be based on the monotherapy and combination RP2Ds from Phase I.

The following methodology applies to all patients (unless otherwise indicated):

- Pre-treatment screening radiographic tumor assessments will be collected within 30 days prior to initial dose for all patients. Photographic assessments of skin lesions will be performed as detailed in a separate photography manual.
- Treatment cycles will be 28 days in duration with lesions injected weekly on Day 1 for the first three weeks of Cycle 1 and then every 2 weeks during Cycles 2 and beyond.
- A single pre-defined lesion/lesion site (longest diameter ≥ 10 mm and ≤ 50 mm) shall be injected throughout study duration, if possible. Where the original injection site is considered by the investigator to become inaccessible, a second lesion/lesion site shall be selected as a replacement and this shall be used henceforth so long as it is considered accessible. Subsequent injection sites shall be replaced when they are considered inaccessible.
- Where no remaining accessible lesions are present and where benefit of IMSA101 therapy is, in the opinion of the investigator, being derived by the patient, continued injections of IMSA101 into the vicinity of an inaccessible lesion or, in the case that a lesion can no longer be radiographically visualized, into the last known location of the non-visible lesion shall be allowed.
- Patients will be admitted to the hospital for observation overnight following intratumoral injection with IMSA101 on Day 1 of Cycle 1. Patients will be followed throughout the study for drug tolerability and safety by collection of clinical and laboratory data, including information on adverse events (AEs) using CTCAE v5.0 criteria, serious AEs (SAEs), DLTs, concomitant medications, vital signs, and ECGs.
- Patients will be assessed for anti-tumor efficacy based on radiographic assessments and if applicable, photographic tumor assessments, and analysis of ORR, DOR, TTP, and PFS using RECIST v1.1 criteria (Appendix 13.2) at screening and the end (≤ 7 days) of even numbered cycles (Cycle 2, Cycle 4, etc.) after the first dosing.

  RECIST v1.1 criteria do not mention including or excluding lesions that are being biopsied or injected. However, for the purposes of this protocol, the injected and biopsied lesions are to be captured as non-target lesions only (Phase I only), as follows:

  - Injected and biopsied lesion = non-target lesion #1
  - Non-injected and biopsied lesion = non-target lesion #2 (if applicable)

See Schedule of Assessments and Study Activities (Table 1 and Table 2) for details.

3.1.1 Phase I – Dose Escalation Plan

The Phase I dose escalation is illustrated in Figure 8 for monotherapy and Figure 9 and Figure 10 for combination therapy.

Phase I Dose Escalation – Monotherapy:

- Each dose escalation cohort will initially recruit at least 3 patients in a standard 3+3 design. To proactively ensure at least 3 patients are considered evaluable, a fourth patient may be enrolled and treated in addition to the initial 3 patients in each cohort (the fourth patient may only be enrolled if they are identified at the time the third patient slot is being filled).
- Dose escalation design in which administered dose levels will be escalated stepwise in successive cohorts of 3 to 6 (NOTE: 7 if fourth slot is filled and a single DLT is identified among the first 4 patients) patients per dose group until the RP2D or MTD level is identified.
- The first patient enrolled in each dose level must complete the first two weeks of Cycle 1 prior to enrolling the second and third (fourth when applicable) patients.
- Dose levels to be evaluated include (although not necessarily limited to) 100 µg (representing 1/60th of the pre-clinical HNSTD dose), 200 µg, 400 µg, 800 µg, and 1,200 µg.
- IMSA101 will initially be administered by intratumoral injections on Day 1 of Weeks 1, 2, and 3 for Cycle 1 (i.e., weekly dosing 3 out of 4 weeks), and on Day 1 of Weeks 1 and 3 (i.e., bi-weekly dosing) for all cycles thereafter.
- No dose escalation decisions will be made until all patients in a dose level complete the first 28 days of treatment. NOTE: this includes a fourth additional patient when applicable. Dose-escalation/de-escalation decisions will be based on the occurrence of DLTs during Cycle 1 of the evaluated dose level and the recommendation of the Cohort Review Committee (CRC).
- If no DLTs are observed among the initial 3 (4 when applicable) patients of an evaluated dose level, the dose will be escalated for the following 3 patients.
- If a single DLT occurs among the initial 3 (4 when applicable) patients of an evaluated dose level, 3 additional patients will be enrolled at the same dose level.
- If ≥ 2 DLTs occur among the initial 3 (4 when applicable) or 6 (7 when applicable) patients in an evaluated dose level, the dose level shall be considered unacceptably toxic and escalation will be discontinued.
- Subsequent to invalidation of a given cohort (e.g., when ≥ 2/3 [4 when applicable] or ≥ 2/6 [7 when applicable] patients in an evaluated dose level experience a DLT), a new cohort (e.g., dosing Cohort Xa) will be evaluated in which IMSA101 will be administered by intratumoral injection at the same dose level but with the Day 1 dose (priming dose) reduced to the next lower dose level.
- For dosing Cohort Xa, if ≥ 2/3 (4 when applicable) or ≥ 2/6 (7 when applicable) patients experience a DLT, the amended dose level shall be considered unacceptably toxic and the next lower dose (DL-1) level shall be provisionally labeled the MTD.

- If the amended dose level Xa is found to be safe, dose escalation shall proceed with the exception of the priming dose (Cycle 1, dose 1) which shall be held constant and not escalated further.
- No fewer than 6 total patients shall be evaluated at a given dose level prior to confirmation of the dose level as the MTD or RP2D.

Phase I Dose Escalation - Combination Therapy:

- Combination therapy with IMSA101 + ICI includes the following IMSA101 dose levels:
  - 800 μg
  - 1,200 μg
  - 2,400 μg (with an initial "priming" dose of 1,200 μg)
  - 3,600 μg (with an initial "priming" dose of 2,400 μg)
  - 4,800 μg (with an initial "priming" dose of 3,600 μg)
- Combination dosing of IMSA101 shall be evaluated in Phase I upon satisfaction of the following criteria:
  A. A given dose level (combo dose level 1) has been confirmed as safe for monotherapy dosing (i.e., < 2/6 [7 when applicable] patients experience Cycle 1 DLT).
  B. The next higher dose level (combo dose level 2) has been confirmed as safe for monotherapy dosing (i.e., < 2/6 [7 when applicable] patients experience Cycle 1 DLT).
  C. The dose level (combo dose level 1) is found to demonstrate adequate IMSA101 PD activity based on exploratory endpoints.

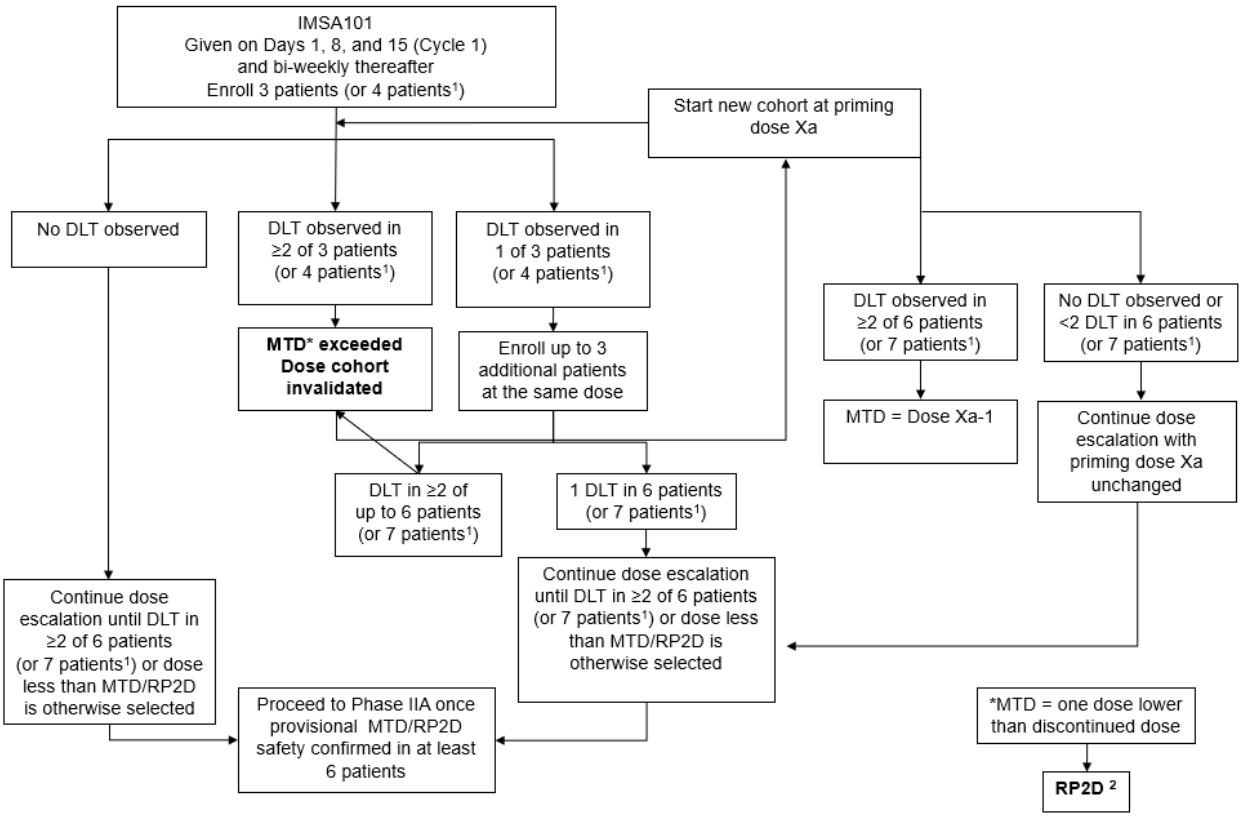
- Eligible patients for Phase I combination dosing shall meet one of the following criteria:
  - have radiographically-confirmed RECIST stable disease through ≥ 2 consecutive cycles of an approved PD-1/PD-L1-targeted immune checkpoint inhibitor (ICI) administered as monotherapy
  - be clinically stable following a first (unconfirmed) follow-up radiographic scan demonstrating progression of disease on ICI monotherapy
  - have progression through prior ICI therapy administered either as mono or combination therapy
  - have received no prior ICI therapy but otherwise be ineligible for all available standards of care
- Phase I combo patients have experienced no prior Grade ≥ 3 CTCAE adverse events on ICI therapy that were considered by the investigator to be at least possibly ICI drug-related
- Phase I combo patients shall either receive de novo the combination of IMSA101 + an ICI of their investigator's choosing or, in cases where they are already receiving ICI monotherapy,

have IMSA101 added to their current therapy such that Day 1 of IMSA101 shall represent Cycle 1, Day 1.

