



## Clinical Study Protocol

# Phase 2 Randomized Clinical Trial Comparing the Safety and Efficacy of PULSAR-Integrated Radiotherapy + Pembrolizumab or Nivolumab Administered with or without STING-Agonist IMSA101 in Patients with Oligoprogressive Solid Tumor Malignancies

## IMSA101-103

<b>Drug Development Phase:</b>	Phase 2
<b>Investigational Product:</b>	IMSA101
<b>IND Number</b>	142445
<b>Indication:</b>	Oligoprogressive Solid Tumor Malignancies
<b>Sponsor:</b>	ImmuneSensor Therapeutics 2110 Research Row #610 Dallas, TX 75235
<b>Protocol Amendment:</b>	4
<b>Protocol Date and Version:</b>	20-AUG-2024 Version 6.0

**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.

### CONFIDENTIAL INFORMATION

This document is the sole property of ImmuneSensor Therapeutics (ImmuneSensor). This document and any and all information contained herein has to be considered and treated as strictly confidential. This document shall be used only for the purpose of the disclosure herein provided. No disclosure or publication shall be made without the prior written consent of ImmuneSensor Therapeutics.

## PROTOCOL APPROVAL SIGNATURE PAGE

### SPONSOR: IMMUNESENSOR THERAPEUTICS

I have reviewed and approved this protocol for Study No. IMSA101-103 (Protocol Amendment 4, Version 6.0) dated 20-AUG-2024, including appendices and confirm that it follows current regulations and GCP guidelines.

**Approved By (Signature):**

**Date:**

A solid black rectangular box used to redact the signature of the Vice President.

**Vice President,  
Clinical Operations and Project Management**

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## PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study No. IMSA101-103 (Protocol Amendment 4, Version 6.0) dated 20-AUG-2024, 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 GCP and applicable Food and Drug Administration (FDA) regulatory requirements:

**Name of Principal Investigator:**

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**Signature**

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**Date**

## PROTOCOL SYNOPSIS

<b>Sponsor:</b>	<b>Investigational Product:</b>	<b>Developmental Phase:</b>
ImmuneSensor Therapeutics	IMSA101	Phase 2
<b>Title of Study:</b> Phase 2 Randomized Clinical Trial Comparing the Safety and Efficacy of PULSAR-Integrated Radiotherapy + Pembrolizumab or Nivolumab Administered with or without STING-Agonist IMSA101 in Patients with Oligoprogressive Solid Tumor Malignancies		
<b>Protocol Number:</b> IMSA101-103		
<b>IND Number:</b> 142445		
<b>Study Center(s):</b> Approximately 15 cancer centers in the United States (US)		
<b>Indication:</b> Oligoprogressive solid tumor malignancies after prior anti-cancer therapy		
<b>Study Population:</b> Adult patients with oligoprogressive solid tumor malignancies after receipt of prior anti-cancer therapy, with 6 or fewer discrete, extracranial metastatic sites that are technically amenable to personalized ultra-fractionated stereotactic adaptive radiotherapy (PULSAR)		
<b>Study Design:</b> Phase 2, open-label, multicenter, randomized study comparing the safety and efficacy of PULSAR combined with ICI immunotherapy (PULSAR-ICI) + IMSA101 and PULSAR-ICI alone in patients with oligoprogressive solid tumor malignancies after prior anti-cancer therapy		
<b>Objectives:</b>		
<b>Objectives</b>	<b>Endpoints</b>	
<b>Primary</b>		
Estimate progression-free rate at 12 months after commencement of therapy, separately for PULSAR-ICI + IMSA101 and PULSAR-ICI alone	<ul style="list-style-type: none"><li>Proportion of patients remaining progression-free at 12 months after commencement of therapy</li></ul>	
<b>Secondary</b>		
Characterize the safety and tolerability of PULSAR-ICI + IMSA101 and compare with PULSAR-ICI alone	<ul style="list-style-type: none"><li>Occurrence of treatment-emergent adverse events (TEAEs), Grade <math>\geq 3</math> TEAEs, and serious adverse events (SAEs)</li></ul>	
Estimate progression-free at 8-week intervals from 6 months to 22 months after commencement of therapy	<ul style="list-style-type: none"><li>Proportion of patients remaining progression-free at 8-week intervals from 6 months to 22 months after commencement therapy</li></ul>	

Sponsor:	Investigational Product:	Developmental Phase:
ImmuneSensor Therapeutics	IMSA101	Phase 2
Estimate time-to-progression (TTP) for PULSAR-ICI + IMSA101 and PULSAR-ICI alone	<ul style="list-style-type: none"><li>Overall TTP as defined by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and by Immune-based Response Evaluation Criteria in Solid Tumors (iRECIST)</li></ul>	
Estimate anti-tumor efficacy for PULSAR-ICI + IMSA101 and PULSAR-ICI alone using additional efficacy endpoints	<ul style="list-style-type: none"><li>Overall response rate (ORR) as defined by RECIST Version 1.1 and by iRECIST</li><li>Duration of treatment response (DOR) per RECIST Version 1.1 and iRECIST</li><li>Progression-free survival (PFS) per RECIST Version 1.1 and iRECIST</li></ul>	
Assess quality of life (QoL) benefit	<ul style="list-style-type: none"><li>Patients reported outcome on QoL using the Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire (Version 4)</li></ul>	
<b>Methodology:</b> <ul style="list-style-type: none"><li>For all potential patients, there will be up to a 30-day screening and eligibility assessment period prior to enrollment.</li><li>Pre-treatment screening radiographic tumor assessments will be collected within 30 days prior to the initial dose for all patients.</li><li>Patients shall be enrolled in 2 treatment arms as follows:<ul style="list-style-type: none"><li>a. Approximately 15 patients in the control arm (PULSAR-ICI alone)</li><li>b. Approximately 30 patients in the experimental arm (PULSAR-ICI + IMSA101)</li></ul></li><li>The study will start with a safety run-in portion for the experimental arm, followed by a randomized portion for both treatment arms.</li><li>Randomization will not be masked nor stratified.</li><li>PULSAR-ICI with or without IMSA101 treatment will be administered to the patients in Cycles 1, 2, and 3, and thereafter only standard of care ICI monotherapy will be administered to all patients. Each treatment cycle will be 28 days in duration for Cycles 1, 2 and 3, then per standard of care thereafter based on the product labels of the prescribed ICI.</li></ul>		

<b>Sponsor:</b> ImmuneSensor Therapeutics	<b>Investigational Product:</b> IMSA101	<b>Developmental Phase:</b> Phase 2
<ul style="list-style-type: none"> <li>Consistent with prior monotherapy and doublet therapy safety evaluations of IMSA101, the experimental arm (PULSAR-ICI + IMSA101) shall employ a 3+3 safety run-in component as follows: <ul style="list-style-type: none"> <li>The safety run-in will be conducted for the experimental arm prior to the randomization of patients to the 2 treatment arms.</li> <li>Patients enrolled in the safety run-in period who are treated at the dose level selected for the experimental arm will be included in the total number of patients of the experimental arm.</li> <li>Only two dose levels will be evaluated potentially: the previously identified selected Phase 2 dose of IMSA101 minus 1 dose level (800 mcg) and the previously identified selected Phase 2 dose of IMSA101 (1200 mcg). Dosing shall not continue beyond the latter dose.</li> <li>3 initial patients shall be enrolled to evaluate 800 mcg IMSA101 administered in combination PULSAR-ICI.</li> <li>If no dose limiting toxicities (DLTs) are observed among these initial 3 patients at the 800 mcg dose level, the dose level of IMSA101 will be escalated for the following 3 patients to 1200 mcg of IMSA101 administered in combination with PULSAR-ICI.</li> <li>If a single DLT occurs among the initial 3 patients at an evaluated dose level, 3 additional patients will be enrolled at the same dose level.</li> <li>If <math>\leq 1</math> DLT occurs among the 6 patients at an evaluated dose level, the dose level shall be considered appropriate, and dose escalation continues (up to but not beyond the previously identified selected Phase 2 dose of 1200 mcg). If this condition occurs at the 1200 mcg level, subsequent patients will be enrolled at the 1200 mcg level.</li> <li>If <math>\geq 2</math> DLTs occur among the initial 3 or 6 patients at an evaluated dose level, the dose level shall be considered unacceptably toxic and dose escalation will be discontinued.</li> <li>If the 1200 mcg level is found to be unacceptably toxic, the IMSA101 dose will be de-escalated to the 800 mcg dose level.</li> <li>If the 800 mcg dose level is found to be unacceptably toxic, additional dose levels of IMSA101 shall be considered and potentially recommended by a protocol amendment.</li> <li>No fewer than 6 total patients shall be evaluated at a given dose level prior to confirmation of the dose level as the Combo selected Phase 2 dose.</li> </ul> </li> </ul>		

<b>Sponsor:</b> ImmuneSensor Therapeutics	<b>Investigational Product:</b> IMSA101	<b>Developmental Phase:</b> Phase 2
<p><u>Definitions:</u></p> <ul style="list-style-type: none"> <li>◦ Combo selected Phase 2 dose: The Combo selected Phase 2 dose is defined as the dose (either at MTD or below MTD) used in combination with PULSAR-ICI that is selected for evaluation in the Phase 2 study.</li> </ul> <ul style="list-style-type: none"> <li>• For the experimental arm (PULSAR-ICI + IMSA101): <ul style="list-style-type: none"> <li>- A single pre-defined progressing lesion/lesion site (longest diameter <math>\geq 5</math> mm and <math>\leq 50</math> mm) shall be injected throughout the study duration, if possible.</li> <li>- The lesion will be injected weekly for the first three weeks of Cycle 1 (Days 1, 8 and 15) and then on Day 1 of Cycles 2 and 3.</li> <li>- 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.</li> <li>- 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 recorded and allowed, if deemed reasonable by the investigator.</li> <li>- 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 intra-tumoral 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.</li> </ul> </li> <li>• All patients will be followed throughout the study for drug tolerability and safety by collecting clinical and laboratory data, including adverse events (AEs) using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 criteria, SAEs, concomitant medications, and vital signs.</li> <li>• A Safety Review Committee will be organized to review the safety of the administered treatments (PULSAR, IMSA101, and ICI) during the study and in the safety run-in period to determine whether dose escalation of IMSA101 should proceed.</li> <li>• All patients will be assessed for anti-tumor efficacy at screening, at the end of Cycle 3 (<math>\leq 7</math> days of C3D28), and at 8-week intervals (<math>\pm 7</math> days) thereafter based on radiographic assessments and analysis of ORR, DOR, TTP, and PFS (all outcome measures per RECIST Version 1.1 and iRECIST).</li> </ul>		

<b>Sponsor:</b> ImmuneSensor Therapeutics	<b>Investigational Product:</b> IMSA101	<b>Developmental Phase:</b> Phase 2
<ul style="list-style-type: none"> <li>Administration of pembrolizumab or nivolumab will follow the instructions in the product labels and scheduling for the products.</li> <li>Tumor types and the corresponding treatment combinations to be evaluated will be identified prior to the first patient enrolled.</li> <li>All patients will continue to receive their assigned treatment throughout the study until the occurrence of disease progression (based on iRECIST), death, or other unacceptable treatment-related toxicity, or until the study is closed by the sponsor.</li> </ul>		
<p><b>Inclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>Male or female patients <math>\geq 18</math> years of age</li> <li>Signed informed consent and mental capability to understand the informed consent</li> <li>Histologically or cytologically documented solid tumor malignancies demonstrating new progression through prior anti-cancer therapy, with a prior 2 months of clinical stability (with at least Stable Disease), with radiographically documented presence of <math>\leq 6</math> metastatic lesions consistent with the diagnosis of “oligoprogressive” disease that are technically amenable to PULSAR</li> <li>Patient’s disease must be evaluable per RECIST Version 1.1</li> <li>All metastatic lesions amenable to administration of radiotherapy, at the discretion of the investigator</li> <li>Must have at least one single pre-defined progressing lesion/lesion site (longest diameter <math>\geq 5</math> mm and <math>\leq 50</math> mm) suitable for intra-tumoral injection</li> <li>Eastern Cooperative Oncology Group (ECOG) performance status of <math>\leq 1</math></li> <li>Electrocardiogram (ECG) without evidence of clinically meaningful conduction abnormalities or active ischemia as determined by the investigator</li> <li>Acceptable organ and marrow function as defined below: <ul style="list-style-type: none"> <li>Absolute neutrophil count (ANC) <math>&gt; 1,500</math> cells/<math>\mu</math>L</li> <li>Platelets <math>&gt; 50,000</math> cells/<math>\mu</math>L</li> <li>Total bilirubin <math>\leq 1.5</math> times (<math>\times</math>) the upper limit of normal (ULN)</li> <li>Aspartate aminotransferase (AST)/alanine aminotransaminase (ALT) <math>\leq 2.5 \times</math> ULN. If liver metastases are present, AST/ALT <math>&lt; 5 \times</math> ULN</li> <li>Creatinine clearance <math>\geq 50</math> mL/min using the Cockcroft-Gault formula</li> <li>Prothrombin time (PT)/partial thromboplastin time (PTT) <math>\leq 1.5 \times</math> ULN</li> </ul> </li> <li>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</li> </ol>		