- A radiographic tumor assessment shall have occurred within 30 prior days of adding IMSA101 to current therapy.
- Phase I combination therapy IMSA101 doses of 800 µg and 1,200 µg will be administered by intratumoral injections each week for 3 weeks in Cycle 1 (Days 1, 8, and 15), and for Cycle 2 and all other cycles thereafter, every other week on Days 1 and 15. Additional combination therapy IMSA101 doses of 2,400 µg, 3,600 µg, and 4,800 µg require the following priming dose on Day 1 of Cycle 1: 1,200 µg for the 2,400 µg dose group, 2,400 µg for the 3,600 µg dose group, and 3,600 µg for the 4,800 µg group. After Day 1 of Cycle 1, the full dose for these groups will be administered on Day 1 of Weeks 2 and 3 of Cycle 1 (i.e., weekly dosing 3 out of 4 weeks), and on Day 1 of Weeks 1 and 3 for all cycles thereafter (i.e., bi-weekly dosing).
- Safety evaluations and dose escalation of IMSA101 administered in combination with current ICI therapy shall proceed in a manner consistent with monotherapy escalation, with the exception of allowed de-escalation, and shall proceed independently of monotherapy dose escalation and evaluations.
- De-escalation: If ≥ 2 DLTs occur among the initial 3 (4 when applicable) or 6 (7 when applicable) patients, de-escalation of IMSA101 is allowed for the combination therapy dose levels as follows:
  - 2,400 µg may be de-escalated to 1,800 µg (with a priming dose of 1,200 µg on Day 1 of Cycle 1)
  - 3,600 µg may be de-escalated to 3,000 µg (with a priming dose of 2,400 µg on Day 1 of Cycle 1)
  - 4,800 µg may be de-escalated to 4,200 µg (with a priming dose of 3,600 µg on Day 1 of Cycle 1)

  If ≥ 2 DLTs occur among the initial 3 (4 when applicable) or 6 (7 when applicable) patients at a de-escalated dose level, the dose level shall be considered unacceptably toxic and escalation will be discontinued.
- Administration of combination drug will follow the labeled instructions for the product.
- IMSA101 dose escalation shall proceed such that there will be generated separate RP2Ds for IMSA101 administered alone or in combination with other agents (although it is possible these will be the same).
- No fewer than 6 total patients shall be evaluated at a given dose level prior to confirmation of the dose level as the MTD or RP2D.

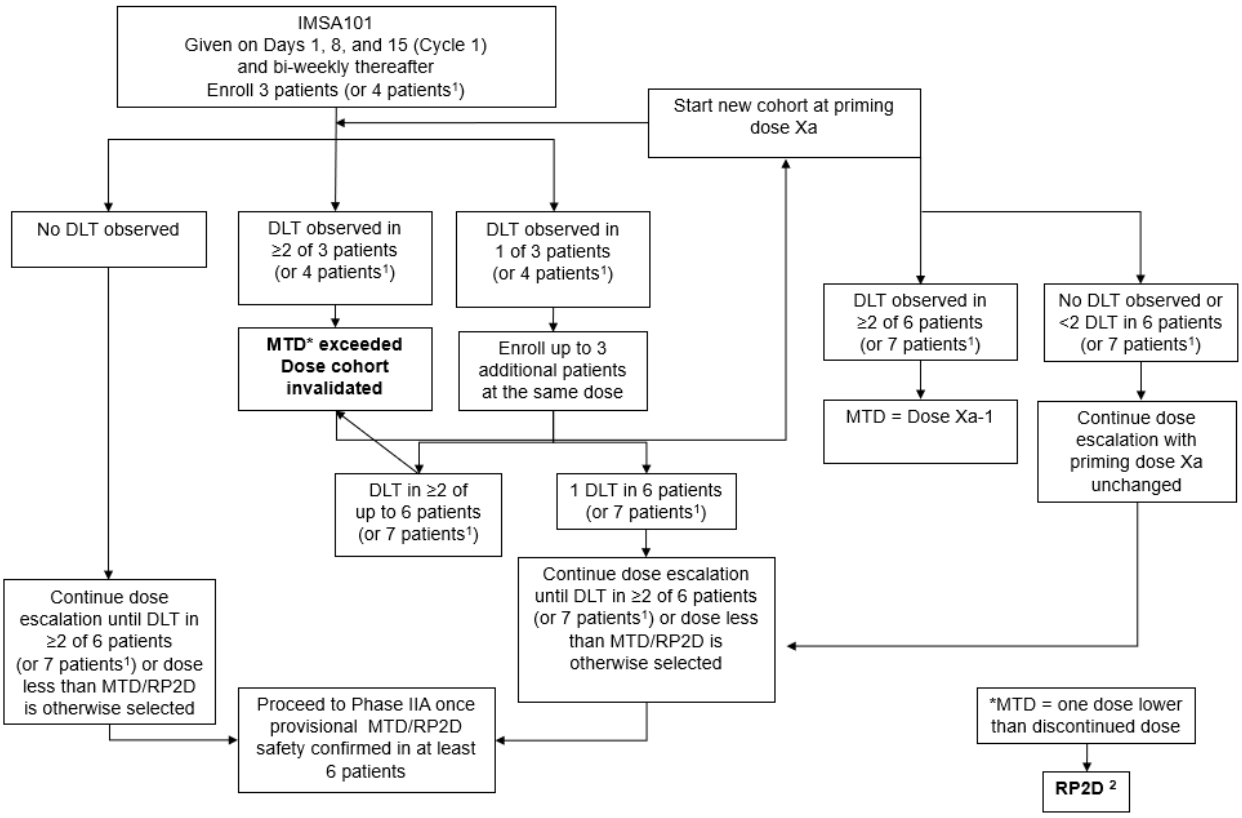
Figure 8 Phase I Dose Escalation for Monotherapy



[1] Each dose escalation cohort will initially recruit at least 3 patients in a standard 3+3 design. To proactively ensure at least 3 patients are considered evaluable, a fourth patient may be enrolled and treated in addition to the initial 3 patients in each cohort (the fourth patient may only be enrolled if they are identified at the time the third patient slot is being filled).

[2] Combination dosing and escalation will lead to separate RP2Ds for IMSA101 administered alone or in combination with other agents (although it is possible these will be the same).

Figure 9 Phase I Dose Escalation for Combination Therapy Doses 800 or 1,200 µg



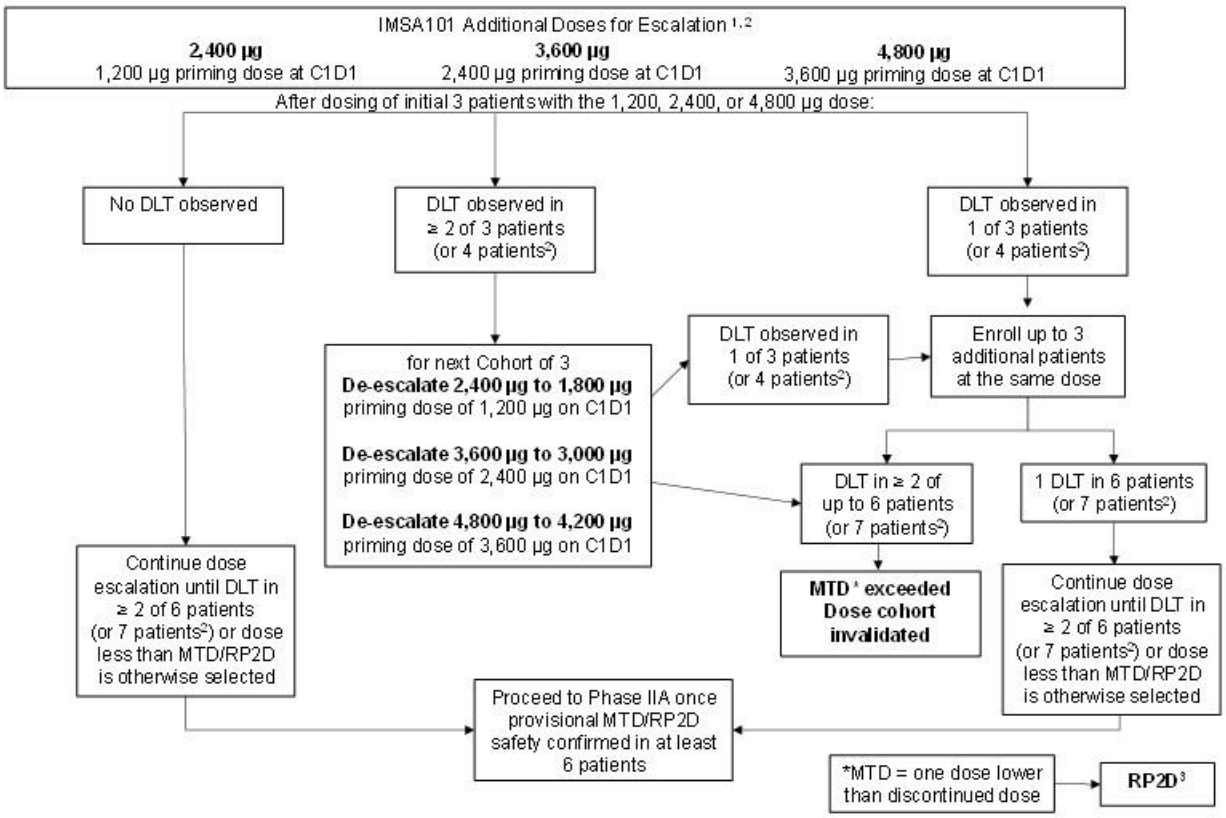
DLT: dose limiting toxicity; RP2D: Recommended Phase II dose

*MTD = one dose lower than discontinued dose

[1] Each dose escalation cohort will initially recruit at least 3 patients in a standard 3+3 design. To proactively ensure at least 3 patients are considered evaluable, a fourth patient may be enrolled and treated in addition to the initial 3 patients in each cohort (the fourth patient may only be enrolled if they are identified at the time the third patient slot is being filled).

[2] Combination dosing and escalation will lead to separate RP2Ds for IMSA101 administered alone or in combination with other agents (although it is possible these will be the same).

Figure 10 Phase I Dose Escalation for Combination Therapy Doses 2400, 3,600, and 4,800 µg



C1D1: Cycle 1, Day 1; DLT: dose limiting toxicity; RP2D: Recommended Phase II dose

*MTD = one dose lower than discontinued dose

1 IMSA101 given on Days 1, 8, and 15 (Cycle 1) and bi-weekly thereafter. ICI therapy administered according to product instructions.

2 Each cohort will initially recruit at least 3 patients in a standard 3+3 design. To proactively ensure at least 3 patients are considered evaluable, a fourth patient may be enrolled and treated in addition to the initial 3 patients in each cohort (the fourth patient may only be enrolled if they are identified at the time the third patient slot is being filled). The first patient enrolled in each dose level must complete the first two weeks of Cycle 1 prior to enrolling the second and third (fourth when applicable) patients.