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<p>the appropriate age, eg, greater than 45 years) must have a negative serum pregnancy test prior to first dose of study treatment</p> <p>11. Male and female patients with reproductive potential must agree to use two forms of highly effective contraception throughout the study</p> <p>12. Life expectancy of at least 3 months as determined by the investigator</p>		
<p><b>Exclusion Criteria:</b></p> <ol style="list-style-type: none"> <li>1. Prior receipt of stimulator of interferon genes (STING) agonist</li> <li>2. Prior receipt of therapeutic radiotherapy to all progressive lesions intended for PULSAR treatment</li> <li>3. Anti-cancer therapy, except pembrolizumab and nivolumab, within 4 weeks or &lt; 5 half-lives of the first dose of study treatment</li> <li>4. Existence of primary tumor that requires therapeutic treatment beyond the provided immune checkpoint inhibitor drug</li> <li>5. Failure to recover, to Grade 1 or less, from clinically significant AEs due to prior anti-cancer therapy, as judged by the investigator</li> <li>6. Previous life-threatening (Grade 4) immune-related adverse event (irAE)</li> <li>7. Known untreated brain metastases or treated brain metastases that have not been stable (scan showing no worsening of central nervous system [CNS] lesion[s] and no requirement of corticosteroids) <math>\geq 4</math> weeks prior to study enrollment</li> <li>8. Existence of actionable mutations that are eligible for a mutation-targeting drug that represents standard-of-care</li> <li>9. Baseline prolongation of QT/corrected QT (QTc) interval (QTc interval &gt; 470)</li> <li>10. 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 the opinion of the investigator would limit compliance with study requirements</li> <li>11. Women who are pregnant or breastfeeding</li> <li>12. Sponsor reserves the right to exclude any patient from the study on the basis of pre-study medical histories, physical examination findings, clinical laboratory results, prior medications, or other entrance criteria</li> </ol>		

<b>Sponsor:</b> ImmuneSensor Therapeutics	<b>Investigational Product:</b> IMSA101	<b>Developmental Phase:</b> Phase 2
<b>Test Products, Doses and Modes of Administration:</b>  <b>IMSA101:</b> 1 mL total volume IMSA101 will be administered via intra-tumoral injection every week for the first 3 weeks in Cycle 1 (Days 1, 8, and 15) followed by the first week only in Cycles 2 and Cycle 3 (Day 1).  <b>Immunotherapy:</b> PD-1-targeted agents (pembrolizumab or nivolumab) will be administered according to the US Food and Drug Administration (FDA)-approved product labels of the products. The initial ICI dose will be administered on Cycle 1 Day 2, then dosing will be according to the product labels.  <b>PULSAR:</b> 12 to 15.5 Gray (Gy) per pulse, per lesion given every 4 weeks (Day 1 of Cycles 1, 2, and 3) for a total of 3 pulses per lesion.		
<b>Number of Patients:</b>  Approximately 51 patients will be enrolled in the study: up to 12 patients in the safety run-in portion and approximately 39 patients in the randomized portion.  The total number of patients in each treatment arm will be as follows: a. Approximately 15 patients in the control arm (PULSAR-ICI) b. Approximately 30 patients in the experimental arm (PULSAR-ICI + IMSA101), including 24 randomized patients and 6 patients in the safety run-in who are treated at the dose level selected for the experimental arm		
<b>Estimated Study Duration:</b>  The estimated total duration of the study will be approximately 3 years.		
<b>Stopping Criteria:</b>  In the safety run-in period for the experimental arm, a DLT will be defined as the occurrence of any of the following hematologic or non-hematologic events that are 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 Version 5.0.  <u>Hematologic AEs</u> <ul style="list-style-type: none"> <li>• <math>\geq</math> Grade 4 neutropenia lasting for <math>&gt; 7</math> days</li> <li>• Febrile neutropenia (defined as <math>ANC &lt; 1000/mm^3</math> with a single temperature of <math>38.3^{\circ}C</math> [<math>101^{\circ}F</math>] or a sustained temperature of <math>38^{\circ}C</math> [<math>100.4^{\circ}F</math>] for <math>&gt; 1</math> hr)</li> <li>• <math>\geq</math> Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with Grade <math>\geq 2</math> bleeding</li> <li>• <math>\geq</math> Grade 4 anemia</li> </ul>		

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<p><b><u>Non-hematologic AEs:</u></b></p> <ul style="list-style-type: none"> <li>Elevation of ALT or AST by <math>\geq 3 \times \text{ULN}</math> with concurrent elevation of serum total bilirubin <math>\geq 2 \times \text{ULN}</math></li> <li>Any <math>\geq</math> Grade 3 non-hematologic AE of any duration will be considered a DLT with the following exceptions: <ul style="list-style-type: none"> <li>Nausea/vomiting/diarrhea: <ul style="list-style-type: none"> <li><math>\geq</math> Grade 3 nausea/vomiting/diarrhea must be refractory to supportive care and last <math>&gt; 3</math> days to be considered a DLT</li> <li><math>\geq</math> Grade 3 nausea/vomiting/diarrhea that lasts <math>\leq 3</math> days is not a DLT</li> </ul> </li> <li>Fatigue: <ul style="list-style-type: none"> <li><math>\geq</math> Grade 3 fatigue must last <math>&gt; 7</math> days to be considered a DLT</li> <li><math>\geq</math> Grade 3 fatigue that lasts <math>\leq 7</math> days is not a DLT</li> </ul> </li> </ul> </li> </ul>		
<p><b>Determination of Sample Size:</b></p> <p>The primary evaluation for efficacy is based on the proportion of patients remaining progression-free at 12 months after the start of the study treatment. The study is designed to enroll 45 patients. If the proportions of patients remaining progression-free at 12 months after commencement of therapy is assumed to be 20% in the control arm and 40% in the experimental arm, a total of 45 subjects (15 subjects in the control arm, 30 subjects in the experimental arm) will provide 53% power, assuming a two-sided hypothesis test with a significance level of 20%.</p>		

<b>Sponsor:</b> ImmuneSensor Therapeutics	<b>Investigational Product:</b> IMSA101	<b>Developmental Phase:</b> Phase 2
<b>Statistical Considerations:</b> <p>The primary efficacy analysis will be conducted on the ITT population, using the ITT principle. The number and proportion of subjects remaining progression-free at 12 months after the start of the study treatment will be descriptively summarized by treatment group and be compared using Fisher’s exact test with the type I error controlled at a two-sided significance level of 0.2. The null and alternative hypotheses regarding the proportion of subjects remaining progression-free at 12 months after the start of the study treatment can be phrased in terms of <math>P_E</math> and <math>P_C</math> for experimental arm and control arm, respectively:</p> $H_0: P_E = P_C \text{ versus } H_1: P_E \neq P_C.$ <p>In addition, for the descriptive purpose, the point estimate of proportion of subjects remaining progression-free at 12 months after the start of the study treatment and its 95% Clopper-Pearson confidence interval (CI) will be provided for each treatment group.</p> <p>The ORR via RECIST Version 1.1 and iRECIST will be presented with exact 2-sided 95% CIs using the Clopper-Pearson method. The TTP, PFS, and DOR will be estimated using Kaplan-Meier methods. Median event times and two-sided 95% CI for each median will be provided based on the Brookmeyer-Crowley method. AEs, and QoL parameters will be described using descriptive summary statistics.</p> <p>A futility analysis for the experimental arm is planned when the tenth (10<sup>th</sup>) patient treated at the selected dose level has had the opportunity to reach 6 months. If 7 out of 10 patients have progressed or died, the study will be declared futile.</p> <p>Additional details describing the statistical analysis will be described in the Statistical Analysis Plan (SAP).</p>		

**Table 1**      **Schedule of Assessments and Study Activities – Safety Run-in and Experimental Arm**

Procedures	Screening <sup>1</sup> Days -30 to 1	Cycle 1			Cycle 2	Cycle 3	Efficacy Assessments	ICI Cycles <sup>3</sup>	EOS <sup>4</sup>
Study Day		Days 1-2	Day 8 <sup>2</sup>	Day 15 <sup>2</sup>	Day 1 <sup>2</sup>	Day 1 <sup>2</sup>	C3D28 <sup>2</sup> + Q8W <sup>2</sup>		
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical History	X								
Concomitant Medications	X	X	X	X	X	X	X	X	X
Demographic data	X								
Height	X								
Vital signs, Weight	X	X <sup>16</sup>	X	X	X	X		X	X
Physical Examination <sup>5</sup>	X								X
ECOG Performance Status	X	X <sup>16</sup>	X	X	X	X		X	X
ECG <sup>6</sup>	X								X
Hematology <sup>7</sup>	X				X	X		X	X
Coagulation <sup>7</sup>	X								
Chemistry <sup>7</sup>	X				X	X		X	X
Thyroid function panel <sup>7</sup>	X					X <sup>17</sup>			
Urinalysis <sup>7</sup>	X								
Pregnancy test <sup>8</sup>	X								X
Tumor assessment using RECIST Version 1.1 and iRECIST <sup>9</sup>	X						X		X
PULSAR Administration <sup>10, 11</sup>		X			X	X			
IMSA101 Administration <sup>10, 12</sup>		X	X	X	X	X			
ICI Administration <sup>10, 13</sup>		X						X	
QoL Assessment (FACT-G) <sup>14</sup>	X						X		X
Assessment for AEs <sup>15</sup>		X	X	X	X	X	X	X	X

Abbreviations: AE: adverse event; C: cycle; CRF: case report form; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOS: end of study; FACT-G: Functional Assessment of Cancer Therapy–General; Gy: Gray; hr: hour; ICI: Immune Checkpoint Inhibitor; iRECIST: immune-based Response

Evaluation Criteria in Solid Tumors PD: pharmacodynamics; PULSAR: personalized ultra-fractionated stereotactic adaptive radiotherapy; QXW: every X weeks; QoL: Quality of Life; RECIST: Response Evaluation Criteria in Solid Tumors.

- <sup>1</sup> All assessments and tests at the screening visit must be completed before the patients start receiving the study treatment.
- <sup>2</sup> A  $\pm 3$  days visit window is allowed for C1D8 and C1D15 visits. A  $\pm 5$  days window is allowed for Cycles 2 and 3 start dates. A  $\leq 7$  window is allowed for C3D28, and  $\pm 7$  days for every 8 weeks (Q8W) efficacy assessments.
- <sup>3</sup> ICI will be administered per product labels. The cycle duration will depend on the ICI regimen which will follow the product labels. Vital signs, laboratory, ECOG, concomitant medication, and AE assessments are to be completed at the ICI treatment time points.
- <sup>4</sup> All patients will receive study treatment until the occurrence of disease progression (by iRECIST), death, or other unacceptable treatment-related toxicity, or until the study is closed by the sponsor. Before discontinuing the study, patients should make all efforts to return to the study site at the EOS visit for the final assessments.
- <sup>5</sup> Full physical examinations will be done at screening and EOS visit only; clinically relevant findings made after the start of study treatment, which meet the definition of an AE, must be recorded on the AE page of the eCRF.
- <sup>6</sup> ECGs will be performed at screening and at EOS visit only, or at visits where the investigator believes the assessment is indicated.
- <sup>7</sup> Clinical laboratory analyses will be performed by local laboratory and include hematology, coagulation, serum chemistry, thyroid function panel, and urinalysis. Creatinine clearance will be measured at screening only. Laboratory tests at screening must be performed  $\leq 96$  hr prior to C1D1. Refer to [Section 6.4.5](#) for details.
- <sup>8</sup> If the patient is a woman of childbearing potential, a serum pregnancy test must be performed at screening and at EOS.
- <sup>9</sup> All tumor assessment findings will be evaluated according to RECIST Version 1.1 ([Appendix 13.2](#)) and iRECIST ([Appendix 13.3](#)). Tumor assessments will include radiographic assessments at screening, at the end of Cycle 3 ( $\leq 7$  days of C3D28), thereafter every 8 weeks ( $\pm 7$  days), and EOS visit. In certain circumstances, a patient experiencing RECIST progression of disease will be allowed to continue therapy on study unless confirmed progression by iRECIST.
- <sup>10</sup> For safety run-in and experimental arm patients, the treatment order is PULSAR first, followed by IMSA101, and then followed by ICI on applicable visits. All treatments can be given on the same day on C1D1 in this order, or on consecutive days as follows: PULSAR will be administered first on Day 1 of Cycles 1, 2, and 3, followed by IMSA101 on the same day or the day after. The initial ICI dose will be administered on the same day as IMSA101 or the day after (C1D2 [ $\pm 1$  day]), and then dosing will be according to the product labels thereafter.
- <sup>11</sup> PULSAR will be administered at a dose of 12-15.5 Gy per pulse/lesion on Day 1 of Cycles 1, 2 and 3 as outlined in [Section 8.1](#). A simulation visit may be performed prior to each PULSAR treatment, as appropriate.
- <sup>12</sup> IMSA101 will be administered by intra-tumoral injection on Days 1 (+1 day), 8 and 15 of Cycle 1 (ie, weekly dosing in the first 3 weeks of the 28-day/4-week cycle), and on Day 1 (+1 day) of Cycles 2 and 3. For Cycle 1 Day 8 and Cycle 1 Day 15, visits are relative to the first IMSA101 dose to maintain the weekly dosing frequency and should be administered no less than 4 days apart.
- <sup>13</sup> ICI (pembrolizumab or nivolumab) will be administered on Cycle 1 Day 2 ( $\pm 1$  day), and thereafter according to the product labels (nivolumab Q2W or Q4W, pembrolizumab Q3W or Q6W treatment schedule).

- <sup>14</sup> FACT-G QoL assessment to be completed using FACT-G questionnaire at screening, at the end of Cycle 3 ( $\leq 7$  days of C3D28), then every 8 weeks thereafter ( $\pm 7$  days), and EOS visit.
- <sup>15</sup> AE reporting begins from the start of study treatment and continues until EOS.
- <sup>16</sup> C1D1 assessments prior to dosing must be performed within 96 hr prior to C1D1.
- <sup>17</sup> C3D1 only and as clinically indicated for the remainder of the study.

**Table 2**      **Schedule of Assessments and Study Activities – Control Arm**

Procedures	Screening <sup>1</sup> Days -30 to 1	Cycle 1	Cycle 2	Cycle 3	Efficacy Assessments	ICI Cycles <sup>3</sup>	EOS <sup>4</sup>
Study Day		Days 1-2	Day 1 <sup>2</sup>	Day 1 <sup>2</sup>	C3D28 <sup>2</sup> + Q8W <sup>2</sup>		
Informed Consent	X						
Inclusion/Exclusion Criteria	X						
Medical History	X						
Concomitant Medications	X	X <sup>15</sup>	X	X	X	X	X
Demographic data	X						
Height	X						
Vital signs, Weight	X	X <sup>15</sup>	X	X		X	X
Physical Examination <sup>5</sup>	X						X
ECOG Performance Status	X	X <sup>15</sup>	X	X		X	X
ECG <sup>6</sup>	X						X
Hematology <sup>7</sup>	X		X	X		X	X
Coagulation <sup>7</sup>	X						
Chemistry <sup>7</sup>	X		X	X		X	X
Thyroid function panel <sup>7</sup>	X			X <sup>16</sup>			
Urinalysis <sup>7</sup>	X						
Pregnancy test <sup>8</sup>	X						X
Tumor assessment using RECIST Version 1.1 and iRECIST <sup>9</sup>	X				X		X
PULSAR Administration <sup>10, 11</sup>		X	X	X			
ICI Administration <sup>10, 12</sup>		X				X	
QoL Assessment (FACT-G) <sup>13</sup>	X				X		X
Assessment for AEs <sup>14</sup>		X	X	X	X	X	X

Abbreviations: AE: adverse event; C: cycle; CRF: case report form; D: day; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; EOS: end of study; FACT-G: Functional Assessment of Cancer Therapy – General; Gy: Gray; hr: hour; ICI: Immune Checkpoint Inhibitor; iRECIST: immune-based Response Evaluation Criteria in Solid Tumors PD: pharmacodynamics; PULSAR: personalized ultra-fractionated stereotactic adaptive radiotherapy; QXW: every X weeks; QoL: Quality of Life; RECIST: Response Evaluation Criteria in Solid Tumors.

- 1 All assessments and tests at the screening visit must be completed before the patients start receiving the study treatment.
- 2 A  $\pm 5$  days window is allowed for Cycles 2 and 3 start dates. A  $\leq 7$  window is allowed for C3D28 and  $\pm 7$  days for every 8 weeks (Q8W) efficacy assessments.
- 3 ICI will be administered per product labels. The cycle duration will depend on the ICI regimen which will follow the product labels. Vital signs, laboratory, ECOG, concomitant medication, and AE assessments are to be completed at the ICI treatment time points.
- 4 All patients will receive study treatment until the occurrence of disease progression (by iRECIST), death, or other unacceptable treatment-related toxicity, or until the study is closed by the sponsor. Before discontinuing the study, patients should make all efforts to return to the study site at the EOS visit for the final assessments.
- 5 Full physical examinations will be done at screening and EOS visit only; clinically relevant findings made after the start of study treatment, which meet the definition of an AE, must be recorded on the AE page of the eCRF.
- 6 ECGs will be performed at screening and at EOS visit only, or at visits where the investigator believes the assessment is indicated.
- 7 Clinical laboratory analyses will be performed by local laboratory and include hematology, coagulation, serum chemistry, thyroid function panel, and urinalysis. Creatinine clearance will be measured at screening only. Laboratory tests at screening must be performed  $\leq 96$  hr prior to C1D1. Refer to [Section 6.4.5](#) for details.
- 8 If the patient is a woman of childbearing potential, a serum pregnancy test must be performed at screening and at EOS.
- 9 All tumor assessment findings will be evaluated according to RECIST Version 1.1 ([Appendix 13.2](#)) and iRECIST ([Appendix 13.3](#)). Tumor assessments will include radiographic assessments at screening, at the end of Cycle 3 ( $\leq 7$  days of C3D28), thereafter Q8W ( $\pm 7$  days), and EOS visit. In certain circumstances, a patient experiencing RECIST progression of disease will be allowed to continue therapy on study unless confirmed progression by iRECIST.
- 10 For the control arm, the treatment order is PULSAR first on C1D1, then followed by ICI on the same day or the day after (C1D2). Subsequent ICI dosing will be according to product label.
- 11 PULSAR will be administered at a dose of 12-15.5 Gy per pulse/lesion on Day 1 of Cycles 1, 2 and 3 as outlined in [Section 8.1](#). A simulation visit may be performed prior to each PULSAR treatment, as appropriate
- 12 ICI (pembrolizumab or nivolumab) will be administered on Cycle 1 Day 2 (-1 day), and thereafter according to the product labels (nivolumab Q2W or Q4W, pembrolizumab Q3W or Q6W treatment schedule).
- 13 FACT-G QoL assessment to be completed using FACT-G questionnaire at screening, at the end of Cycle 3 ( $\leq 7$  days of C3D28), then every 8 weeks thereafter ( $\pm 7$  days), and EOS visit.
- 14 AE reporting begins from the start of study treatment and continues until EOS.
- 15 C1D1 assessments prior to dosing must be performed within 96 hr prior to C1D1.
- 16 C3D1 only and as clinically indicated for the remainder of the study.

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## LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
3D	three-dimensional
AE	adverse event
ALT	alanine aminotransferase
AMP	adenosine monophosphate
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC <sub>0-inf</sub>	area under the plasma concentration-time curve from time zero to infinity
AUC <sub>0-t</sub>	area under the plasma concentration-time curve from time zero to time t
C1D1	Cycle 1 Day 1
CBC	complete blood count
CCL2	chemokine (C-C motif) ligand 2
CD	cluster of differentiation
CDN	cyclic dinucleotide
CFR	Code of Federal Regulations
cGAMP	cyclic-GMP-AMP
cGAS	cyclic GMP-AMP synthase
CI	confidence interval
cm	centimeter
CNS	central nervous system
COMPTV	center of mass of Planning Treatment Volume
COVID-19	coronavirus disease 2019
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DC	Dendritic cells
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of treatment response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDTA	ethylenediaminetetraacetic acid
EOS	End of Study
FACT-G	Functional Assessment of Cancer Therapy - General
FAS	Full analysis set

Abbreviation	Definition
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	guanosine monophosphate
GTV	Gross Tumor Volume
Gy	Gray
HIPAA	Health Insurance Portability and Accountability Act
hr	hour
IB	Investigator's Brochure
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
IO	immuno-oncology
IL	interleukin
IMRT	Intensity Modulated Radiation Therapy
INR	international normalization ratio
IP-10	interferon- $\gamma$ -induced protein 10
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	Immune-based Response Evaluation Criteria in Solid Tumors
ITT	Intention-to-Treat
IUD	intrauterine device
kg	kilogram
kV	kilovolt
LC-MS/MS	liquid chromatography–tandem mass spectrometry
MCP-1	monocyte chemoattractant protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MV	megavoltage
NHP	non-human primate
NSCLC	non-small cell lung cancer
ORR	overall response rate

Abbreviation	Definition
OS	overall survival
PD	pharmacodynamics
PD-1	programmed cell death 1
PDF	portable document format
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PPS	Per protocol set
PT	prothrombin time
PTT	partial thromboplastin time
PTV	Planning Treatment Volume
PULSAR	Personalized Ultra-fractionated Stereotactic Adaptive Radiotherapy
QoL	quality of life
QTc	corrected QT
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
RT	radiation therapy
SAbR	stereotactic ablative radiotherapy
SAE	serious adverse event
SAF	Safety analysis set
SAP	statistical analysis plan
SD	standard deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SRC	Safety Review Committee
STING	stimulator of interferon genes
SUSAR	suspected unexpected serious adverse reaction
T3	tri-iodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
TILs	tumor-infiltrating leukocytes
TNF- $\alpha$	tumor necrosis factor- $\alpha$
TRAE	treatment-related adverse event
TSH	thyroid-stimulating hormone
TTP	time-to-progression
ULN	upper limit of normal

Abbreviation	Definition
US	United States
USP	United States Pharmacopeia
WBC	white blood cell
WMA	World Medical Association

# 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, treatments with cytotoxic chemotherapy and targeted kinase inhibitors lead to the emergence of drug-resistant tumor clones and subsequent tumor progression and metastasis.

Oligoprogressive disease is a relatively new clinical concept and is described as disease progression at a limited number of sites of metastasis occurring following an initial response to systemic treatment in patients with otherwise controlled widespread disease. The optimal approach to the management of this disease state is not yet established ([Patel et al., 2019](#)).

In recent years, notable treatment success has been achieved through alternate approaches oriented around activation of immune-mediated tumor destruction. Immuno-oncology (IO) approaches, including antibodies against checkpoint proteins, have shown remarkable efficacy in several types of human cancers. However, existing cancer immunotherapy through immune checkpoint blockade is effective for only a small fraction (on average 20-30%) of cancer patients. The patients who are refractory to immune checkpoint blockade often have tumors that are not inflamed, or so-called “cold” tumor cells, ie, 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 ([Bonaventura et al., 2019](#); [Liu and Sun, 2021](#)).

Radiation therapy (RT) aims to increase tumor control while sparing healthy tissue. RT induces tumor-cell killing by creating deoxyribonucleic acid (DNA) lesions and it also induces an anti-tumor immune response by enhancing the immunogenicity of tumors and stimulating the accumulation and activation of CD8+ T cells. RT is able to enhance the immunogenicity of tumors by activating the immune system when combined with immune checkpoint inhibitors (ICIs). Studies combining RT with ICIs suggest a synergistic potential of this strategy ([Boustani et al., 2021](#)). Stereotactic ablative radiotherapy (SAbR), also known as stereotactic body RT (SBRT), is a modern high focus radiation technique that delivers high doses of radiation to small tumor targets while conforming the dose to the target tissue.

Combination therapy has been shown to be no more toxic than ICI monotherapy in metastatic non-small cell lung cancer (NSCLC) according to retrospective analysis and limited published prospective trials. Studies delivering SAbR concurrently with immunotherapies have commonly shown good toxicity profiles. A pooled analysis of two Phase 1/2 trials examining single site SAbR + pembrolizumab vs. pembrolizumab alone demonstrated overall survival (OS) benefit with SAbR + pembrolizumab ([Akanda et al., 2021](#)). Advanced disease progression most often occurs in original sites of disease. Early intervention with SAbR at the localized disease potentially improved progression-free survival (PFS) and OS compared with maintenance chemotherapy alone ([Iyengar et al., 2018](#)). SAbR is thought to induce a pro-immunogenic response in the tumor microenvironment and has the capacity to

potentially turn a “cold” unresponsive tumor “hot” and receptive to further ICI treatment (Akanda et al., 2021).

A few retrospective studies were performed to shed light on the role of ICI treatment and local therapy in treating oligoprogressive sites. In a retrospective analysis at a single institution between 2011 and 2017 (Sindhu et al., 2020), patients with advanced solid tumors (excluding glioblastoma multiforme) were treated with ICIs. Out of the 16 patients who experienced oligoprogression (defined as progression at  $\leq 3$  metastatic lesions outside of the brain after achieving at least stable disease on ICIs for 3 months), 15 patients received local therapy (including RT and surgical resection). At a median follow-up of 25.8 months, the oligoprogressive patients showed a median second PFS (defined as the time from the end of local therapy to second progression or death from any cause) of 15.4 months. This indicated that applying local therapy to oligoprogressive sites may result in durable disease control. These findings were reiterated in a second retrospective analysis of 208 Stage IV NSCLC patients who underwent ICI treatment and suffered disease progression after a stable disease state on immunotherapy for more than 3 months. Most of the patients in the oligoprogression group were treated with local RT combined with continued ICIs (33.0%) and they showed significantly longer second PFS (defined as the time from the first cycle of immunotherapy to the second progression or death) and OS (Xu et al., 2021).

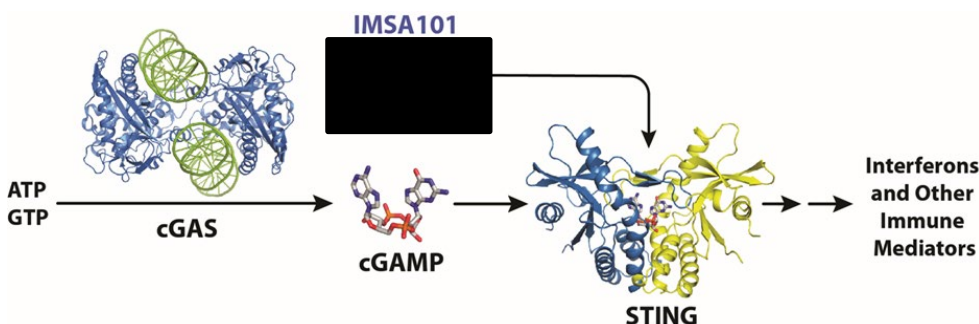
The use of RT as ablative treatment is an appealing treatment option for patients experiencing resistance before resorting to a change in the systemic treatment which in many cases is the standard procedure at the onset of oligoprogressive disease (Onal et al., 2021, Patel et al., 2019, Bahig et al., 2022). A retrospective study showed that the treatment of oligoprogressive lesions in lymph nodes or bones with SBRT extended the patients’ current systemic therapies for a median of 8.6 months (Onal et al., 2021). In another retrospective study, patients with oligoprogressive prostate cancer who underwent SBRT had prolonged ongoing systemic therapy with a median time to systemic treatment-free survival of 15.2 months (Franzese et al., 2022). Similarly, patients with oligoprogressive castration-resistant prostate cancer who had a second course of SBRT had a median time to systemic treatment-free survival of 21.8 months (Triggiani et al., 2019).

RT (including SAbR) has been a “one-size” therapy based mostly on histology, stage, and tumor location. RT is historically delivered in a single course without interruption. “Booster cycles” are commonly used in conventional vaccines to generate long-term memory and immunity. The use of pulsed-RT involving repeated RT cycles has the potential to build on the concept of “booster cycles” by generating tumor-associated antigens with each treatment cycle to build cellular and humoral memory leading to the production of long-lived immune memory cells, which could be amplified by the addition of immunotherapy (He et al., 2021).