3 Combination dosing and escalation will lead to separate RP2Ds for IMSA101 administered alone or in combination with other agents (although it is possible these will be the same).

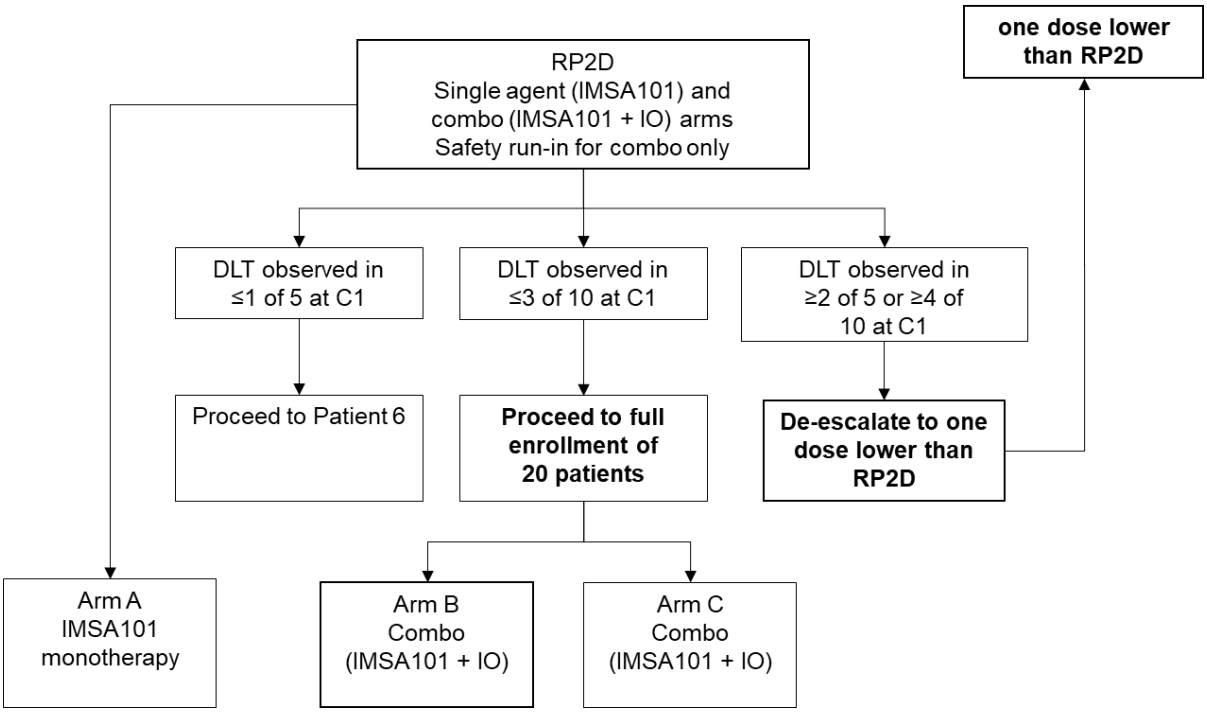
3.1.2 Phase IIA – Dose Expansion Plan

The Phase IIA dose expansion is illustrated in Figure 11.

- This dose-expansion stage is intended to confirm the tolerability of the RP2D and identify provocative signals of IMSA101 anti-tumor activity.
- It is anticipated that the monotherapy and combination RP2Ds will be evaluated in 3 discrete arms of 20 patients each with a single arm evaluating monotherapy (Arm A) and 2 arms evaluating IMSA101 in combination with IO therapies (Arm B and Arm C).
  - Arm B will be a combination of IMSA101 with PD-1/PD-L1-targeted ICIs. Dosing will be predicated by the combination RP2D identified in Phase I.
  - Arm C will be a combination of IMSA101 with non-PD-1/PD-L1-targeted immuno-oncology drugs approved by the Food and Drug Administration (FDA).
- Administration of approved drugs to be combined with IMSA101 will follow the labeled instructions for the product.
- Combination arms evaluating IMSA101 combinations shall include a safety run-in of 5-10 patients to be conducted as follows:
  - If ≤ 1 of 5 initial safety evaluable patients experience a DLT during Cycle 1, enrollment shall proceed to Patient 6.
  - If ≤ 3 of 10 initial safety evaluable patients experience a DLT during Cycle 1, enrollment shall proceed to its entirety (20 patients in that arm).
  - If ≥ 2 of 5 or ≥ 4 of 10 patients experience a DLT, dose de-escalation shall occur to the next lower dose level evaluated in Phase I and the run-in shall be repeated at the next lower dose.
- Tumor types and corresponding treatment combinations to be evaluated will be identified prior to Phase IIA commencement with patients enrolled separately into tumor-specific arms of 20 patients each. **This change will be documented in a protocol amendment before it occurs.**
- The need for futility criteria to be evaluated in any of the arms following enrollment of a pre-defined number of patients < 20 shall be determined at a later date depending on tumor types evaluated. **This change will be documented in a protocol amendment before it occurs.**
- For all potential patients, there will be up to a 30-day screening and eligibility assessment period prior to enrollment.

All patients will continue to receive their assigned treatment throughout the study until the occurrence of disease progression, death, or other unacceptable treatment-related toxicity, or until the study is closed by the sponsor.

Figure 11 Phase IIA Dose Expansion



C1: Cycle 1; DLT: dose limiting toxicity; IO: immuno-oncology; RP2D: Recommended Phase II dose
*MTD = one dose lower than discontinued dose

3.1.3 Dose-limiting Toxicities

A DLT will be defined as the occurrence of any of the following hematologic or non-hematologic AEs that are considered definitely, probably, or possibly related to IMSA101 in the first 28 days (first cycle) of treatment. The severity of AEs will be graded according to CTCAE v5.0. For safety run-ins for Phase IIA combination arms, DLTs will be defined as DLT-qualifying events considered at least possibly related to the drug combination, including AEs already characterized for the partner drug.

Hematologic AEs

- ≥ Grade 4 neutropenia lasting for > 7 days
- Febrile neutropenia (defined as absolute neutrophil count (ANC) < 1000/mm^3 with a single temperature of 38.3ºC (101°F) or a sustained temperature of 38ºC (100.4°F) for > 1 h)
- ≥ Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with Grade ≥ 2 bleeding
- ≥ Grade 4 anemia

Non-hematologic AEs:

- Elevation of alanine transaminase (ALT) or aspartate transaminase (AST) by ≥ 3X upper limit of normal (ULN) with concurrent elevation of serum total bilirubin ≥ 2X ULN
- Any ≥ Grade 3 non-hematologic AE of any duration will be considered a DLT with the following exceptions:
  - Nausea/vomiting/diarrhea:
    - To be considered a DLT, ≥ Grade 3 nausea/vomiting/diarrhea must be refractory to supportive care and last > 3 days.
      - ≥ Grade 3 nausea/vomiting/diarrhea that lasts ≤ 3 days is not a DLT.
  - Fatigue:
    - To be considered a DLT, ≥ Grade 3 fatigue must last > 7 days.
    - ≥ Grade 3 fatigue that lasts ≤ 7 days is not a DLT.

3.1.4 Maximum Tolerated Dose/Recommended Phase II Dose

The MTD is defined as the highest dose level of IMSA101 at which no more than 1 out of 6 (7 when applicable) patients experiences a DLT during the first cycle (28 days) of therapy.

The MTD/RP2D of IMSA101 will be determined by the sponsor and the CRC.

The RP2D is defined as the dose (either at MTD or below MTD) that is selected for evaluation in the Phase IIA component of the study.

3.2 STOPPING RULES

The entire study or treatment of individual patients may be stopped under defined circumstances as outlined in Section 7.

3.3 COHORT REVIEW COMMITTEE

An independent CRC will be organized to review the safety of IMSA101 during the study. The CRC will be composed of principal investigators (and their representatives), medical monitor, and sponsor representatives. Prior to escalating to next dose level, this committee will review all available safety data and determine whether to proceed with escalation. Meeting results will be documented and formal notification of decisions will be provided to all participants.

3.4 BLINDING AND RANDOMIZATION

This is an open-label and non-randomized study; no blinding and randomization will be conducted.

4 SELECTION OF PATIENTS

4.1 NUMBER OF PATIENTS

Approximately 115 patients are expected to be treated in this study.

- Phase I: approximately 45 patients in 5 dose cohorts. Any patient who discontinues the study before completing Cycle 1 (and before receiving all 3 doses of IMSA101) for reasons other than DLT, will be replaced.
- Phase IIA: approximately 70 patients in 3 arms of approximately 20–25 patients each. Any safety lead-in patient who discontinues the study before completing Cycle 1 (and before receiving all 3 doses of IMSA101) for reasons other than DLT, will be replaced.

4.2 INCLUSION CRITERIA

Patients meeting all of the following criteria will be considered for enrollment into the study.

Phase I combination only:

1. Eligible patients will meet one of the following criteria:
   - Have radiographically-confirmed RECIST stable disease through ≥ 2 consecutive cycles of an approved PD-1 or PD-L1 targeted ICI administered as monotherapy
   - Be clinically stable following a first (unconfirmed) follow-up radiographic scan demonstrating progression of disease on ICI monotherapy
   - Have progression through prior ICI therapy administered either as mono or combination therapy
   - Have received no prior ICI therapy but otherwise be ineligible for all available standards of care
2. Have experienced no prior Grade ≥ 3 CTCAE adverse events on ICI therapy that were considered by the investigator to be at least possibly ICI drug-related.