Personalized Ultra-fractionated Stereotactic Adaptive Radiotherapy (PULSAR) is a variation of stereotactic radiotherapy with longer, infrequent intervals between treatment fractions compared to daily fractions in the conventional schedules. This method activates the immune system but avoid the potentially immunosuppressive effect from SAbR. The advantages of PULSAR include: 1) the interval between each pulse can be irregular, episodic, or triggered, depending on the response profile for each individual patient and can elicit additional tumor kill as well as an *in situ* vaccination booster, which, in combination with systemic

immunotherapy, can synergize and improve disease control; 2) each radiotherapy pulse can be adapted in real time, depending on changes with the patient and disease status (eg, anatomy, tumor microenvironment, systemic markers, patient status); 3) radiotherapy can be continued as needed until the tumor is eradicated or becomes a chronic, manageable disease.

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 Guanosine monophosphate (GMP)-Adenosine monophosphate (AMP) Synthase (cGAS)-Stimulator of Interferon Genes (STING) pathway plays a critical role in anti-tumor immunity. cGAS is a DNA sensing enzyme that activates the type 1 interferon (IFN) 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 1 IFNs, cytokines, and other immune mediators, which are essential for mounting immune response to invading microbials, as well as malignancies (Figure 1). There is increasing evidence that the cGAS pathway is essential for generating anti-tumor immunity (Bose, 2017; Wang et al., 2017).



**Figure 1 The cGAS-cGAMP-STING Pathway**

Cytosolic DNA binds to and activates the enzyme cGAS, which then catalyzes the synthesis of 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 1 IFNs and other immune stimulatory molecules. IMSA101 is an analogue of cGAMP and directly stimulates STING.

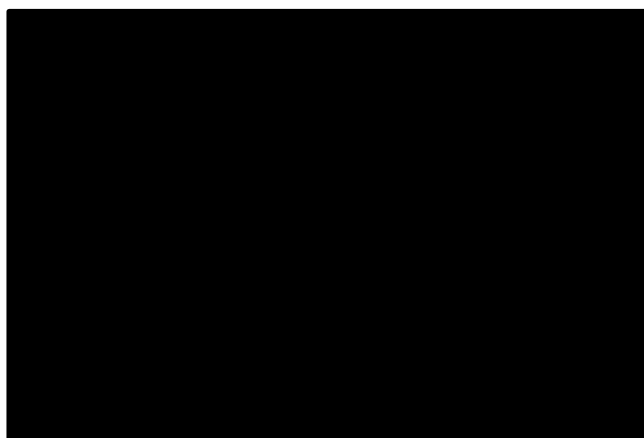
As expected, surviving tumor cells develop mechanisms to antagonize host immunity. For example, high expression of immune checkpoint molecules such as programmed cell death ligand 1 (PD-L1) on their cell surface bind programmed cell death 1 (PD-1) on T cells to inhibit the latter’s function. PD-L1 inhibitor therapy can reverse the inhibition of anti-tumor immunity and restore T cell function. However, in patients with very low anti-tumor immunity, the PD-L1 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 anti-tumor immunity. This activity has demonstrated encouraging therapeutic efficacy in several mouse syngeneic tumor models (Li et al., 2016; Wang et al., 2017).

## 1.2 STUDY DRUG – IMSA101

IMSA101 is a small molecule analogue of cGAMP. It contains



The drug product (IMSA101 for Injection) is a sterile and nonpyrogenic solution containing 5 mg of IMSA101 in 1.0 mL of which is used for intra-tumoral injection.



**Figure 2** Chemical Structure of IMSA101 for Injection

## 1.3 NONCLINICAL STUDIES

Nonclinical studies showed that IMSA101 induces an innate immune response in cells from multiple species with comparable potency, supporting the translation of therapeutic efficacy from mouse to human. Suppression of tumor growth and improved survival, without the induction of high cytokine levels, were observed in multiple mouse tumor models, including those tumors resistant to PD-L1 antibody upon subcutaneous or intra-tumoral administration of IMSA101 alone or in combination with PD-L1 antibody, thus supporting the use of IMSA101 on a broad range of cancers that are refractory to immune checkpoint antibody therapies. Moreover, an abscopal effect (an immune-mediated phenomenon wherein direct treatment of a primary tumor can lead to a response in a distant tumor) was observed in 2 studies using IMSA101 on B16 melanoma model in which the sizes of non-injected tumors decreased, survival was prolonged, and lung metastases was reduced. In addition, safety pharmacology studies demonstrated that IMSA101 does not affect cardiovascular function in *in vitro* system and monkeys.

In multiple syngeneic tumor models, the combination of a PD-L1 antibody with IMSA101 showed higher efficacy as compared to IMSA101 alone at each dose level tested in the range from 0.1 mcg to 10 mcg. This included restored responsiveness to PD-L1 antibody in several types of syngeneic tumors which were otherwise refractory to ICIs. These studies provide a rationale for evaluating combination therapy in clinical settings.

The toxicological evaluations of IMSA101 included studies in the rat and non-human primate (NHP). These species were chosen based on the conservation of the STING pathway ([Harrington et al., 2018](#)) and on the similar immune responses to IMSA101 noted in *in vitro* studies using mouse, rat, monkey and human cells. 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 IFNs and proinflammatory cytokines. The findings were similar in the rat and NHP. The most consistent dose-related findings were increases in IFN- $\alpha$ , tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukin (IL)-6 in the rat and monkey; IL-8 in the rat; IL-1ra, IFN- $\gamma$ -inducible protein 10 (IP-10), and monocyte chemoattractant protein (MCP-1) in the monkey. The cytokine levels showed increases in the first 3-6 hours (hr) with return to baseline in most cases by 6-24 hr.

The evaluations of the PK, including the absorption, protein binding, and metabolic stability of IMSA101 in mouse, rat, and monkey were conducted. These studies are described in detail in the Investigator's Brochure (IB) ([Version 5.0, 2024](#)).

In summary, the PK parameters of IMSA101 were estimated following administration by intravenous, subcutaneous, or intra-tumoral routes in mice at doses of 0.1 or 0.5 mg/kg. IMSA101 concentrations in plasma were measured using a qualified liquid chromatography – tandem mass spectrometry (LC-MS/MS) method. The calculated, dose corrected area under the plasma concentration-time curves from time zero to time t ( $AUC_{0-t}$ ) were similar by each route. When administered at the dose of 0.5 mg/kg, the area under the plasma concentration-time curve from time zero to infinity ( $AUC_{0-inf}$ ) 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 of the subcutaneous dose was 1.21. The  $AUC_{0-inf}$  of the intra-tumoral 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 of the intra-tumoral 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 intra-tumoral dose routes provided a rationale for using the subcutaneous route of administration in the toxicology studies to approximate the intra-tumoral route that will be used in the clinical studies.

A detailed description of the chemistry, pharmacology, efficacy, and safety of IMSA101 is provided in the IB ([Version 5.0, 2024](#)).

In addition to the monotherapy data referenced above, there now exists a growing body of published pre-clinical research supporting the benefit of combining radiotherapy (RT) with immune checkpoint inhibitors (ICI) or STING agonists in the treatment of solid tumor

malignancies. Combinations of RT with cGAMP, the endogenous STING agonist, appear to synergize to completely reverse tumor growth and lead to complete survival of tested animals in an MC38 colorectal tumor model. Observed efficacy further appears to depend on STING agonism in a proportional fashion. Other published studies demonstrate that with an MC38 model, the combination of PD-L1 antibody and RT (in a PULSAR schedule) generates more robust and long-lasting anti-tumor response than IO alone. In addition to these published studies, our internal ImmuneSensor data with IMSA101 + RT in a B16 melanoma tumor model demonstrate that, in contrast to either monotherapy agent alone, the combination of IMSA101 and RT not only reverses growth of directly treated tumors but also generates considerable abscopal effect at distal tumors.

## 1.4 CLINICAL EXPERIENCE

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 (CDNs) 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. These desired pharmacological effects were achieved at dose levels without dose-limiting toxicities ([Harrington et al., 2018](#); [Meric-Bernstam et al., 2018](#)).

IMSA101 was evaluated both as monotherapy and in combination with ICI in a first-in-human Phase 1/2a clinical trial at six cancer centers in the United States (US) (Protocol number: IMSA101-101, NCT04020185). This trial was an open-label, dose escalation (Phase 1), and dose expansion (Phase 2a) study of patients receiving IMSA101 alone or in combination with an ICI with the primary objective to establish safe recommended Phase 2 doses (RP2Ds) of IMSA101. Patients older than 18 years old with histologically or cytologically documented locally advanced or metastatic solid tumor malignancies refractory to or otherwise ineligible for treatment with standard of care agents/regimens are enrolled. IMSA101 at 100, 200, 400, 800, and 1200 mcg in 1 mL total volume are administered as monotherapy to the patients by intra-tumoral injection every week for 3 weeks in Cycle 1 (Days 1, 8, and 15) followed by every other week from Cycles 2 onwards (Days 1 and 15). For combination treatment regimen, IMSA101 up to 800, 1200, and 2400 mcg in 1 mL total volume plus current ICI therapy administered according to the product label was administered to the patients by intra-tumoral injection. Dose priming was applied in Cycle 1 Day 1 (C1D1) for dose of 2400 mcg.

To date, IMSA101 has been studied as a single agent and in combination with PD-1 and PD-L1 inhibitors for solid tumors in NSCLC, breast cancer, prostate cancer, colorectal cancer, cecal adenocarcinoma, head and neck cancer, pancreatic cancer, melanoma, mesothelioma, triple-negative breast cancer, ampullary cancer, uveal melanoma, neuroendocrine pheochromocytoma paraganglioma, and renal cell carcinoma.

Based on the safety results from the Phase 1/2a study, IMSA101 in the dose escalation monotherapy treatment was generally safe and well tolerated. The majority of patients (21 patients [95.5%]) reported at least 1 treatment-emergent adverse event (TEAE). The most frequently reported TEAEs by preferred term across all dose levels were fatigue (11 patients

[50.0%]); injection site pain (8 patients [36.4%]); nausea (5 patients [22.7%]); dyspnea, decreased appetite and headache (each in 4 patients [18.2%]). All other preferred terms were each reported by  $\leq 3$  patients (13.6%). Nine serious adverse events (SAEs) have been reported for 6 patients, of which 3 SAEs were fatal. None of the SAEs or deaths were assessed by the investigator as related to IMSA101. A detailed description of the safety results of the ongoing IMSA101-101 study is provided in the IB ([Version 5.0, 2024](#)).

In the combination treatment in the Phase 1/2a study, data demonstrate favorable tolerability through 2400 mcg. All 18 patients reported at least 1 TEAE. The most frequently reported TEAEs across all dose levels was fatigue (9 patients [50.0%]); decreased appetite and dyspnea (each in 8 patients [44.4%]); abdominal pain, constipation, cough, headache, pyrexia and vomiting (each in 6 patients [33.3%]); chills, diarrhea and nausea (each in 5 patients [27.8%]); asthenia, injection site pain and myalgia (each in 4 patients [22.2%]). All other preferred terms were reported in  $\leq 3$  patients (16.7%) each. One patient experienced a dose limiting toxicity (DLT) of Grade 3 immune arthropathy in the 1200 mcg cohort. The event was considered to be possibly related to IMSA101 and possibly related to the PD-1 immune checkpoint inhibitor pembrolizumab. Eleven patients reported SAEs, of which none were fatal. One SAE (Grade 3 immune arthropathy) was considered possibly related to IMSA101.

In summary, IMSA101 has been evaluated at dose levels up to 1200 mcg as monotherapy and 2400 mcg in combination with PD-1 targeted immune checkpoint inhibitors. 1200 mcg (3/4 weeks followed by bi-weekly thereafter) was identified as the provisional monotherapy recommended phase 2 dose (RP2D) based on cytokine/PD and PK data. Of note is that both  $C_{\max}$  and AUC levels, as well as cytokine levels in response to dosing, increased in a dose proportional manner.

Based on the totality of monotherapy and combination therapy data evaluated to-date, triplet dosing of IMSA101 administered in combination with both PD-1 checkpoint inhibitor therapy and pulsed radiotherapy will commence in a safety run-in to this Phase 2 randomized clinical trial at 800 mcg. Depending on the safety data observed, either 800 mcg or 1200 mcg will most likely be brought into the randomized component of this study.

## 1.5 SUMMARY OF KNOWN RISKS AND BENEFITS

A more detailed description of anticipated risks associated with IMSA101 nonclinical studies and clinical trials evaluating other STING agonists is provided in Section 6.6 of the IB ([Version 5.0, 2024](#)).

A summary of adverse events (AEs) based on preliminary safety results from the dose escalation monotherapy cohorts in the ongoing trial IMSA101-101 is provided in Section 5.3.2 of the IB ([Version 5.0, 2024](#)).

Briefly, the following risks may reasonably be anticipated in clinical trials evaluating the study treatments (PULSAR, IMSA101, and ICI):

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
<b>Study Treatment</b>		
<b>PULSAR</b>	Complications associated with SAbR may include radiation pneumonitis, brachial plexopathy, gastritis, toxicity in the chest wall, skin, airway, esophagus, and bowel (Lo et al., 2013; Siva et al., 2018). The risk of dosing error is rare.	PULSAR will be performed by qualified and trained personnel only. A treatment plan with dose calculations will be applied individually. The organs will be contoured individually. Dose constraint guidelines used in prior national protocols are included in this study.
<b>IMSA101</b> <ul style="list-style-type: none"> <li>• Body temperature increases (fever)</li> <li>• Chills</li> <li>• Alterations in serum chemistries</li> <li>• Altered serum hematology parameters</li> <li>• Headache</li> <li>• Injection site pain</li> <li>• Vomiting</li> <li>• Fatigue</li> <li>• Myalgia</li> <li>• Diarrhea</li> <li>• Decreased appetite</li> <li>• Dyspnea</li> </ul>	Based on nonclinical findings with IMSA101 and toxicity events reported in clinical trials evaluating other STING agonists (IB Section 6.6 “Anticipated Clinical Risks”)	<p>AE assessments will be performed throughout the study.</p> <p>Clinical laboratory assessments will be performed at the same frequency as the study treatment.</p>
<b>ICI</b> Potential severe or fatal immune-related adverse events (irAE), laboratory abnormalities, and other adverse reactions	Some patients in this study will be treated with a combination of IMSA101 and the ICIs nivolumab or pembrolizumab. ICIs are associated with a variety of irAEs which arise from general immunologic enhancement. These side effects can include skin, gastrointestinal, liver,	Prompt recognition and management will be performed throughout the study. The irAEs are generally managed through interruption of the ICI and temporary immunosuppression with corticosteroids and other drugs. The prescribing information and specific risks associated with particular ICIs used in this study will be discussed by

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	endocrine/hormonal, and other less common inflammatory events. Although extremely rare, fulminant and even fatal side effects can occur with ICIs.	investigators with their patients and referenced during informed consent.
<b>Study Procedures</b>		
Blood draw for clinical laboratory tests	The procedure of blood draw involves insertion of an intravenous needle. This may cause pain, tenderness, bruising, bleeding, dizziness, vasovagal response, syncope, and in rare occasion, infection at the site where the needle is inserted.	Blood draw will be performed by appropriately trained and qualified personnel.
Intralesional (cutaneous) or percutaneous injection	Complications of intralesional injection may include hematoma, hemorrhage, infection, needle tract seeding, systemic air embolism, and pneumothorax ( <a href="#">Gillams 2005</a> ).	Intralesional injections will be performed by appropriately trained and qualified personnel. All invasive procedures will be performed at the study site with medical treatment available promptly whenever necessary.

Benefits to individual participants receiving IMSA101 may include:

- Receive treatment which potentially has enhanced anti-tumor activity
- Contribute to the process of developing a new treatment for patients with advanced cancer and with limited therapeutic options.
- Access to medical assessments associated with study procedures (eg, laboratory evaluations, quality of life [QoL], disease progression)

Taking into account the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with IMSA101 are justified by the anticipated benefits that may be afforded to patients with oligoprogressive solid tumor malignancies.

## 1.6 RATIONALE FOR THE STUDY

The immune system plays a pivotal role in defending humans and animals against cancer. Cancer cells accumulate mutations encoding neoantigens that are recognizable by immune

system. In addition, they are constantly under stresses that result from chromosomal abnormality, genomic DNA damage, and hyperproliferation, which promotes the detection of their neoantigens by immune system. However, under selective pressure, cancer cells develop mechanisms to evade immunosurveillance. For example, tumors are able to foster an immunosuppressive microenvironment by hijacking the immune checkpoint signaling. ICI therapy has made a rapid progress recently and shown remarkable efficacies in clinics. Despite great successes, ICI is only effective in treating approximately 20% of cancer patients. Therefore, novel therapies that can better harness the immune system and benefit the majority of cancer patients is in urgent need.

The purpose of this study is to compare the safety and efficacy of a novel combination therapy PULSAR + ICI (pembrolizumab or nivolumab) administered with or without IMSA101 in patients with oligoprogressive solid tumor malignancies.

## 2 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
<b>Primary</b>	
Estimate progression-free rate at 12 months after commencement of therapy, separately for PULSAR-ICI + IMSA101 and PULSAR-ICI alone	<ul style="list-style-type: none"> <li>Proportion of patients remaining progression-free at 12 months after commencement of therapy</li> </ul>
<b>Secondary</b>	
Characterize the safety and tolerability of PULSAR-ICI + IMSA101 and compare with PULSAR-ICI alone	<ul style="list-style-type: none"> <li>Occurrence of treatment-emergent adverse events (TEAEs), Grade <math>\geq 3</math> TEAEs, and SAEs</li> </ul>
Estimate progression-free at 8-week intervals from 6 months to 22 months after commencement of therapy	<ul style="list-style-type: none"> <li>Proportion of patients remaining progression-free at 8-week intervals from 6 months to 22 months after commencement therapy</li> </ul>
Estimate time-to-progression (TTP) for PULSAR-ICI + IMSA101 and PULSAR-ICI alone	<ul style="list-style-type: none"> <li>Overall TTP as defined by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 and by Immune-based Response Evaluation Criteria in Solid Tumors (iRECIST)</li> </ul>
Estimate anti-tumor efficacy for PULSAR-ICI + IMSA101 and PULSAR-ICI alone using additional efficacy endpoints	<ul style="list-style-type: none"> <li>Overall response rate (ORR) as defined by RECIST Version 1.1 and by iRECIST</li> <li>Duration of treatment response (DOR) per RECIST Version 1.1 and iRECIST</li> <li>PFS per RECIST Version 1.1 and iRECIST</li> </ul>
Assess QoL benefit	<ul style="list-style-type: none"> <li>Patients reported outcome on QoL using the Functional Assessment of Cancer Therapy – General (FACT-G) questionnaire (Version 4)</li> </ul>

## 3 STUDY DESIGN

### 3.1 STUDY DESIGN OVERVIEW

This is an open-label, multicenter, Phase 2 randomized study comparing the safety and efficacy of PULSAR combined with ICI immunotherapy (PULSAR-ICI) + IMSA101 and PULSAR-ICI alone in patients with oligoprogressive solid tumor malignancies after prior anti-cancer therapy.

- For all potential patients, there will be up to a 30-day screening and eligibility assessment period prior to enrollment.
- Pre-treatment screening radiographic tumor assessments will be collected within 30 days prior to the initial dose for all patients.
- Patients shall be enrolled in 2 treatment arms as follows:
  - a. Approximately 15 patients in the control arm (PULSAR-ICI alone)
  - b. Approximately 30 patients in the experimental arm (PULSAR-ICI + IMSA101)
- The study will start with a safety run-in portion for the experimental arm, followed by a randomized portion for both treatment arms.
- Randomization will not be masked nor stratified.
- PULSAR-ICI with or without IMSA101 treatment will be administered to the patients in Cycles 1, 2, and 3, and thereafter only standard of care ICI monotherapy will be administered to all patients. Each treatment cycle will be 28 days in duration for Cycles 1, 2 and 3, then per standard of care thereafter based on the product labels of the prescribed ICI.
- Consistent with prior monotherapy and doublet therapy safety evaluations of IMSA101, the experimental arm (PULSAR-ICI + IMSA101) shall employ a 3+3 safety run-in component as follows:
  - The safety run-in will be conducted for the experimental arm prior to the randomization of patients to the 2 treatment arms.
  - Patients enrolled in the safety run-in period who are treated at the dose level selected for the experimental arm will be included in the total number of patients of the experimental arm.
  - Only two dose levels will be evaluated potentially: the previously identified selected Phase 2 dose of IMSA101 minus 1 dose level (800 mcg) and the previously identified selected Phase 2 dose of IMSA101 (1200 mcg). Dosing shall not continue beyond the latter dose.
  - 3 initial patients shall be enrolled to evaluate 800 mcg IMSA101 administered in combination PULSAR-ICI.
  - If no dose limiting toxicities (DLTs) are observed among these initial 3 patients at the 800 mcg dose level, the dose level of IMSA101 will be escalated for the following 3 patients to 1200 mcg of IMSA101 administered in combination with PULSAR-ICI.

- If a single DLT occurs among the initial 3 patients at an evaluated dose level, 3 additional patients will be enrolled at the same dose level.
- If  $\leq 1$  DLT occurs among the 6 patients at an evaluated dose level, the dose level shall be considered appropriate, and dose escalation continues (up to but not beyond the previously identified selected Phase 2 dose of 1200 mcg). If this condition occurs at the 1200 mcg level, subsequent patients will be enrolled at the 1200 mcg level.
- If  $\geq 2$  DLTs occur among the initial 3 or 6 patients at an evaluated dose level, the dose level shall be considered unacceptably toxic and dose escalation will be discontinued.
- If the 1200 mcg level is found to be unacceptably toxic, the IMSA101 dose will be de-escalated to the 800 mcg dose level.
- If the 800 mcg dose level is found to be unacceptably toxic, additional dose levels of IMSA101 shall be considered and potentially recommended by a protocol amendment.
- No fewer than 6 total patients shall be evaluated at a given dose level prior to confirmation of the dose level as the Combo selected Phase 2 dose.

Definitions:

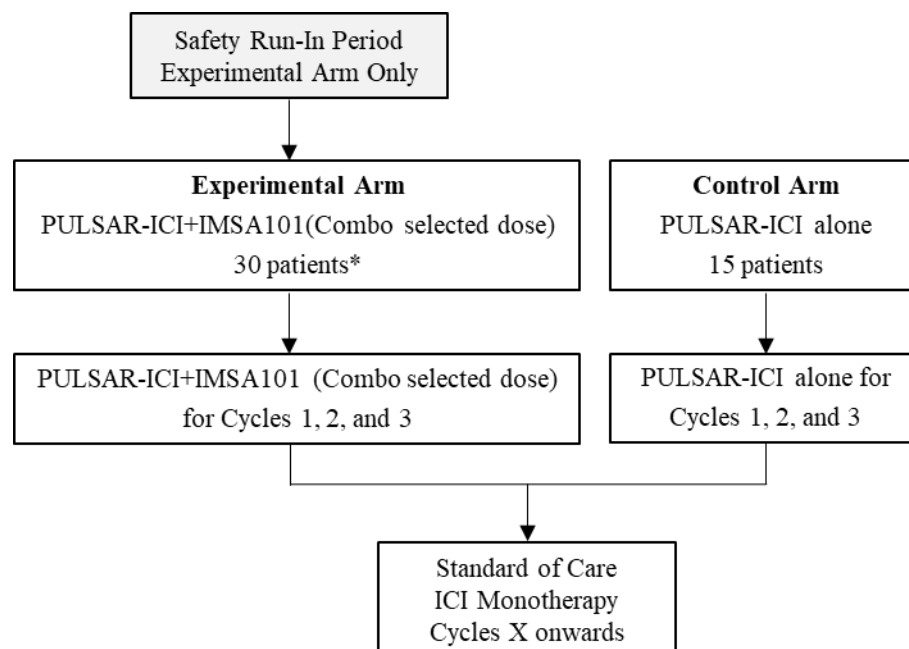
- Combo selected Phase 2 dose: The Combo selected Phase 2 dose is defined as the dose (either at MTD or below MTD) used in combination with PULSAR-ICI that is selected for evaluation in the Phase 2 study.
- For the experimental arm (PULSAR-ICI + IMSA101):
  - A single pre-defined progressing lesion/lesion site (longest diameter  $\geq 5$  mm and  $\leq 50$  mm) shall be injected throughout study duration, if possible.
  - The lesion will be injected weekly for the first three weeks of Cycle 1 (Days 1, 8 and 15) and then on Day 1 of Cycles 2 and 3.
  - 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 recorded and allowed, if deemed reasonable by the investigator.
  - 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 intra-tumoral 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.

- All patients will be followed throughout the study for drug tolerability and safety by collecting clinical and laboratory data, including AEs using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 criteria, SAEs, concomitant medications, and vital signs.
- A Safety Review Committee (SRC) will be organized to review the safety of the administered treatments (PULSAR, IMSA101, and ICI) during the study and in the safety run-in period to determine whether dose escalation of IMSA101 should proceed.
- All patients will be assessed for anti-tumor efficacy at screening, at the end of Cycle 3 ( $\leq 7$  days of C3D28), and at 8-week intervals ( $\pm 7$  days) thereafter based on radiographic assessments and analysis of ORR, DOR, TTP, and PFS (all outcome measures per RECIST Version 1.1 and iRECIST).
- Administration of pembrolizumab or nivolumab will follow the instructions in the product labels and scheduling for the products.
- Tumor types and corresponding treatment combinations to be evaluated will be identified prior to the first patient enrolled.
- All patients will continue to receive their assigned treatment throughout the study until the occurrence of disease progression (based on iRECIST), death, or other unacceptable treatment-related toxicity, or until the study is closed by the sponsor.

A study design schema is illustrated in [Figure 3](#), and the safety run-in procedures for the experimental arm is illustrated in [Figure 4](#).

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

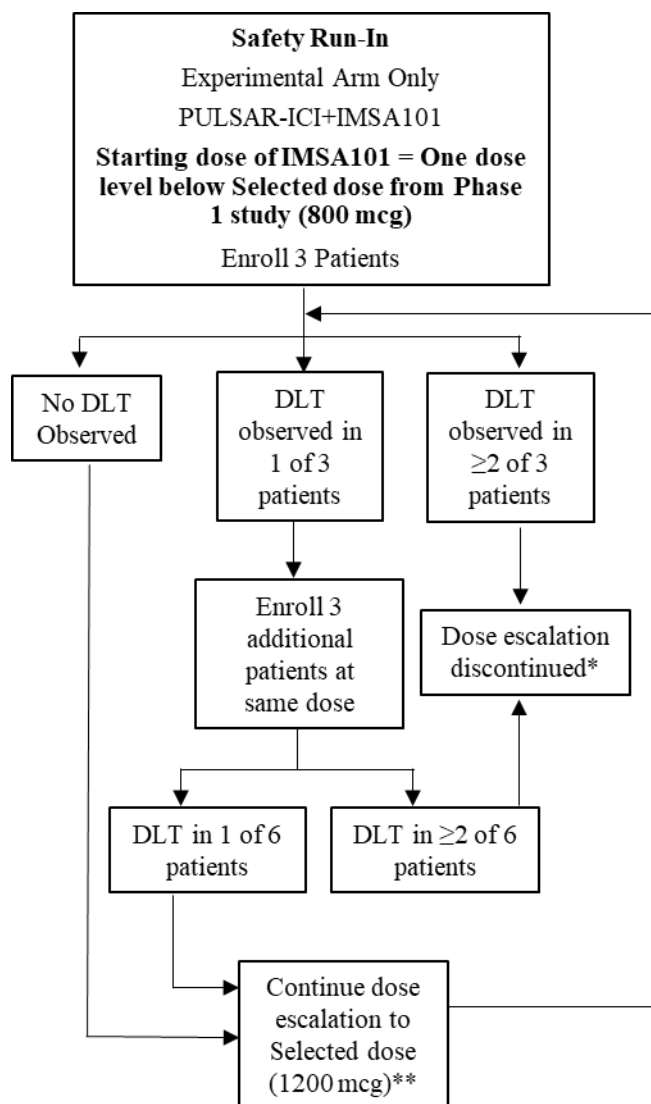


**Figure 3 Study Schema of Protocol IMSA101-103**

Abbreviations: DLT: dose limiting toxicity; ICI: immune checkpoint inhibitor; MTD: maximum tolerated dose; PULSAR: Personalized Ultra-fractionated Stereotactic Adaptive Radiotherapy

\* The patients enrolled in the safety run-in period who are treated at the dose level selected for the experimental arm will be included in the total number of patients of the experimental arm.