All patients (unless otherwise indicated):

1. Signed informed consent and mental capability to understand the informed consent
2. Male or female patients ≥ 18 years of age
3. Histologically or cytologically documented locally advanced or metastatic solid tumor malignancies refractory to or otherwise ineligible for treatment with standard-of-care agents/regimens, including but not limited to:
   - Malignant melanoma
   - Hormone receptor negative breast cancer
   - Gastro-esophageal cancer
   - Non-small cell lung cancer

- Head and neck cancer
- Hepatoma
- Renal cell carcinoma

4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 (Appendix 13.1)
5. Evaluable or measurable disease as follows:
   - 2 or 3 RECIST evaluable lesions: one that is suitable for injection and biopsied; an optional non-injected second lesion that will be biopsied for abscopal effect (only 1 patient per cohort required to have non-injected lesion biopsied; optional for all other patients in that cohort); and one measurable lesion that will be followed for response only.
   - Injectable tumors shall be accessed by intralesional (cutaneous) or percutaneous injection only, including those lesions that are visible, palpable, or detectable by standard radiographic or ultrasound methods. Neither surgical procedures nor endoscopically-guided injections including those to endobronchial, endoluminal, or endosinusoidal spaces shall be allowed. While no anatomic locations are required or disallowed, lesions selected for intratumoral injection must, in the opinion of the investigator:
     - Not be immediately adjacent to blood vasculature or other physiologic landmarks in such a way that will accrue undue safety risk to the patient
     - Have longest diameter ≥ 10 mm and ≤ 50 mm
     - Be fully evaluable per RECIST v1.1 criteria (Appendix 13.2)
6. Life expectancy > 3 months (Phase I) and > 6 months (Phase IIA)
7. ECG without evidence of clinically meaningful conduction abnormalities or active ischemia as determined by the investigator
8. Acceptable organ and marrow function as defined below:
   - Absolute neutrophil count > 1,500 cells/µL
   - Platelets > 50,000 cells/µL
   - Total bilirubin ≤ 1.5 times the ULN
   - AST/ ALT ≤ 2.5 X ULN. If liver metastases are present, AST/ALT < 5 times ULN
   - Serum creatinine < 1.5 mg/dL and a measured creatinine clearance ≥ 50 mL/min using the Cockcroft-Gault formula (Appendix 13.3)
   - Prothrombin time (PT)/partial thromboplastin time (PTT) ≤ 1.5 times ULN
9. Women of child-bearing potential (defined as a female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea for at least 12 consecutive months with an appropriate clinical profile at the appropriate age, e.g., greater than 45 years) must have a negative serum pregnancy test prior to first dose of study drug
10. Male and female patients with reproductive potential must agree to use two forms of highly effective contraception throughout the study

4.3 EXCLUSION CRITERIA

All patients:

1. Anti-cancer therapy within 4 weeks or ≤ 5 half-lives of the first dose of study drug
2. Failure to recover, to Grade 1 or less, from clinically significant AEs due to prior anti-cancer therapy, as judged by the investigator.
3. Known untreated brain metastases or treated brain metastases that have not been stable (scan showing no worsening of CNS lesion[s] and no requirement of corticosteroids) ≥ 4 weeks prior to study enrollment
4. Baseline prolongation of QT/QTc interval (QTc interval > 470)
5. Uncontrolled intercurrent illness (including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations) that in opinion of the investigator would limit compliance with study requirements
6. Women who are pregnant or breastfeeding
7. Sponsor reserves right to exclude any patient from the study on basis of pre-study medical histories, physical examination findings, clinical laboratory results, prior medications, or other entrance criteria.

4.4 PATIENTS OF REPRODUCTIVE POTENTIAL

Pregnancy and breastfeeding are exclusion criteria for this study. It is important that female patients and the female partners of male patients do not become pregnant during the study and for a recommended period of 30 days after last dose of IMSA101.

Women of childbearing potential and male patients who are partners of women of childbearing potential must agree to use two forms of highly effective contraception during the study and for 30 days following the last dose of study drug. Highly effective contraception is defined as use of one or more methods that result in a low failure rate (i.e., less than 1%). The following are examples of acceptable methods of contraception: oral, injected, or implanted hormonal methods, intrauterine devices (IUD), condoms with spermicide product, vasectomy, or tubal ligation or occlusion.

A woman of childbearing or reproductive potential is defined as any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea for at least 12 consecutive months with an appropriate clinical profile at the appropriate age, e.g., greater than 45 years).

A serum pregnancy test for all women of childbearing potential will be performed during screening. A pregnancy test will also be carried out at the End of Study (EOS) visit.

Female patients who become pregnant and male patients whose female partners become pregnant must report to the investigator and be removed from the study immediately.

5 STUDY PROCEDURES AND SCHEDULE

Study procedures will be performed as described in Section 3: Study Design and as shown in the Schedule of Assessments and Study Activities (Table 1 and Table 2).

5.1 DESCRIPTION OF STUDY DAYS AND STUDY TREATMENTS

5.1.1 Screening/Baseline (Day -30 to Day 1)

- Obtain written informed consent before the start of any study-specific procedures.
- Review inclusion and exclusion criteria.
- Complete medical history including all previous cancer treatments.
- Record concomitant medications including start dates, indication, dose, and frequency.
- Record demographic data including year of birth, current age, age when informed consent is signed, gender, race, and smoking status.
- Measure and record height (cm) and weight (kg).
- Record vital signs (blood pressure, respiration rate, heart rate, body temperature).
- Perform full physical examination.
- Perform neurologic examination.
- Assess and record ECOG performance status (Appendix 13.1).
- Perform a 12-lead ECG.
- Collect blood samples for hematology tests (including coagulation parameters and CBC with differential) within 72 h prior to Cycle 1 Day 1.
- Collect blood samples for serum chemistry tests and creatinine clearance (using the Cockcroft-Gault formula, Appendix 13.3) within 72 hours of Cycle 1 Day 1.
- Urinalysis
- Perform a serum pregnancy test for female patients of childbearing potential.
- Radiographic assessments and, if applicable, photographic assessments of skin lesions will be performed by a formal photography vendor at the same time points as the radiographic assessments. Detailed instructions for photography will be included in a photography manual.
- Collect archival tumor tissue, if available (Phase I only).

5.1.2 Cycle 1 Day 1 (± 0 Days)

- Record concomitant medications taken since screening including start dates, indication, dose, and frequency within 72 h prior to Cycle 1 Day 1.

- Measure and record weight (kg) within 72 h prior to Cycle 1 Day 1.
- Record vital signs (blood pressure, respiration rate, heart rate, body temperature) within 72 h prior to Cycle 1 Day 1.
- Perform neurologic examination within 72 h prior to Cycle 1 Day 1.
- Assess and record ECOG performance status within 72 h prior to Cycle 1 Day 1 (Appendix 13.1).
- Perform a 12-lead ECG 30 to 60 minutes post-dose.
- PK blood samples (Phase I monotherapy only). Detailed instructions outlined in the laboratory manual.
- PD blood samples (Phase I monotherapy and combo therapy). Detailed instructions outlined in the laboratory manual.
    - 24 h post-dose sample will require patient to return to clinic on Cycle 1 Day 2.
- PD tissue samples/biopsy of injected and non-injected tumor, if applicable (non-injected tumor biopsy required in at least 1 patient per cohort) (Phase I monotherapy and combo therapy). Core biopsies should be obtained; if not appropriate, biopsies via fine needle aspirate (FNA) or excision are permitted. Detailed instructions outlined in the laboratory manual.
- Administer study drug(s).
- Observe patient for 1 h following intratumoral injection.
- Assess and record AEs.
- Admit patient to the hospital for observation overnight. Patient may be released from the hospital when clinically indicated.

5.1.3 Cycle 1 Day 8 (+/- 3 Days)

- Record concomitant medications taken since the last visit including start dates, indication, dose, and frequency.
- Measure and record weight (kg).
- Record vital signs (blood pressure, respiration rate, heart rate, body temperature).
- Perform neurologic examination.
- Assess and record ECOG performance status (Appendix 13.1).
- Perform a 12-lead ECG 30 to 60 minutes post-dose.
- Collect blood samples for hematology tests (coagulation parameters, not required).
- Collect blood samples for complete serum chemistry.

- Administer study drug. For Cycle 1 Day 8 and Cycle 1 Day 15, IMSA101 doses should be administered no less than 4 days apart.
- Observe patient for 1 h following intratumoral injection.
- Assess and record AEs.

5.1.4 Cycle 1 Day 15 (+/- 3 Days)

- Record concomitant medications taken since the last visit including start dates, indication, dose, and frequency.
- Measure and record weight (kg).
- Record vital signs (blood pressure, respiration rate, heart rate, body temperature).
- Perform neurologic examination.
- Assess and record ECOG performance status (Appendix 13.1).
- Perform a 12-lead ECG 30 to 60 minutes post-dose.
- Collect blood samples for hematology tests (coagulation parameters, not required).
- Collect blood samples for serum chemistry tests.
- PD tissue samples/biopsy of injected and non-injected tumor, if applicable (non-injected tumor biopsy required in at least 1 patient per cohort) (Phase I monotherapy and combination therapy). Core biopsies should be obtained; if not appropriate, biopsies via FNA or excision are permitted.
- Administer study drug(s). For Cycle 1 Day 8 and Cycle 1 Day 15, IMSA101 doses should be administered no less than 4 days apart.
- Observe patient for 1 h following intratumoral injection.
- Assess and record AEs.

5.1.5 Day 1 (+/- 3 Days) of Each Subsequent Cycle

- Record concomitant medications taken since the last visit including start dates, indication, dose, and frequency.
- Measure and record weight (kg).
- Record vital signs (blood pressure, respiration rate, heart rate, body temperature).
- Perform neurologic examination.
- Assess and record ECOG performance status (Appendix 13.1).
- Collect blood samples for hematology tests (coagulation parameters, not required).
- Collect blood samples for complete serum chemistry.

- Administer study drug(s).
- Observe patient for 1 h following intratumoral injection.
- Assess and record AEs.
- PD blood samples (Phase I monotherapy and combo therapy). Samples to be collected pre-dose Day 1 of Cycles 2 and 3.

5.1.6 Day 15 (+/- 3 Days) of Each Subsequent Cycle

- Record concomitant medications taken since the last visit including start dates, indication, dose, and frequency.
- Measure and record weight (kg).
- Record vital signs (blood pressure, respiration rate, heart rate, body temperature).
- Perform neurologic examination.
- Assess and record ECOG performance status (Appendix 13.1).
- Collect blood samples for hematology tests (coagulation parameters, not required).
- Collect blood samples for complete serum chemistry.
- PK blood samples (Phase I monotherapy patients but only if detectable signal was noted in Cycle 1 PK results)
- PD blood samples (Phase I monotherapy and combo therapy Cycle 2 Day 15)
- PD tissue samples/biopsy of injected and non-injected tumor, if applicable (non-injected tumor biopsy required in at least 1 patient per cohort) (Phase I monotherapy and combo therapy Cycle 2 Day 15 only). Core biopsies should be obtained; if not appropriate, biopsies via FNA or excision are permitted.
- Administer study drug(s).
- Observe patient for 1 h following intratumoral injection.
- Assess and record AEs.

5.1.7 End of Even-numbered Cycle (≤ 7 Days)

- Perform disease assessment according to RECIST Criteria (v1.1) (Appendix 13.2). In certain circumstances a patient experiencing RECIST progression of disease may be allowed to continue therapy on study where there is agreement between the investigator and sponsor that the patient is deriving clinical benefit.
- Radiographic assessments and, if applicable, photographic assessments of skin lesions will be performed by a formal photography vendor at the same time points as the radiographic assessments. Detailed instructions for photography will be included in a photography manual.

5.1.8 End of Treatment Visit

- Record concomitant medications taken since the last visit including start dates, indication, dose, and frequency.
- Measure and record weight (kg).
- Record vital signs (blood pressure, respiration rate, heart rate, body temperature).
- Perform and record full physical examination.
- Perform neurologic examination.
- Assess and record ECOG performance status (Appendix 13.1).
- Perform a 12-lead ECG 30 to 60 minutes post-dose.
- Collect blood samples for hematology tests (coagulation parameters, not required).
- Collect blood samples for complete serum chemistry.
- Perform a serum pregnancy test for female patients of childbearing potential.
- Perform disease assessment according to RESIST Criteria (v1.1) as described in Appendix 13.2. If applicable, photographic assessments of skin lesions will be performed. Perform a CT scan (or MRI or other appropriate assessment), if a recent scan within the past month is not available in the medical records.
- Assess and record AEs.