Combo Selected Phase 2 dose = the highest dose level of IMSA101 at which no more than 1 out of 6 patients experiences a DLT during the first cycle (28 days) of therapy or the dose (either at MTD or below MTD) used in combination with PULSAR-ICI that is selected for evaluation in the Phase 2 study.



**Figure 4 Safety Run-In for the Experimental Arm**

Abbreviations: DLT: dose limiting toxicity; ICI: immune checkpoint inhibitor; PULSAR: Personalized Ultra-fractionated Stereotactic Adaptive Radiotherapy

\* When DLTs are observed in  $\geq 2$  of the initial 3 or 6 patients at the Selected Phase 2 dose level (1200 mcg), the dose level will be de-escalated to the Selected Phase 2 dose level -1 (800 mcg). The Selected Phase 2 dose level -1 level will then be selected for the experimental arm when DLTs are observed in no more than 1 of 6 patients at this dose level.

\*\* When DLTs are observed in no more than 1 of 6 patients at Selected Phase 2 dose level, the dose level will be selected for the experimental arm.

## 3.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The role of cGAS-cGAMP-STING pathway in anti-tumor immunity has been demonstrated by independent research groups, as well as ImmuneSensor's own preclinical studies. 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 DC maturation and tumor antigen presentation to T cells. IFNs and cytokines

produced by DCs and other innate immune cells cooperatively stimulate T cell infiltration and function, leading to cytotoxic killing of tumor cells. In multiple syngeneic tumor models, the combination of a PD-L1 antibody with IMSA101 showed higher efficacy as compared to IMSA101 alone at each dose level tested. The administration of IMSA101 restored responsiveness to PD-L1 antibody in several types of syngeneic tumors which were otherwise refractory to ICIs. These studies provide a rationale for evaluating combination therapy in clinical settings.

For its part, RT has been used to treat approximately 50% of all cancer patients ([Begg et al., 2011](#)). Recent advancements in technology allow precise deposition of radiation simultaneously to multiple tumors with minimal leakage to surrounding healthy tissues. In addition to directly causing tumor cell death, radiation induces anti-tumor immune responses through the following mechanisms: 1) radiation causes exposure of tumor neoantigen to host phagocytes such as DCs and macrophage; 2) leakage of genomic or mitochondrial DNA activates cGAS-STING pathway, predominantly in DCs, which produces IFNs and other cytokines to promote antigen presentation and T cell-mediated adaptive immunity against tumors. However, abscopal effect from RT is extremely rare, whereas relapse of even directly irradiated tumors is very common, likely because immune response induced by RT is very weak and RT also causes upregulation of PD-L1 and recruitment of immunosuppressive cells into tumor ([Deng et al., 2014](#)). This can be partially overcome by optimizing the RT dose schedule to favor immune response and/or combining with either a STING agonist, or ICI, both of which have been demonstrated in pre-clinical studies ([Moore et al., 2021](#)).

There now exists extensive experience combining ICI with SAbR for the treatment of various advanced solid tumor malignancies ([Belluomini et al., 2019](#); [Ko and Formenti, 2018](#)). This combination appears safe and effective and is increasingly applied in the treatment of oligoprogressive disease ([Schoenhals et al., 2021](#); [Mahmood et al., 2022](#)). Immune checkpoint blockade is hypothesized to benefit from pre-established anti-tumor immune response and interest focuses on the immunomodulatory effects of RT to induce endogenous antigen-specific immune responses. In particular, PULSAR is being investigated as an optimal strategy for RT delivery. Furthermore, it is now hypothesized that cGAS-STING-mediated stimulation of the body's innate immune system can enhance RT-ICI synergy through the bridging of RT DNA damaging capacity and ICI activation of CD8<sup>+</sup> cytotoxic T cell-mediated tumor destruction ([Kho et al., 2021](#); [Yum et al., 2020](#)).

Based on these findings, this Phase 2 trial will combine PULSAR-integrated RT and ICI, administered with or without IMSA101 in patients with oligoprogressive solid tumor malignancies. This is an open-label, randomized clinical trial in adult patients with oligoprogressive solid tumor malignancies. The rationale of the IMSA101 repeated dosing regimen is supported by the nonclinical data and the clinical data collected so far (IB, [Version 5.0, 2024](#)).

### 3.3 DLT DEFINITIONS

In the safety run-in period for the experimental arm of PULSAR-ICI + IMSA101, a DLT will be defined as the occurrence of any of the following hematologic or non-hematologic events

that are 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 Version 5.0.

#### Hematologic AEs

- $\geq$  Grade 4 neutropenia lasting for  $> 7$  days
- Febrile neutropenia (defined as absolute neutrophil count [ANC]  $< 1000/\text{mm}^3$  with a single temperature of  $38.3^\circ\text{C}$  [ $101^\circ\text{F}$ ] or a sustained temperature of  $38^\circ\text{C}$  [ $100.4^\circ\text{F}$ ] for  $> 1$  hr)
- $\geq$  Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia associated with Grade  $\geq 2$  bleeding
- $\geq$  Grade 4 anemia

#### Non-hematologic AEs:

- Elevation of alanine aminotransaminase (ALT) or aspartate aminotransferase (AST) by  $\geq 3$  times ( $\times$ ) upper limit of normal (ULN) with concurrent elevation of serum total bilirubin  $\geq 2 \times \text{ULN}$
- Any  $\geq$  Grade 3 non-hematologic AE of any duration will be considered a DLT with the following exceptions:
  - Nausea/vomiting/diarrhea:
    - $\geq$  Grade 3 nausea/vomiting/diarrhea must be refractory to supportive care and last  $> 3$  days to be considered a DLT
    - $\geq$  Grade 3 nausea/vomiting/diarrhea that lasts  $\leq 3$  days is not a DLT
  - Fatigue:
    - $\geq$  Grade 3 fatigue must last  $> 7$  days to be considered a DLT
    - $\geq$  Grade 3 fatigue that lasts  $\leq 7$  days is not a DLT

For the discontinuation criteria of the study, see [Section 7](#).

### **3.4 SAFETY REVIEW COMMITTEE**

An independent SRC will be organized to review the safety of the administered treatments (PULSAR, IMSA101, and ICI) during the study. The SRC will be composed of principal investigators (and their representatives), medical monitor, and the sponsor representatives. In the safety run-in period for the experimental arm, the SRC will review all available safety data and determine whether to proceed with dose escalation of IMSA101 or a dose level should be invalidated. Meeting results will be documented, and formal notification of decisions will be provided to all patients.

### **3.5 BLINDING AND RANDOMIZATION**

This is an open-label randomized study. No blinding will be conducted. Patients will be randomized to the appropriate treatment based on a pre-defined randomization list. Patients

will be randomized to PULSAR-ICI alone or PULSAR-ICI + IMSA101 treatments. Randomized patients in the experimental arm will be capped at 24. Patients enrolled in the experimental arm for the safety run-in will not be randomized but the patients who are treated at the dose level selected for the experimental arm will be counted toward the 30 total patients (see [Section 4.1](#)).

In the randomized portion, patients will not be stratified.

### **3.6 DEFINITION OF TREATMENT CYCLE AND END OF STUDY**

Each treatment cycle from Cycle 1 to Cycle 3 will consist of 4 weeks (28 days) in duration. Details are outlined in the Schedule of Assessments and Study Activities ([Table 1](#) for the Safety Run-in and Experimental Arm, and [Table 2](#) for the Control Arm). Study treatment will be administered at all scheduled visits after screening.

ICI treatment time points will be per product labels; the duration of each cycle will depend on the ICI regimen.

Patients will receive treatment in the study until documented disease progression based on iRECIST or unacceptable toxicity.

The estimated total duration of the study will be approximately 3 years. End of study will be defined as the time point when all patients permanently discontinue the treatment in the study due to disease progression based on iRECIST, death, or other unacceptable toxicity, or when the study is closed by the sponsor.

## 4 SELECTION OF PATIENTS

### 4.1 NUMBER OF PATIENTS

Approximately 51 patients will be enrolled in the study. The sample sizes in the study are not based on statistical criteria or calculations.

Up to approximately 12 patients will be enrolled in the experimental arm for the safety run-in period. Any patients who discontinue the study before completing the first 28 days (first cycle) of treatment (before receiving all 3 doses of IMSA101, PULSAR, and ICI treatments) in the safety run-in for reasons other than DLT will be replaced.

Upon completion of the safety run-in, approximately 39 patients shall be randomized to 2 treatment arms as follows:

- Approximately 15 patients in the control arm (PULSAR-ICI)
- Approximately 24 patients in the experimental arm (PULSAR-ICI + IMSA101)  
(The total number of patients in the experimental arm will be 30 after including the 6 patients in the safety run-in who are treated at the dose level selected for this treatment arm.)

### 4.2 INCLUSION CRITERIA

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

1. Male or female patients  $\geq 18$  years of age
2. Signed informed consent and mental capability to understand the informed consent
3. Histologically or cytologically documented solid tumor malignancies demonstrating new progression through prior anti-cancer therapy, with a prior 2 months of clinical stability (with at least Stable Disease), with radiographically documented presence of  $\leq 6$  metastatic lesions consistent with the diagnosis of “oligoprogressive” disease that are technically amenable to PULSAR
4. Patient’s disease must be evaluable per RECIST Version 1.1
5. All metastatic lesions amenable to administration of radiotherapy, at the discretion of the investigator
6. Must have at least one single pre-defined progressing lesion/lesion site (longest diameter  $\geq 5$  mm and  $\leq 50$  mm) suitable for intra-tumoral injection
7. Eastern Cooperative Oncology Group (ECOG) performance status of  $\leq 1$
8. Electrocardiogram (ECG) without evidence of clinically meaningful conduction abnormalities or active ischemia as determined by the investigator
9. Acceptable organ and marrow function as defined below:
  - ANC  $> 1,500$  cells/ $\mu$ L

- Platelets  $> 50,000$  cells/ $\mu$ L
  - Total bilirubin  $\leq 1.5 \times$  ULN
  - AST/ALT  $\leq 2.5 \times$  ULN. If liver metastases are present, AST/ALT  $< 5 \times$  ULN
  - Creatinine clearance  $\geq 50$  mL/min using the Cockcroft-Gault formula
  - Prothrombin time (PT)/partial thromboplastin time (PTT)  $\leq 1.5 \times$  ULN
10. 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, eg, greater than 45 years) must have a negative serum pregnancy test prior to first dose of study treatment
  11. Male and female patients with reproductive potential must agree to use two forms of highly effective contraception throughout the study
  12. Life expectancy of at least 3 months as determined by the investigator

### 4.3 EXCLUSION CRITERIA

Patients are excluded from the study if any of the following criteria is met:

1. Prior receipt of STING agonist
2. Prior receipt of therapeutic radiotherapy to all progressive lesions intended for PULSAR treatment
3. Anti-cancer therapy, except pembrolizumab and nivolumab, within 4 weeks or  $< 5$  half-lives of the first dose of study treatment
4. Existence of primary tumor that requires therapeutic treatment beyond the provided immune checkpoint inhibitor drug
5. Failure to recover, to Grade 1 or less, from clinically significant AEs due to prior anti-cancer therapy, as judged by the investigator
6. Previous life-threatening (Grade 4) irAE
7. Known untreated brain metastases or treated brain metastases that have not been stable (scan showing no worsening of central nervous system [CNS] lesion[s] and no requirement of corticosteroids)  $\geq 4$  weeks prior to study enrollment
8. Existence of actionable mutations that are eligible for mutation-targeted drug that represent standard-of-care
9. Baseline prolongation of QT/corrected QT (QTc) interval (QTc interval  $> 470$ )
10. 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
11. Women who are pregnant or breastfeeding

12. 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 treatments with PULSAR, IMSA101, and ICI.

Female patients 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 treatments. For IMSA101, highly effective contraception should be used at least until 30 days following the last dose of IMSA101. Refer to the product labels (for ICI) and the standard practice (for PULSAR) for the recommended period of contraception for other components of the study treatment.

Highly effective contraception is defined as use of one or more methods that result in a low failure rate (ie, less than 1%). The following are examples of acceptable methods of contraception: oral, injected, or implanted hormonal methods, intrauterine devices (IUDs), 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, eg, greater than 45 years).

A serum pregnancy test for all female patients of childbearing potential will be performed during screening. A pregnancy test will also be carried out at the 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. The investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hrs of learning of the pregnancy (for female participant or female partner of male participant [after obtaining the necessary signed informed consent from the female partner]).

## 5 STUDY PROCEDURES AND SCHEDULE

Study procedures and their timing are summarized in the Schedule of Assessments and Study Activities ([Table 1](#) and [Table 2](#)).

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the Schedule of Assessments and Study Activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

### 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 cancer history and 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 in centimeters (cm) and weight in kilogram (kg)
- Record vital signs (blood pressure, respiration rate, heart rate, body temperature)
- Perform full physical 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 complete blood count [CBC] with differential) within 96 hr prior to C1D1
- Collect blood samples for complete serum chemistry tests and creatinine clearance (using the Cockcroft-Gault formula, [Appendix 13.4](#)) within 96 hr of C1D1
- Collect blood sample for thyroid function panel within 96 hr prior to C1D1
- Perform urinalysis within 96 hr of C1D1
- Perform a serum pregnancy test for female patients of childbearing potential

- Perform tumor assessment according to RECIST Version 1.1 ([Appendix 13.2](#)) and iRECIST ([Appendix 13.3](#))
- Complete QoL assessment using FACT-G questionnaire

### **5.1.2 Cycle 1 Day 1 ( $\pm$ 0 Day)**

- Record concomitant medications taken since screening including start dates, indication, dose, and frequency within 96 hr prior to C1D1
- Measure and record weight (kg) within 96 hr prior to C1D1
- Record vital signs (blood pressure, respiration rate, heart rate, body temperature) within 96 hr prior to C1D1
- Assess and record ECOG Performance Status within 96 hr prior to C1D1 ([Appendix 13.1](#))
- Administer PULSAR treatment
- Safety run-in and experimental arm: Administer IMSA101 by intra-tumoral injection following PULSAR treatment on the same day or the day after
- Control arm: Administer ICI following PULSAR treatment on the same day or the day after
- Assess and record AEs

### **5.1.3 Cycle 1 Day 2 ( $\pm$ 1 Day)**

- Safety run-in and experimental arm: Administer the first ICI treatment after PULSAR and IMSA101 treatment, and according to the product label thereafter.
- Assess and record AEs

### **5.1.4 Cycle 1 Day 8 ( $\pm$ 3 Days) – Safety Run-in and Experimental Arm Only**

For Cycle 1 Day 8 and Cycle 1 Day 15, visits are relative to the first IMSA101 dose to maintain the weekly dosing frequency and should be administered no less than 4 days apart.

- 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)
- Assess and record ECOG Performance Status ([Appendix 13.1](#))
- Safety run-in only: Collect blood samples for hematology tests (coagulation parameters are not required)

- Safety run-in only: Collect blood samples for complete serum chemistry tests
- Administer IMSA101 by intra-tumoral injection
- Assess and record AEs

### **5.1.5 Cycle 1 Day 15 ( $\pm 3$ Days) – Safety Run-in and Experimental Arm Only**

For Cycle 1 Day 8 and Cycle 1 Day 15, visits are relative to the first IMSA101 dose to maintain the weekly dosing frequency and should be administered no less than 4 days apart.

- 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)
- Assess and record ECOG Performance Status ([Appendix 13.1](#))
- Safety run-in only: Collect blood samples for hematology tests (coagulation parameters are not required)
- Safety run-in only: Collect blood samples for serum chemistry tests
- Administer IMSA101 by intra-tumoral injection
- Assess and record AEs

### **5.1.6 Cycle 2 Day 1 / Cycle 3 Day 1 ( $\pm 5$ 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)
- Assess and record ECOG Performance Status ([Appendix 13.1](#))
- Collect blood samples for hematology tests (coagulation parameters are not required)
- Collect blood samples for complete serum chemistry tests
- Collect blood sample for thyroid function panel (C3D1 only)
- Perform tumor assessment according to RECIST Version 1.1 ([Appendix 13.2](#)) and iRECIST ([Appendix 13.3](#)) prior to the end ( $\leq 7$  days) of Cycle 3, and thereafter every 8 weeks ( $\pm 7$  days).
- Administer PULSAR treatment
- Administer IMSA101 by intra-tumoral injection (for the experimental arm only) following PULSAR treatment on the same day or the day after

- Administer ICI treatment according to the product label
- Complete QoL assessment using FACT-G questionnaire (prior to the end ( $\leq 7$  days) of Cycle 3, and thereafter every 8 weeks ( $\pm 7$  days))
- Assess and record AEs

### 5.1.7 Efficacy Assessments

Efficacy assessments are to be performed at the end of Cycle 3, and approximately every 8 weeks thereafter. If C3D1 is delayed, so will the efficacy assessments.

- Perform tumor assessment according to RECIST Version 1.1 ([Appendix 13.2](#)) and iRECIST ([Appendix 13.3](#)) at the end of Cycle 3 ( $\leq 7$  days of C3D28), and thereafter every 8 weeks ( $\pm 7$  days))
- Complete QoL assessment using FACT-G questionnaire at the end of Cycle 3 ( $\leq 7$  days of C3D28), and thereafter every 8 weeks ( $\pm 7$  days))

### 5.1.8 ICI Cycles

The following assessments are to be completed at the ICI treatment time points (ICI will continue to be administered per product label):

- 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)
- Assess and record ECOG Performance Status ([Appendix 13.1](#))
- Collect blood samples for hematology tests (coagulation parameters are not required)
- Collect blood samples for complete serum chemistry tests
- Collect blood samples for thyroid function panel if clinically indicated
- Administer ICI treatment according to the product label
- Assess and record AEs

### 5.1.9 End of Study (EOS) 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
- Assess and record ECOG Performance Status ([Appendix 13.1](#))
- Perform a 12-lead ECG
- Collect blood samples for hematology tests (coagulation parameters are not required)
- Collect blood samples for complete serum chemistry tests
- Collect blood sample for thyroid function panel if clinically indicated
- Perform a serum pregnancy test for female patients of childbearing potential
- Perform tumor assessment according to RECIST Version 1.1 ([Appendix 13.2](#)) and iRECIST ([Appendix 13.3](#))
- Complete QoL assessment using FACT-G questionnaire
- Assess and record AEs

#### **5.1.10 Cycle Extensions**

With the approval of the investigator and sponsor, a patient may be allowed a 1-week delay or extension between cycles for the first 3 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.

### **5.2 Restrictions, Precautions, and Potential Adverse Effects**

#### **IMSA101:**

There are no known restrictions or precautions relative to the use of nicotine, caffeine, alcohol, physical activity, dietary restriction, or medications for patients receiving IMSA101 treatment.

Based on the nonclinical findings with IMSA101 and toxicity events reported in clinical trials evaluating other STING adaptor 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.

Based on the preliminary safety data of the monotherapy and combination treatment in the ongoing Phase 1/2a study (Protocol number: IMSA101-101), the most frequently reported TEAEs by preferred term across all dose levels were fatigue (53.3% of patients), and injection site pain, hyponatremia, decreased appetite, dyspnea, headache, and lymphocyte count decreased (each in 20% of patients).

### **ICI Treatment:**

The investigator is to refer to the prescribing information or other known sources of the respective ICI drugs for any specific restrictions or precautions relative to the use nicotine, caffeine, alcohol, physical activity, dietary restrictions, or medications for patients receiving ICI treatment.

The most common adverse reactions (reported in the  $\geq 20\%$  of patients) of pembrolizumab as a single agent were: fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, and abdominal pain ([KEYTRUDA® \[Pembrolizumab\]](#)).

The most common adverse reactions (reported in the  $\geq 20\%$  of patients) of nivolumab as a single agent were: fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, pyrexia, headache, and abdominal pain ([OPDIVO® \[Nivolumab\]](#)).

The common adverse reactions (reported in the  $\geq 20\%$  of patients) of pembrolizumab in combination with RT include fatigue, rash, dyspnea, cough, and flu-like symptoms ([Theelen et al., 2019](#); [Welsh et al., 2020](#)). The reported adverse reactions of nivolumab in combination with RT include pneumonitis, lethargy, diarrhea, skin erythema, pancreatitis, and hearing loss ([Ansari et al., 2021](#); [Amin et al., 2018](#)).

### **PULSAR:**

The investigator is to follow the specific restrictions or precautions relative to food, medications, allergies, clothing or personal items for patients undergoing the PULSAR or SAbR procedure.

Complications associated with PULSAR or SAbR may include radiation pneumonitis, brachial plexopathy, gastritis, toxicity in the chest wall, skin, airway, esophagus, and bowel ([Lo et al., 2013](#); [Siva et al., 2018](#)).

## **6 METHODS OF ASSESSMENTS AND ENDPOINTS**

### **6.1 MEDICAL HISTORY**

At screening and until start of study treatment, a complete medical history will be obtained from each patient. Medical history includes baseline symptoms, cancer history, 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.

### **6.2 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. Concomitant medications taken from Cycle X onwards are to be completed at the ICI treatment time points.

Necessary supportive care such as anti-emetic, anti-diarrheal medications, and pre-infusion medications for ICI treatment per local guidelines will be allowed. Prophylactic pre-treatment for headache, nausea, and vomiting is permitted (see [Section 8.4](#)). Pre-infusion medications for ICI treatment, when administered, should be given per local guidelines. For concomitant medications allowed during PULSAR, see [Section 8.1.2](#).

Any medication that in the opinion of the investigator will interfere with the MOA of IMSA101, ICI, and PULSAR is prohibited (see [Section 8.4](#)).

### **6.3 DEMOGRAPHIC DATA**

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

### **6.4 SAFETY ASSESSMENTS**

#### **6.4.1 Vital Signs**

Vital signs including body temperature, blood pressure (systolic and diastolic), respiration rate, and heart rate will be measured at each scheduled visit. From Cycle X onwards, vital signs are to be measured at the ICI treatment time points.

All vital sign readings will be documented in the electronic case report form (eCRF). The investigator will review all vital sign values for clinical significance. Additional vital signs will be obtained when clinically indicated. Any clinically significant change in the vital signs from before the start of study treatment should be recorded as an AE.

## 6.4.2 Physical Examination

A full physical examination will be performed at screening and EOS visit. A full physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, neurological, skin, and lymphatic systems.

In addition, height (cm) will be measured at screening; body weight (kg) will be measured at screening/baseline and each scheduled visit.

Information of 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 treatment must be included in the Relevant Medical History/Current Medical Conditions page of the eCRF. Clinically relevant findings made after the start of study treatment, which meet the definition of an AE, must be recorded on the AE page of the eCRF.

## 6.4.3 ECOG Assessment

The ECOG Performance Status Scale is a widely accepted tool in cancer clinical trials to measure and monitor the level of functioning in cancer patients in terms of their ability to care for themselves, daily activity, and physical ability ([Oken et al., 1982](#)).

The ECOG Performance Status assessments ([Appendix 13.1](#)) will be performed at each scheduled visit.

## 6.4.4 Electrocardiogram

A complete standard 12-lead ECG recording (rhythm, VR, PR interval, QRS duration, QT and QTc) will be performed at screening and EOS visit, or at any other visit where the investigator believes the assessment is indicated. The results of ECG will be reported to the investigator and recorded in the eCRF.

## 6.4.5 Clinical Laboratory Evaluations

Clinical laboratory evaluations (hematology, serum chemistry, coagulation, urinalysis) will be performed at the indicated visits in [Table 1](#) and [Table 2](#). Coagulation and urinalysis will be performed only at screening.

All clinical laboratory evaluations will be carried out by the local laboratory and in accordance with the standard operating procedures or the laboratory manual. All results of the clinical laboratory measurements will be reported to the investigator and recorded in the eCRF.

The following clinical laboratory evaluations will be performed:

- **Hematology** (blood sample with ethylenediaminetetraacetic acid [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, direct bilirubin, lactate dehydrogenase, total protein, albumin.
- **Thyroid Function Panel** (blood serum sample): a thyroid test panel will include thyroid-stimulating hormone (TSH), tri-iodothyronine (T3) (free and total), thyroxine (T4) (free and total).
- **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 EOS and that is considered clinically significant will be followed according to accepted medical standards for up to 30 days after the EOS or until resolution of the abnormality.

#### 6.4.6 Pregnancy Test

A serum pregnancy test will be performed for female patients of childbearing potential at screening and the EOS visit to establish the absence of pregnancy.

#### 6.4.7 Adverse Events and Toxicities

Patients will be observed for 1 hr at the study site following intra-tumoral injections. All TEAEs will be collected and recorded in the eCRF. Toxicities and DLTs will be assessed using the CTCAE Version 5.0.

See [Section 3.3](#) for the definition of DLTs. See [Section 9](#) for definitions and the reporting of AEs.

### 6.5 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 the study (see [Appendix 13.2](#)). Assessments may include the following:

- Tumor assessment at screening and subsequent scheduled time points must include computed tomography (CT) scans or magnetic resonance imaging (MRI) (with intravenous contrast unless contraindicated and oral contrast as appropriate per institutional standards).
- 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.

- Further investigations such as bone scans, brain MRI, etc. 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 (eg, 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 responses according to RECIST Version 1.1 ([Appendix 13.2](#)) and iRECIST ([Appendix 13.3](#)) criteria and the Schedule of Assessments and Study Activities ([Table 1](#)).
- In certain circumstances, a patient experiencing RECIST progression of disease will be allowed to continue therapy on study unless confirmed progression by iRECIST.
- Outcome measures that will be extracted from the radiographic imaging, as defined by RECIST Version 1.1 and iRECIST, include TTP, ORR, DOR, and PFS.
  - TTP: defined as the time from the first dose of study treatment until the time of objective disease progression
  - ORR: defined as the proportion of patients with confirmed partial or complete response from the first dose of study treatment until disease progression
  - DOR: defined as the time from initial objective response (partial or complete response, whichever status is recorded first) until the time of disease progression or death from any cause
  - PFS: defined as the time from the first dose of study treatment until objective disease progression or death from any cause

## 6.6 QUALITY OF LIFE ASSESSMENT

FACT-G ([Cella et al., 1993](#)) is a 27-item questionnaire using a 5-point Likert-type scale. This is a reliable, sensitive, and validated tool developed to measure four domains of health related QoL, namely physical, social, emotional, and functional well-being, in cancer patients. FACT-G Version 4.0 will be used in this study.