5.1.9 End of Study Visit (Safety Follow-up 30 days after Last Dose)

- Assess and record AEs.

5.1.10 Cycle Extensions

During this study, with the approval of the investigator and sponsor, a patient may be allowed a 2 week delay or extension between cycles. Rationale for delay or extension should be documented.

5.1.11 Unscheduled Visits

Additional visits may be performed as appropriate and at the discretion of the investigator. Any of the procedures or assessments may be performed based on the reason for the visit.

5.1.12 Restrictions, Precautions, and Potential Adverse Effects

There are no known restrictions or precautions relative to nicotine, caffeine, alcohol, physical activity, fasting, diet, or medications for patients' ongoing IMSA101 treatment.

Based on pre-clinical findings with IMSA101 and toxicity events reported in clinical trials evaluating other STING (stimulator of interferon genes) adapter protein agonists, the following risks may reasonably be anticipated in clinical trials evaluating IMSA101: body temperature increases (fever), chills, alterations in serum chemistries, altered serum hematology parameters, headache, injection site pain, vomiting, fatigue, myalgia, and/or diarrhea.

6 METHODS OF ASSESSMENT AND ENDPOINTS

6.1 MTD/RP2D

Definition of Maximum Tolerated Dose (MTD): The MTD is defined as the highest dose level of IMSA101 at which no more than 1 out of 6 (7 when applicable) patients experiences a DLT during the first cycle (28 days) of therapy.

Definition of Recommended Phase 2 Dose (RP2D): The RP2D is defined as the dose (either at MTD or below MTD) that is selected for evaluation in the Phase IIA component of the study.

The MTD/RP2D of IMSA101 will be determined by the sponsor and the CRC.

6.2 DEMOGRAPHIC DATA

At screening, patient demographic data will be collected. These data include: year of birth, age, gender, race, smoking history, tumor type, and molecular abnormalities, if known.

6.3 MEDICAL HISTORY

At screening, a complete medical history will be obtained from each patient. Medical history includes baseline symptoms as well as a detailed history of prior procedures and prior cancer therapies including therapy start and stop dates, best response, disease progression during or after therapy, as well as discontinuations due to intolerability or toxicity. For female patients of child-bearing potential, the date of the last menstrual period should be noted. Data will be updated at subsequent visits as appropriate.

6.4 CONCOMITANT MEDICATIONS

A detailed history of medications and procedures will be documented for each patient at screening. Concurrent medications (especially changes in medication) will be documented for each patient at each scheduled visit. Necessary supportive care such as anti-emetic and anti-diarrheal medications, etc., will be allowed (see Section 8.3). Prophylactic pretreatment for headache, nausea, and vomiting (after Cycle 1) is permitted. Any medication that in the opinion of the investigator will interfere with the MOA of IMSA101 is prohibited.

6.5 PHYSICAL EXAMINATION AND VITAL SIGNS

Full physical examinations will be performed at screening and End of Treatment (EOT) Visit. An assessment of interval changes and AEs will be performed at each visit.

- Height in centimeters (cm) will be measured at screening.
- Body weight in kilogram (kg) will be measured at screening/baseline, and all study visits.
- Vital signs including body temperature, blood pressure, respiration rate, and heart rate will be measured at all study visits.

Information about the physical examination must be present in the source documentation at the study site. The result of the physical examination prior to the start of study drug treatment must be included in the Relevant Medical History/Current Medical Conditions Case Report Form. Clinically relevant findings made after the start of study drug treatment, which meet the definition of an AE, must be recorded on the Adverse Event Case Report Form.

6.6 SAFETY ASSESSMENTS

Safety assessments will include TEAEs, DLTs, vital signs, 12-lead ECG, physical examination, and laboratory safety evaluations. Toxicities will be graded according to CTCAE v5.0 criteria. Patients will be observed for 1 h in the clinic following intratumoral injections. In addition, following intratumoral injection on Day 1 of Cycle 1, patients will be admitted to the hospital for observation overnight.

Safety data will be listed by study site, patient number, and cycle. All TEAEs will be summarized by study phase and assigned dose. In addition, all SAEs, including deaths will be listed separately and summarized.

Grade 3 and 4 laboratory data will be summarized by study phase and assigned dose.

For patients who experience a DLT, data on AEs leading to treatment/study discontinuation will be listed.

Coagulation and urinalysis will be performed only at screening.

Safety evaluations (vital signs, ECOG assessment, and clinical laboratory studies) will be conducted at screening, Cycle 1 Day 1; baseline, then on Days 8 and 15 of Cycle 1, then Day 1 and Day 15 of every cycle thereafter for patients who continue treatment, or any time it is clinically indicated in the judgment of the investigator.

Neurologic examinations and ECOG performance status assessments (Appendix 13.1) will be performed at each study visit.

A complete standard 12-lead ECG recording (rhythm, VR, PR interval, QRS duration, QT and QTc) will be performed at screening, 30 minutes post-dose on C1D1, C1D8, C1D15, at EOT, and at any other visit where the investigator believes the assessment is indicated.

The following clinical laboratory tests will be performed:

- **Hematology** (blood sample with EDTA): hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, white blood cell (WBC) count, WBC differential, red blood cell count, lymphocytes, monocytes, neutrophils, band neutrophils, eosinophils, basophils, platelets. The WBC differential may be automated or manual as per institutional standards. Reticulocytes should be done only when clinically indicated.

- **Serum Chemistry** (blood serum sample): Complete Serum Chemistry will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, ALT, AST, alkaline phosphatase, total bilirubin, lactate dehydrogenase, total protein, albumin.
- **Coagulation (screening only):** PT, international normalization ratio (INR), and activated partial thromboplastin time (aPTT).
- **Urinalysis (screening only):** appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, urobilinogen, and microscopy.

Any laboratory value that remains abnormal at the EOT and that is considered clinically significant will be followed according to accepted medical standards for up to 30 days after the last dose or until resolution of the abnormality.

Toxicity will be assessed using the CTCAE v5.0 criteria.

6.7 PHARMACOKINETIC PROCEDURES

6.7.1 Blood Sampling and Processing

Blood plasma samples for PK analysis will be collected from Phase I monotherapy patients at the times/days outlined below and in Table 1. Further details and instructions will be provided in a separate laboratory manual.

Cycle 1 Day 1:
Pre-Dose, 10 min, 20 min, 30 min, 1 h, 2 h, 4 h post-dose

Cycle 2 Day 15 (if any detectable signal noted in Cycle 1):
Pre-Dose, 10 min, 20 min, 30 min, 1 h, 2 h, 4 h post-dose**.** Additionally**,** 6 h, 24 h post-dose if previous 4 h post-dose measurement was found detectable in Cycle 1

The following time windows for plasma PK sample collection are allowed: ≤ 24 h for the pre-dose sample, ± 5 min for the 10-, 20-, and 30-min post-dose samples, ± 10 min for the 1-h post-dose sample, ±15 min for the 2-, 4-, and 6-h post-dose samples, and ± 2 h for the 24-h post-dose sample.

Plasma concentrations for all PK parameters at each time point will be listed and summarized by each dose level. Plasma concentrations versus time profiles (with concentrations on both a log and linear scale) will be plotted for each patient; similar summary plots will be constructed for each dose level. PK parameters will be analyzed by a validated bioanalytical method from a central laboratory.

6.8 PHARMACODYNAMIC PROCEDURES

6.8.1 Blood and Tissue Sampling and Processing (Phase I only)

Blood and tumor samples are to be collected at multiple time points as shown in Section 2.4.5 and Table 1 for exploratory assessment of numerous biomarkers.

The following time windows for PD cytokines sample collection are allowed: ≤ 24 h for the pre-dose sample, ±15 min for the 2-, 4-, and 6-h post-dose samples, and ± 2 h for the 24-h post-dose sample.

The following time windows for PD flow cytometry sample collection are allowed: ≤ 24 h for the pre-dose C1, C2, and C3 samples.

The following time windows for PD mIF sample collection are allowed: ≤ 24 h for the pre-dose C1D1, C1D15, and C2D15 samples.

An aliquot of tumor sample for injected and non-injected tumor is to be obtained and stored for later RNA isolation and sequencing when the analysis is warranted based on clinical or immunological responses.

PD markers will be analyzed by a validated bioanalytical method from a central laboratory. Further details and instructions will be provided in a separate laboratory manual.

6.9 TUMOR ASSESSMENTS

All known tumor sites will be documented at screening and re-assessed at each subsequent time point for tumor evaluation, using a single and consistent methodology throughout all evaluations. Assessments may include the following:

- Screening (if a recent scan within the past month is not available in the medical records) and subsequent tumor assessments must include CT scans (with IV contrast unless contraindicated and oral contrast as appropriate per institutional standards) or MRI of the chest, abdomen, and pelvis (or other appropriate assessment). Photographic assessments of skin lesions will be performed through a photography vendor as detailed in a separate photography manual. At screening, photography assessment can be performed within 30 days prior to Day 1.
- If a CT scan is performed in a positron emission tomography/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast CT scan.
- Brain imaging (by either MRI or contrast-enhanced CT) is required at screening for all patients displaying clinical signs of possible central nervous system involvement.
- Further investigations such as bone scans should be performed if there is any clinical suspicion of disease at any site that may not be observed using the methods above.

- The same radiographic procedures used to assess disease sites at screening should be used throughout the study (e.g., the same contract protocol for CT scans). Assessments should be performed by the same evaluator if possible to ensure internal consistency across visits.
- All findings will be assessed for response according to RECIST v1.1 criteria as defined in (Appendix 13.2) and according to the Schedule of Assessments and Study Activities (Table 1 and Table 2).

  RECIST v1.1 criteria do not mention including or excluding lesions that are being biopsied or injected. However, for the purposes of this protocol, the injected and biopsied lesions are to be captured as non-target lesions only (Phase I only), as follows:

  - Injected and biopsied lesion = non-target lesion #1
  - Non-injected and biopsied lesion = non-target lesion #2 (if applicable)

- In certain circumstances a patient experiencing RECIST progression of disease may be allowed to continue therapy on study where there is agreement between the investigator and sponsor that the patient is deriving clinical benefit.

7 DISCONTINUATION CRITERIA

7.1 DISCONTINUATION OF INDIVIDUAL PATIENTS

Patients are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The treatment of individual patient(s) may be stopped by the investigator under defined circumstances as outlined below.

- Patient request
- Use of non-permitted concurrent therapy
- Non-compliance with the study drug or study schedule
- Patient lost to follow-up
- Occurrence of AEs not compatible with the continuation of patient participation in the study, in the investigator's opinion, or unacceptable to the patient to continue
- Investigator/sponsor request
- Intercurrent illness warranting removal by the investigator
- Disease progression warranting removal by the investigator

The reason(s) for withdrawal (by the patient or investigator) and date will be documented in the electronic case report form (eCRF).

All patients who withdraw from the study with an ongoing AE must be followed until the event is resolved or deemed stable. Any patient who withdraws consent as a result of an AE, regardless of intensity or investigator's opinion, must be reported as a discontinuation due to AE. Patients withdrawing from the study will be encouraged to complete the final evaluations as detailed for termination in the Schedule of Assessments (Table 1 and Table 2), particularly safety evaluations.

If a patient refuses to complete early termination procedures, this information will be recorded in the source documentation. A patient who prematurely discontinues from the study for any reason will not be allowed to re-enter the study.

In certain circumstances, a patient experiencing RECIST progression of disease may be allowed to continue therapy on study where there is agreement between the investigator and sponsor that the patient is deriving clinical benefit.

7.2 EARLY DISCONTINUATION OF THE STUDY

The sponsor has the right to terminate the study at any time in case of SAEs or if special circumstances concerning the IMSA101 or the company itself occur, making further treatment of patients impossible. In this event, the investigator(s) will be informed of the reason for study termination.

In particular cases, the study may be terminated at a single study site at any time if it becomes apparent that patient enrolment or quality of the data is unsatisfactory, or the conduct of the study at this site is not in accordance with the Good Clinical Practice (GCP) guidelines.

Study materials must be returned, disposed of or retained as directed by the sponsor.

8 TREATMENT

8.1 DOSING AND ADMINISTRATION OF IMSA101

IMSA101 is a sterile, nonpyrogenic solution containing 10 mg of IMSA101 in 1.0 mL of [redacted]. Prior to dosing, IMSA101 will be thawed and further diluted [redacted] in order to be delivered intratumorally at the following dose levels:

Monotherapy: 100, 200, 400, 800, and 1,200 µg.

Combination Therapy IMSA101 + current ICI therapy (administered according to the label of that product):

- 800 and 1,200 µg
- 2,400 µg (with an initial "priming" dose of 1,200 µg)
- 3,600 µg (with an initial "priming" dose of 2,400 µg)
- 4,800 µg (with an initial "priming" dose of 3,600 µg)

This drug is **NOT SAFE** to be administered without proper dilution. Composition of IMSA101 is presented in Table 4.

Table 4 Composition of IMSA101 for Injection

Ingredients	Grade	Function	Composition (1.2 mL per vial)
[redacted]			

NF: National Formulary; USP: United States Pharmacopeia

8.1.1 Preparation of IMSA101

Prior to dosing, IMSA101 will be thawed and diluted [redacted] as detailed in a separate pharmacy manual. A single pre-defined tumor/tumor site per patient will be selected and injected intratumorally throughout study participation. Injections of tumors that are not superficial will be performed under image guidance.

8.1.2 Administration of IMSA101

Phase I (dose escalation):

For monotherapy, IMSA101 will be administered at dose levels of (but not necessarily be limited to) 100, 200, 400, 800, and 1,200 µg (Table 5). One mL total volume will be administered each week for 3 weeks in Cycle 1 (Days 1, 8, and 15). For Cycle 2 and all other cycles thereafter, study drug will be given by intratumoral injection every other week on Days 1 and 15.

For combination therapy, IMSA101 will be administered at dose levels of 800 and 1,200 µg. One mL total volume will be administered each week for 3 weeks in Cycle 1 (Days 1, 8, and 15). For Cycle 2 and all other cycles thereafter, study drug will be given by intratumoral injection every other week on Days 1 and 15. Additional combination therapy dose levels of 2,400, 3,600, and 4,800 µg require the following priming dose on Day 1 of Cycle 1: 1,200 µg for the 2,400 µg dose, 2,400 µg for the 3,600 µg dose, and 3,600 µg for the 4,800 µg dose. After Day 1 of Cycle 1, the full dose for these groups will be administered on Day 1 of Weeks 2 and 3 of Cycle 1 (i.e., weekly dosing 3 out of 4 weeks), and on Day 1 of Weeks 1 and 3 for all cycles thereafter (i.e., bi-weekly dosing).

IMSA101 is injected directly into the selected tumor. Patients will be observed for 1 h following each intratumoral injection. In addition, following intratumoral injection on Day 1 of Cycle 1, patients will be admitted to the hospital for observation overnight.

Injectable tumors shall be accessed by intralesional (cutaneous) or percutaneous injection only, including those lesions that are visible, palpable, or detectable by standard radiographic or ultrasound methods. The administration technique and procedures for internal lesions (i.e., whether CT or ultrasound guided) will be per institutional policy and guidelines. Neither surgical procedures nor endoscopically-guided injections including those to endobronchial, endoluminal, or endosinusoidal spaces shall be allowed. While no anatomic locations are required or disallowed, lesions selected for intratumoral injection must, in the opinion of the investigator:

- Not be immediately adjacent to blood vasculature or other physiologic landmarks in such a way that will accrue undue safety risk to the patient
- Have longest diameter ≥ 10 mm and ≤ 50 mm
- Be fully efficacy evaluable per RECIST v1.1 criteria (Appendix 13.2)

Where no remaining accessible lesions are present and where benefit of IMSA101 therapy is, in the opinion of the investigator, being derived by the patient, continued injections of IMSA101 into the vicinity of an inaccessible lesion shall be allowed. In the case that a lesion can no longer be radiographically visualized, continued injections into the last known location of the non-visible lesion shall be allowed.

For those patients receiving a combination regimen, the combination partner drug will be administered per product label.

Table 5 Dose Levels of IMSA101 for Injection

Dose Level	IMSA101 Dose
Monotherapy	
1	100 µg*
2	200 µg
3	400 µg
4	800 µg
5	1,200 µg
Combination Therapy	
1	800 µg
2	1,200 µg
3	2,400 µg with an initial priming dose of 1,200 µg
4	3,600 µg with an initial priming dose of 2,400 µg
5	4,800 µg with an initial priming dose of 3,600 µg

* The lowest dose (100 µg) represents 1/60th of the preclinical highest non-severe toxic dose (HNSTD).

Dose escalation design in which administered dose levels will be escalated stepwise in successive cohorts of 3 to 6 (4 to 7 when applicable) patients each (standard 3+3 study design) until the MTD or RP2D level is identified.

Phase I (dose de-escalation for combination therapy):

If ≥ 2 DLTs occur among the initial 3 (4 when applicable) or 6 (7 when applicable) patients, de-escalation of IMSA101 is allowed for the combination therapy dose levels as follows:

- 2,400 µg may be de-escalated to 1,800 µg (with a priming dose of 1,200 µg on Day 1 of Cycle 1)
- 3,600 µg may be de-escalated to 3,000 µg (with a priming dose of 2,400 µg on Day 1 of Cycle 1)
- 4,800 µg may be de-escalated to 4,200 µg (with a priming dose of 3,600 µg on Day 1 of Cycle 1)

If ≥ 2 DLTs occur among the initial 3 (4 when applicable) or 6 (7 when applicable) patients at a de-escalated dose level, the dose level shall be considered unacceptably toxic and escalation will be discontinued.

Phase IIA (dose expansion):

IMSA101 will be given at the RP2D through intratumoral injection as described for Phase I above.

Patients will receive either IMSA101 monotherapy or in combination with IO therapy. A safety run-in component will establish safety of the combination before further patients are enrolled (Section 3.1.2).

8.2 STORAGE OF IMSA101

The drug product is packaged in a container-closure system that is composed of pharmacopoeia-compliant components. The primary container, composed of United States Pharmacopeia (USP) Type 1 glass, is stoppered with a 13 mm Fluortec coated lyophilization stopper, and sealed with a 13 mm flip-off overseal and 13 mm cap. A 24-unit paper carton is used to distribute the product to clinical sites.

The product (IMSA101 for Injection) is stored at -20 ± 5°C and is being tested for 5 years of shelf-life through a stability protocol. Currently, the product has completed the 3-year time point for stability with all tests meeting specification. Clinical trial sites will be provided specific expiry and stability updates via memoranda as new data become available.

8.3 RESCUE MEDICATIONS AND CONCOMITANT TREATMENTS

All medications administered from the beginning of study treatment (Cycle 1 Day 1, including during the overnight hospitalization) through the end of treatment and study participation will be recorded on the eCRF. Any change in medication dosage will also be noted.

Necessary supportive care (i.e., antiemetic and/or antidiarrheal medications, etc.) will be allowed. Prophylactic pretreatment for headache, nausea, and vomiting (after Cycle 1) is permitted.

8.4 TREATMENT COMPLIANCE

The investigator and/or his study staff will administer IMSA101 study medication only for use by patients enrolled in the study as described in this protocol. The study medication is not to be used for reasons other than those described herein.

The investigator or other study staff will supervise study drug treatment given in the clinic and record all treatments in the eCRF. Study personnel associated with the sponsor will monitor IMSA101 drug treatment compliance.

9 ADVERSE EVENTS

9.1 DEFINITIONS

9.1.1 Adverse Event

An AE is defined as any undesired medical occurrence in a patient or clinical investigation patient receiving a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable sign and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a study drug, whether or not related to the study drug. AE reporting begins at the time of study drug administration and continues until 30 days after the last dose.

9.1.2 Serious Adverse Events

An SAE is any untoward medical event that occurs at any dose from the time of study drug administration and continuing until 30 days after the last dose that:

- results in death
- is life-threatening (patient is at immediate risk of death from the event as it occurred) [1]
- requires inpatient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization [2]
- results in persistent or significant disability/incapacity [3]
- results in a congenital anomaly/birth defect
- is an important medical event [4]

[1] "Life-threatening" means that the patient was at immediate risk of death at the time of the SAE; it does not refer to a SAE that hypothetically might have caused death if it were more severe.

[2] This means that hospital inpatient admission or prolongation of hospital stay was required for the treatment of the AE, or that one or the other occurred as a consequence of the event. Hospitalizations for elective surgery or other medical procedures that are not related to a TEAE are not considered SAEs. The planned overnight hospitalization on Day 1 of Cycle 1 is exempt from this definition and is not considered an SAE since it is a study procedure and not for treatment of an SAE, unless an AE occurs during the hospitalization that meets the criteria above.

[3] "Persistent or significant disability or incapacity" means a permanent or significant and substantial disruption of a person's ability to carry out normal life functions.

[4] Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to

prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious.

All other AEs are considered non-serious. All non-serious AEs will be followed to resolution, or until the study ends, and reported to the sponsor as requested, to the Institutional Review Boards (IRBs)/Institutional Ethics Committees (IECs) according to IRB/IEC policies (to include annual Continuing Review Reports), to the CRC as required, and to the U.S. Food and Drug Administration (FDA) as required for the annual report.

AEs meeting the stopping criteria outlined in Section 7 of this protocol will be reported to the sponsor, the IRBs/IECs, and the CRC following the SAE reporting guidelines.

Management of all AEs including hypersensitivity or hyperimmune reactions will be managed by treating physicians in conjunction with relevant institutional guidelines and with the consultation of the sponsor's medical monitor.

9.1.3 Adverse Event by Severity or Intensity

The assessment of severity of an AE will be rated according to the criteria in Table 6.

Table 6 Definitions of Adverse Events Severity

Grade 1 (Mild)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. The adverse event (AE) does not interfere with routine activities. The patient may experience slight discomfort.
Grade 2 (Moderate)	Moderate; minimal, local or noninvasive intervention indicated; The AE interferes with routine activities. The patient may experience significant discomfort.
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated. The patient is unable to perform routine activities. The patient may experience intolerable discomfort or pain.
Grade 4 (Life-Threatening)	Life-threatening consequences; urgent intervention indicated.
Grade 5 (Fatal)	Death related to AE

Based on the Common Terminology Criteria for Adverse Events v 5.0 (CTCAE).

The term "severe" is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., 'severe' headache). This is not the same as "serious".

Seriousness of AEs is based on the outcome of an AE and usually associated with events that pose a threat to a patient's life or functioning.

9.1.4 Relationship between Adverse Events and Study Drug

Determination of the relationship (if any) between the AE and the study drug will be made using the guidelines presented in Table 7.

Table 7 Guidelines for Determining the Relationship (if any) Between Adverse Event and the Study Drug

Definitely Related:	This causal relationship is assigned if the AE starts a reasonable time after the administration of study drug, stops/improves when the study drug is stopped, and could reasonably be explained by known characteristics of the study drug.
Probably Related:	This causal relationship is assigned when the AE starts a reasonable time after the administration of study drug, stops/improves when the study drug is stopped, and could not be reasonably explained by known characteristics of the patient's clinical state.
Possibly Related:	This causal relationship is assigned when the AE starts a reasonable time after the administration of study drug, but could be produced by the patient's clinical state or other modes of therapy administered to the patient.
Unlikely Related	This causal relationship is assigned when the time association or the patient's clinical state is such that the study drug was not likely to have had an association with the observed AE.
Not Related:	This causal relationship is assigned when there is clearly no evidence of association with the study drug and the observed AE.

Pregnancy or lactation are exclusion criteria for this study. Pregnancy per se is not considered an AE unless there is cause to believe that the investigational drug may have interfered with the effectiveness of a contraceptive medication. Refer to Section 4.4 for details.

9.1.5 Adverse Event Follow-up

All AEs occurring during the study are to be followed up in accordance with good medical practice until they are resolved, stabilized or judged no longer clinically significant or, if a chronic condition, until fully characterized. Any AEs that are considered drug-related (possibly related, probably related, or definitely related) must be followed until resolution or until stabilization.

All unresolved AEs following the study should be followed by the investigator until the events are resolved, the patient is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator should instruct each patient to report any subsequent event(s) that the patient, or the patient's personal physician, believes might reasonably be related to participation in this study.

Prior to the conclusion of the study at the site, the investigator should notify the ImmuneSensor Therapeutics (ImmuneSensor), Safety Associate, or designee of any death or AE occurring at any time after a patient has discontinued or terminated study participation that may reasonably be

related to this study. After study conclusion, the investigator should notify ImmuneSensor of any death or AE they are aware of occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study.

The investigator should notify ImmuneSensor or its designee, of any death or AE occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study.

9.1.6 Overdose

Any dosing errors should be immediately reported to the sponsor. The dosing error should be fully documented in the patient's source documentation/case report form (CRF) and where applicable, filed promptly with IRB and regulatory authorities.

Subsequent dosing shall be discontinued until the investigator and sponsor have both determined it's safe to resume treatment.

9.1.7 Pregnancies

No clinical data on the effects on pregnancy or lactation are available. Precautions relative to patients of reproductive potential are discussed in Section 4.4.

9.2 SERIOUS ADVERSE EVENT REPORTING

9.2.1 Reporting Requirements

Any SAE made known to the investigator must be reported by the investigator if it occurs during the clinical study, whether or not the SAE is considered to be related to the IMSA101 treatment. An SAE report consists of the SAE form, the AE form, and the concomitant medication form.

A copy of these forms must be forwarded within 24 h of awareness. Contact details will be provided in the study reference manual.

The investigator should not wait to receive additional information to document fully the event before notification of an SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation of study drug administration and linked by the investigator to this study, should be reported to the medical monitor.

Progression of disease by itself is not considered an AE but rather an expected outcome and a study endpoint and should not be reported as AEs or SAEs, unless it results in hospitalization or death. AEs associated with progressive disease (such as a pleural effusion or gastrointestinal obstruction) and associated hospitalizations to treat the AE or SAE are reportable events.

10 STATISTICAL METHODS

10.1 GENERAL CONSIDERATIONS

10.1.1 Statistical and Analytical Plans

A formal detailed statistical analysis plan (SAP) will be created prior to the analysis of any data.

The purpose of the Phase I dose escalation study is to determine the safety and tolerability of IMSA101 and to define the MTD/RP2D of the drug when administered by intratumoral injection. Groups of 3 to 6 patients will be treated at each dose level until the MTD is reached as detailed in Section 3.1. All patients meeting the eligibility criteria and receiving at least 1 dose of IMSA101 will be evaluable for safety in the Safety Population.

Phase IIA statistics will be mainly descriptive and informed by the ultimate selection of tumor types to be evaluated. Statistical methods including pre-defined criteria for signal detection and drug differentiation from standard-of-care benchmarks as well as stage progression and futility assessment will be included in the final SAP.

10.1.2 Disposition of Patients

A tabulation of patient disposition will be presented, including the number in each analysis population, the number lost to follow-up, the number that withdrew prior to completing the study, and reason(s) for withdrawal.

10.1.3 Blinding and Randomization

This clinical study is open-label and non-randomized.

10.2 ANALYSIS DATASETS

10.2.1 Safety Population

The safety population will consist of all patients receiving at least 1 dose of study medication.

10.2.2 Definition of Study Cycles

Each treatment cycle will be 4 weeks (28 days) in duration. There will be 3 clinic visits in Cycle 1 (Day 1, on Day 8, and Day 15). Thereafter for all other cycles, there will be 2 clinic visits on Day 1 and Day 15. Study drug will be administered at all visits following screening except the EOT and EOS visits.

10.3 DATA PRESENTATION

10.3.1 Demographic

Demographic characteristics of patients will be summarized in appropriate tables and analyzed with descriptive statistics.

Demographic variables to be captured include (but not necessarily limited to):

- Age
- Gender
- Race
- Smoking history
- Tumor type

10.3.2 Baseline Characteristics

Baseline characteristics will be summarized in appropriate tables with descriptive statistics.

Baseline characteristics to be captured include (but not necessarily limited to):

- Body weight
- Height
- ECOG performance status
- Previous chemotherapy
- Previous immunotherapy

10.3.3 Medical History and Physical Examination

Descriptive statistics will be generated to summarize data. For continuous variables, descriptive statistics may include the number of patients, mean, standard deviations, medians, minimums, and maximums. Frequencies and percentages may be displayed for categorical data.

10.3.4 Concomitant Medications or Treatments

The number and percentage of patients taking concomitant medication will be summarized. All data will be recorded as follows:

- Prior use ended before first day of study medication
- Concomitant use on or after first day of study medication (initiation date, stop date)

10.3.5 Safety Data

- All safety summaries will be provided for the Safety Population.
- Summaries for safety variables (TEAEs, DLTs, vital signs, 12-lead ECG, physical examination, and laboratory safety assessments) will be given. Toxicities will be graded using CTCAE v5.0 criteria.
- All safety variables will be presented in by-patient listings. Safety data will be listed by study site, patient number, and cycle.
- All TEAEs will be summarized by study phase and assigned dose.
- In addition, all SAEs, including deaths will be listed separately and summarized.
- Grade 3 and 4 laboratory data will be summarized by study phase and assigned dose.
- For patients who experience a DLT, data on AEs leading to treatment/study discontinuation will be listed.

10.3.6 Adverse Events

- AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. A listing of all events, with seriousness, severity, relationship, sequelae, and beginning and end times will be provided.
- Narratives for any SAEs will be provided.
- Deaths, SAEs, and AEs leading to discontinuation of trial medication will be summarized by primary system organ class and preferred terms.
- Listings will be provided.

10.3.7 Tumor Assessments

All known sites of disease must be documented at screening and re-assessed at each subsequent tumor evaluation according to procedures described in Section 6.9.

Patients will be assessed for anti-tumor efficacy using RECIST v1.1 criteria (Appendix 13.2) at the end (≤ 7 days) of every even numbered cycle (Cycle 2, Cycle 4, etc.) after the first dosing.

10.3.8 Missing and Spurious Data

No imputation of missing or spurious data is planned.

For AEs, missing dates will not be imputed; however if partial dates are available, they will be used to assess if the AE occurred during the treatment period. Missing severities of AEs will not be imputed and will be considered missing in any tabulations of AE severity. If an AE is missing a response to the question regarding relationship to treatment, the event will be considered to be related.

10.4 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, the IRB/IEC, and the Health Authorities prior to implementation.

11 REGULATORY, ETHICAL AND LEGAL OBLIGATIONS

11.1 DECLARATION OF HELSINKI

The Principal Investigator will ensure that this study is conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and applicable national and local laws (World Medical Association (WMA) 2013).

11.2 GOOD CLINICAL PRACTICE

The study will be conducted according to the study protocol and to Standard Operating Procedures (SOPs) that meet the guidelines provided by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) for Good Clinical Practice in clinical studies (ICH E6 R2).

11.3 INSTITUTIONAL REVIEW BOARDS/ETHICS COMMITTEES

Before implementing this study, the protocol, amendments (if any), the proposed informed consent forms (ICFs), patient recruitment procedures (e.g., advertisements), and other information for the patients must be reviewed by the appropriate IRB/IEC at each study center in conformance with ICH E6 R2, the Code of Federal Regulations (CFR), Title 21, Part 56 and any other applicable local laws. The IRB/IEC written, signed approval letter/form must contain approval of the designated principal investigator, the protocol (identifying protocol title, date, and version number), and of the informed consent form (date, version).

The investigator is responsible for supplying the IRB/IEC with a copy of the current Investigator's Brochure (IB), Package Insert, or Summary of Product Characteristics (SmPC) as well as any updates issued during the study. During the course of the study, the investigator will provide timely and accurate reports to the IRB/IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB/IEC of SAEs or other significant safety findings, per the policy of the IRB/IEC.

11.4 REGULATORY AUTHORITY APPROVAL

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor, the IRB/IEC, and/or other agency if applicable.

11.5 INFORMED CONSENT

The investigator must fully inform the patient (or the patient's legal representative, if applicable) of all pertinent aspects of the study including the written information approved by the IRB/IEC.

Prior to the start of the pre-study examination, the written ICF must be signed and personally dated by the patient and by the physician who conducted the informed consent discussion. One copy of the written information and signed consent form must be given to the patient and the original copy must be retained in the investigator's study records.

11.6 PATIENT CONFIDENTIALITY AND DISCLOSURE

In compliance with federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized monitors, auditors, and other authorized agents of the sponsor and/or its designee, the IRB/IEC approving this research, and the United States (US) FDA, as well as that of any other applicable agency or agencies, direct access to review the patient's original medical records for verification of study-related procedures and data. The investigator is obligated to inform the patient that his/her study-related records will be reviewed by the above-named representatives without violating the confidentiality of the patient.

All personal data collected and processed for the purposes of this study should be managed by the investigator and his/her staff with adequate precautions to ensure confidentiality of those data, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA), applicable to national and/or local laws and regulations on personal data protection (US HHS 2002).

The investigator must ensure that each patient's anonymity will be strictly maintained. On CRF/eCRFs or other documents submitted to the sponsor, patients must not be identified by their name, but by an identification code consisting of the identification number. If patients' names are included on copies of documents submitted to the sponsor, the names must be obliterated and the assigned identification number must be added to the documents instead.

11.7 PROTOCOL AMENDMENT

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents (or amendments) will be submitted to the appropriate authorities such as the FDA and/or local IRB/IEC with a cover letter or a form listing the documents submitted, their intended dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval from the IRB/IEC of an amendment. The only exceptions are where necessary to eliminate an immediate hazard(s) to study patients, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor[s], change of telephone number[s]). Non-substantial protocol amendments may or may not be required to be submitted for approval/notification to the appropriate authorities (i.e., FDA, IRB/IEC).

As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

- to the appropriate authorities for review and approval/favorable opinion
- to the sponsor for agreement

The party initiating an amendment must confirm it clearly in writing and it must be signed and dated by the sponsor and the principal investigator. The sponsor or its designee will ensure that the investigators submit necessary protocol amendments to the appropriate IRB/IEC.

All agreed protocol amendments must be clearly documented using standard procedures as defined by the sponsor, and must be signed and dated by the sponsor and the investigator.

11.8 COLLECTION, MONITORING AND AUDITING STUDY DOCUMENTATION

11.8.1 Data Collection

The sponsor or the designee will utilize qualified monitors to review and evaluate activities conducted at investigator sites for Quality Assurance.

Data for each patient will be recorded on an eCRF. Data collection must be completed for each patient who signs an ICF and is administered treatment.

The data will be entered into the clinical study database and verified for accuracy, following procedures defined by the sponsor (or designee). Data will be processed and analyzed following procedures defined by the sponsor (or designee).

The medical monitor will review any SAEs that occur during the study.

In accordance with ICH GCP guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the eCRF are accurate and reliable.

Data that is not captured directly via an electronic device or instrument will be collected from source documents and entered into an eCRF within an electronic data capture system. Electronic data capture security features will include the requirement for a unique user identification and password for each individual who make entries, reviews, or makes changes to the data.

The investigator will be responsible for ensuring data is electronically captured or that it is entered into the eCRF in a timely manner relative to the patient visit. The investigator will ensure the accuracy and completeness of all patient data specified in the protocol. Upon study completion, the data collected in the eCRF will be provided to each study center in portable document format (PDF).

11.8.2 Study Monitoring

A representative of the sponsor or the designee will meet with the investigator and his/her staff prior to the entrance of the first patient to review study procedures and methods of recording study data.

After enrollment of the first patient, representative of the sponsor or the designee will be assigned to monitor at least once a year each study site for study progress and to verify that

standards of GCP and/or ICH guidelines were followed. The investigator is expected to prepare for the monitor visit, ensuring that all source documents, completed eCRFs, signed consent forms, and other study-related documents are readily available for review. Source documents that will be reviewed include but are not limited to accuracy of CRFs, protocol compliance, accuracy of entries and AE/SAE management and reporting. Documentation of monitoring will be maintained along with other protocol-related documents and will be reviewed during internal audit.

11.8.3 Auditing of Study Documentation

Study centers and study documentation may be subject to a Quality Assurance audit at any time during or after the study. In addition, inspections may be conducted by regulatory authorities at their discretion.

The investigator must permit the monitor, the IRB/IEC, the sponsor's internal auditors, and representatives from regulatory authorities, direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the eCRFs.

The study will be monitored and/or audited at intervals to ensure that the clinical study is conducted and data are generated, documented (recorded), and reported in compliance with the study protocol; ICH E6 R2 consolidated guidelines; and other applicable regulations. The extent, nature, and frequency of monitoring and/or audits will be based on such considerations as the study objectives and/or endpoints, the purpose of the study, study design complexity, and enrollment rate. At the conclusion of a program, a compliance statement will be generated by the sponsor (or designee) listing all audit activities performed during the clinical study.

All data recordings and source documentation (including electronic health records) must be made available to the sponsor (or designee), FDA, IRB/IEC, and any other regulatory agencies that request access to study records, including source documents, for inspection and copying, in keeping with federal and local regulations.

11.9 RECORD RETENTION

According to ICH guidelines, source documentation and other "essential documents" must be archived. Essential documents include those documents which individually and collectively permit the evaluation of the conduct of a study and the quality of the data produced (ICH 2016). This may include observations and source data contained in medical records (certified copies or originals are acceptable for archiving purposes), data collection forms or eCRFs and research-related records held in support departments. All hard copies of source documents must be retained. If electronic records of documents exist, these must be backed up and retained with the hard copies.

Essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. However, these documents should be retained for a

longer period if required by the applicable legal requirements and/or written agreements with the sponsor (i.e., Master Service Agreement).

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the study and make them available upon request from the regulatory authorities.

11.10 DISCLOSURE OF INFORMATION

All information provided to the investigator by ImmuneSensor or its designee, will be kept strictly confidential. No disclosure will be made except in accordance with a right of publication granted to the investigator.

No information about this study or its progress will be provided to anyone not involved in the study other than to ImmuneSensor or its authorized representatives, or in confidence to the IRB, or similar committee, except if required by law.

11.11 DISCONTINUATION OF THE STUDY

It is agreed that, for reasonable cause, either the investigator or ImmuneSensor may terminate the investigator's participation in this study after submission of a written notice. ImmuneSensor may terminate the study at any time upon immediate notice for any reason, including the sponsor's belief that discontinuation of the study is necessary for the safety of patients.

11.12 STUDY REPORT, PUBLICATION POLICY AND ARCHIVING OF STUDY DOCUMENTATION

An ICH-compliant integrated clinical and statistical report will be prepared upon completion of the study and data analysis. The results of the study will be published in a relevant peer-reviewed journal, with authorship status and ranking designated according to the acknowledged contributions of participating investigators, institutions, and the sponsor.

11.12.1 Data Capture

This study will use a 21 CFR Part 11 compliant electronic data capture system. An eCRF will be used for data recording. Any data requested on the eCRF must be entered and a reasonable effort should be made to retrieve any missing data.

The data will be checked for completeness and correctness and discrepancy reports will be generated accordingly and transferred to the study center for resolution by the investigator or his/her designee.

Accurate and reliable data collection will be assured by verification and cross–check of the eCRF against the investigator's records by the study monitor (source document verification), and the maintenance of a study drug accountability log by the investigator.

11.12.2 **Study Documents**

The investigator must maintain source documents for each patient in the study, including all demographic and medical information, laboratory data, ECGs, etc., and keep a copy of the signed and dated ICFs. All information on the eCRFs must be traceable to these source documents in the patient's file. Data without a written or electronic record will be defined before study start and will be recorded directly on the eCRFs, which will be documented as being the source data.

11.12.3 **Archiving of Documents**

Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with national and international regulations. The sponsor will notify the investigator(s)/institution(s) when the study-related records are no longer required. The investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:

1. IRB/IEC/REB approvals for the study protocol and all amendments
2. All source documents and laboratory records
3. CRF copies (electronic copies on a CDROM)
4. Patients' ICFs (with study number and title of trial)
5. FDA form 1572
6. Any other pertinent study documents

12 REFERENCES

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13 APPENDICES

13.1 EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE SCALE

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* *As published in Am. J. Clin. Oncol* (Oken, 1982)

13.2 RECIST GUIDELINE (VERSION 1.1)

All findings will be assessed for response according to RECIST v1.1 criteria (Eisenhauer, 2009) at the end (≤ 7 days) of every even numbered cycle (Cycle 2, Cycle 4, etc.), and EOT. Refer to Section 6.9 for details.

RECIST v1.1 criteria do not mention including or excluding lesions that are being biopsied or injected. However, for the purposes of this protocol, the injected and biopsied lesions are to be captured as non-target lesions only (Phase I only), as follows:

- Injected and biopsied lesion = non-target lesion #1
- Non-injected and biopsied lesion = non-target lesion #2 (if applicable)

All patients will have their BEST RESPONSE on study classified as outlined below:

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in the short axis to < 10mm.

Partial Response (PR)

At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum LD.

Stable Disease (SD)

Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

Progressive Disease

At least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded since the treatment started. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Appearance of one or more new lesions will also constitute progressive disease.

Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded since the treatment started.

Stable Disease Duration

Stable disease duration will be measured from the time of start of therapy until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Evaluation of Best Overall Response – Patient with Target (+/- non-target) disease

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR-Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD/ or not all evaluated	No	PR
SD	Non-PD/ or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Evaluation of Best Overall Response – Patient with Non-Target Disease

Non-Target lesions	New Lesions	Overall response
CR	No	CR
Non-CR-Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

Method of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Chest X-ray

Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

CT / MRI.

CT and MRI might be the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to the chest, abdomen and pelvis. Head & neck and extremities usually require specific protocols.

Ultrasound

When the primary endpoint of the study is objective response evaluation, ultrasound should not be used to measure tumor lesions that are clinically not easily accessible. It is a possible alternative to clinical measurements for superficial palpable nodes, subcutaneous lesions and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Cytology / Histology

These techniques can be used to differentiate between PR and CR in rare cases (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

13.3 CREATININE CLEARANCE

Creatinine clearance will be calculated using the Cockcroft-Gault formula (Cockcroft, 1976) as follows:

Females:

For serum creatinine concentration in mg/dL:

$$\text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in Kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

Males:

For serum creatinine concentration in mg/dL:

$$\text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in Kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

13.4 CONTACT LIST

SPONSOR:

[redacted]

Senior Director,
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