The questionnaire will be provided to and self-administered by the patients, or performed in an interview if needed, at the scheduled time points in [Table 1](#) and [Table 2](#).

## 7 DISCONTINUATION CRITERIA

### 7.1 DISCONTINUATION OF STUDY TREATMENT

The treatment of individual patient(s) may be stopped by the investigator under the defined circumstances as outlined below.

- Use of prohibited concurrent therapy
- Non-compliance with the study treatment or study schedule
- Abnormal clinical laboratory tests
- Intercurrent illness warranting treatment discontinuation by the investigator
- Disease progression warranting treatment discontinuation by the investigator
- Pregnancy
- Other safety criteria warranting treatment discontinuation by the investigator

If, based on the investigator's judgement, the study treatment of a patient is permanently discontinued, the patient will be withdrawn from the study (see [Section 7.2](#) for procedures of withdrawal from the study).

#### 7.1.1 Temporary Discontinuation of Study Treatment

After the safety run-in period in the experimental arm, the administration of IMSA101 may need to be temporarily interrupted, if deemed appropriate by the investigator, when suspected toxicity of IMSA101 is observed. See [Section 3.3](#) for the AEs that may warrant temporary interruption of the IMSA101.

For PULSAR or ICI treatments, any dose modifications or treatment interruptions should follow the instructions in the product labels of the prescribed ICI drugs and the standard guideline of the RT. Patients should be removed from the trial if the ICI treatment interruption lasts more than 12 weeks. Exceptions can be made on a case-by-case basis following discussion between investigator and sponsor.

An agreement from the sponsor and the investigator should be obtained prior to re-initiating treatment in a patient after an interruption in the treatment.

Tumor assessments should continue as per protocol even if the treatment is interrupted or delayed.

### 7.2 PATIENT WITHDRAWAL FROM THE STUDY

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

- Use of non-permitted concurrent therapy
- Non-compliance with the study treatment 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
- The investigator determines that a change of therapy would be in the best interest of the patient
- Intercurrent illness warranting removal by the investigator
- Disease progression warranting removal by the investigator
- Pregnancy

The reason(s) for withdrawal (by the patient or investigator) and date will be documented in the 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 an AE leading to study withdrawal. Patients withdrawing from the study will be asked to complete the final evaluations as detailed for the EOS visit in the Schedule of Assessments ([Table 1](#) and [Table 2](#)).

If a patient refuses to complete the final evaluations upon withdrawal from the study, this information will be recorded in the source documentation. A patient who prematurely withdraws from the study for any reason will not be allowed to re-enter the study.

If a patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a patient withdraws from the study, the patient may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

In certain circumstances, a patient experiencing RECIST progression of disease will be allowed to continue therapy on study unless confirmed progression by iRECIST.

### **7.3 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 PULSAR, IMSA101, and ICI, or the company itself occur, making further treatment of patients impossible.

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 protocol, the requirements of the

Institutional Review Boards (IRB)/ Institutional Ethics Committees (IEC) or local health authorities, the sponsor's procedures, or the Good Clinical Practice (GCP) guidelines.

If the study is prematurely terminated or suspended, the sponsor or delegate shall promptly inform the investigators, the IRB/IEC, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patients and should assure appropriate patient therapy and/or follow-up. Study materials must be returned, disposed of or retained as directed by the sponsor.

## 8 TREATMENT

### 8.1 ADMINISTRATION OF PULSAR

PULSAR is part of the combination therapy in both the control arm and experimental arm from Cycle 1 to Cycle 3.

PULSAR will be administered to the patients first on Day 1 of Cycles 1, 2, and 3 (for both treatment arms), followed by IMSA101 on the same day or the day after (of Cycles 1, 2, and 3; for the experimental arm only).

PULSAR will be delivered with the targeting planning and directing of treatment fields guided to a target based on known three-dimensional (3D) coordinates related to reliable fiducial markers. This differs from conventional RT in which treatment is guided by skin or bony landmarks assumed to correlate to the target volume based on the initial simulation. Treatment will account for inter-/intra-fractional errors with careful dosimetry that delivers an ablative dose to the metastatic lesion(s) while respecting normal tissue constraints.

#### 8.1.1 Prescription Dose and Interval

The treating radiation oncologist will deliver 3 pulses (treatments) to each selected lesion. Each RT pulse will encompass the 95% of the planning target volume to be considered compliant to the protocol. The following table lists the acceptable number of pulses, the dose per lesion/per pulse, and total dose to be administered. Any dose delivered that is beyond the recommended doses will be considered an unacceptable variation. Isotoxic doses were calculated using the Universal Survival Model using H460 Homo sapiens lung carcinoma cell line data.

Number of Pulses	Dose Per Lesion, Per Pulse	Total Dose
3	12 – 15.5 Gy*	36 – 46.5 Gy*

\* a lesion close to the spinal cord should only receive 9 Gy per pulse, for a total of 27 Gy

The PULSAR “pulse” is to be delivered on Day 1 of Cycles 1, 2, and Cycle 3, for a total of 3 pulses per lesion. PULSAR may be held if the patient does not have any targetable disease. Each PULSAR treatment and date of treatment delivery will be recorded.

#### 8.1.2 Treatment Concerns and Concurrent Medications

Corticosteroid medications for inflammatory conditions can be used at the discretion of the treating oncologist (in which case, its use needs to be reported as concomitant medication). However, the use of corticosteroid medications is generally discouraged, given its immunosuppressive properties. Analgesic pre-medication to avoid general discomfort during long treatment durations is recommended when appropriate.

### 8.1.3 Technical Factors and Considerations

#### **Physical factors**

Only photon (X-ray) beams produced by linear accelerators with photon energies of 4-15 megavoltage (MV) will be allowed. Cobalt-60 and charged particle beams (including electrons, protons, and heavier ions) are not allowed. Restriction of photon beam energies > 10 MV but less than 15 MV will be based on clinical appropriateness taking into account distance the beam must travel to the target.

#### **Dose Verification at Treatment**

*In vivo* dosimeter measurements (eg, diode, thermoluminescent dosimeter) may be obtained for surface dose verification for accessible beams. This information is not required by the protocol.

#### **Treatment Platforms**

The study allows most commercially available photon or proton producing treatment units. Treatment units should include image guidance. Both 3D conformal and intensity-modulated RT (including volumetric-modulated arc therapy [VMAT]) are allowed. Proton or other charged particle units are not allowed in this study. Other specialized accelerators (eg, the CyberKnife® or Tomotherapy) are allowed as long as they meet the technical specifications of the protocol.

### 8.1.4 Simulation and Image Guidance

#### **Patient Positioning**

Patients will be positioned in a stable position that allows accurate reproducibility of the target between treatments. Positions uncomfortable for the patient should be avoided so as to prevent uncontrolled movement during treatments. A variety of immobilization systems may be utilized including stereotactic frames that surround the patient on three sides and large rigid pillows (conforming to patients' external contours) with reference to the stereotactic coordinate system. Patient immobilization must be reliable enough to ensure that the Gross Tumor Volume (GTV) does not deviate beyond the confines of the Planning Treatment Volume (PTV) with any significant probability (ie, < 5%).

At the time of simulation for patients who will receive pulses to the lung, liver, or other targets likely to move greater than 0.5 cm with respiration, the movement of the dome of the diaphragm (superior portion of the liver) is to be observed under fluoroscopy or other acceptable means to estimate respiratory movement during treatment if no breathing control device is used. Patients will be assessed for suitability for tolerance of a respiratory control device using a breath-hold technique, respiratory gating, or abdominal compression to limit diaphragmatic excursion during respiration. Patients with severe lung disease and patients who cannot tolerate diaphragmatic or breathing control devices for other reasons will be treated without them. A larger margin to account for breathing related intra-fractional organ movement is required but no greater than a margin of 1.5 cm.

## **Image Guidance**

Isocenter or reference point port localization images should be obtained on the treatment unit immediately before treatment to ensure proper alignment of the geometric center (ie, isocenter) of the simulated fields. These image-guided RT images can be obtained with planar kilovolt (kV) imaging devices or cone-beam CT equipment. For treatment systems that use kV imaging but also allow electronic portal imaging device imaging using the treatment beam, orthogonal images verifying the isocenter also should be obtained.

### **8.1.5 Treatment Planning and Target Volumes**

#### **Image Acquisition**

CT scans will be the primary image platform for targeting and treatment planning. The planning of CT scans must allow simultaneous view of the patient anatomy and fiducial system for stereotactic targeting. CT scan with intravenous contrast is recommended unless the patient has allergy to contrast or renal insufficiency. Oral gastrointestinal contrast to highlight the stomach and duodenum is recommended for patients with medial liver lesions or lesions of the caudate lobe. Axial acquisitions will be required with spacing  $\leq 3.0$  mm between scans. Images will be transferred to the treatment planning computers.

#### **Target Volumes**

The target lesion will be outlined by an appropriately trained physician and designated the GTV. The target will generally be drawn using appropriate windowing based on location of the metastatic lesion(s). Four-dimensional CT image guided GTV delineation to take tumor motion into consideration will be allowed.

For treatment to the lung, the target will generally be drawn using CT pulmonary windows; however, soft tissue windows with contrast may be used to avoid inclusion of adjacent vessels, atelectasis, or mediastinal or chest wall structures within the GTV. This target will not be enlarged whatsoever for prophylactic treatment (including no “margin” for presumed microscopic extension); rather, include only abnormal CT signal consistent with gross tumor (ie, the GTV and the clinical target volume [CTV] are identical). An additional 0.5 cm in the axial plane and 0.5 cm in the longitudinal plane (craniocaudal) will be added to the GTV to constitute the PTV.

For treatment to the liver, the following structures are contoured: entire liver, each individual liver GTV, each kidney, small bowel, large, bowel, duodenum, stomach, and the spinal cord. The PTV is constructed to account for the positional uncertainty of the GTV during treatment with a PTV margin of 0.5 cm is recommended. Larger margins may be used in cases where greater motion of the hemidiaphragm is observed in simulation despite standard maneuvers to diminish motion. Four-dimensional CT image acquisition is recommended to be utilized to evaluate for motion, and motion management techniques such as breath hold or abdominal compression can be utilized at the discretion of the treating physicians. Fiducial markers can also be utilized to facilitate image guidance if available at the institution.

Treatment to skeletal and paraspinal lesions may be accomplished with any 3D conformal radiotherapy or intensity-modulated radiotherapy technique suitable for this application with performance specifications adequate to provide proper tumor dose distribution and normal tissue sparing.

### **8.1.6 Dosimetry**

#### **3D Conformal Planning**

3D coplanar or non-coplanar beam arrangements will be custom designed for each case to deliver highly conformal prescription dose distributions. Non-opposing, non-coplanar beams are preferable. Generally, more beams are used for larger lesion sizes. For this protocol, the isocenter is defined as the common point of gantry and couch rotation for the treatment unit. Prescription lines covering the PTV will typically be the 60-90% line (rather than 95-100%); however, higher isodoses (hotspots) must be manipulated to occur within the target and not in adjacent normal tissue. The isocenter in stereotactic coordinates will be determined from system fiducials (or directly from the tumor in the case of volumetric imaging) and translated to the treatment record.

The treatment dose plan will be made up of multiple static beams or arcs as described above. The plan should be normalized to a defined point corresponding closely to the center of mass of the PTV (COMPTV). Typically, this point will be the isocenter of the beam rotation; however, it is not a protocol requirement for this point to be the isocenter. Regardless, the point identified as COMPTV must have defined stereotactic coordinates and receive 100% of the normalized dose. Because the beam apertures coincide nearly directly with the edge of the PTV (little or no added margin), the external border of the PTV will be covered by a lower isodose surface than usually used in conventional radiotherapy planning typically around 80% but ranging from 60-90%. The prescription dose will be delivered to the margin of the PTV. As such, a “hotspot” will exist within the PTV centrally at the COMPTV with a magnitude of prescribed dose times the reciprocal of the chosen prescription isodose line (ie, 60-90%).

#### **Intensity Modulated Radiation Therapy (IMRT)**

IMRT, including volumetric-modulated arc therapy (VMAT) and modulated charged particles is allowed in this study. The use of IMRT in this study is at the discretion of the treating physician. However, IMRT should be considered only when target coverage, organ-at-risk dose limits, or dose spillage are not achievable with 3D conformal planning. In addition, IMRT plans should follow the same planning principles as discussed above for 3D conformal planning. The number of segments (control points) and the area of each segment should be optimized to ensure deliverability and avoid complex beam fluences. Ideally, the number of segments should be minimized, and the area of each segment should be maximized (the aperture of one segment from each beam should correspond to the projection of the PTV along a beam’s eye view).

## **Dose Calculations**

For purposes of dose planning and calculation of monitor units for actual treatment, this protocol will require tissue density heterogeneity correction.

Successful treatment planning will require accomplishment of all of the following criteria:

1. Maximum dose: The treatment plan should be created such that 100% corresponds to the maximum dose delivered to the patient. This point must exist within the PTV.
2. Prescription isodose: The prescription isodose surface must be  $\geq 60\%$  and  $< 90\%$  of the maximum dose.
3. Prescription Isodose Surface Coverage: The prescription isodose surface will be chosen such that 95% of the target volume (PTV) is conformally covered by the prescription isodose surface (PTV V95%RX = 100%) and 99% of the target volume (PTV) receives a minimum of 90% of the prescription dose (PTV V90%RX  $> 99\%$ ).

### **8.1.7 Normal Tissue Dose Constraints**

The following table lists the specific organ and dose fractionation constraints on normal tissue. Given the irregular, long intervals between each radiotherapy pulse, total dose will be calculated to a particular organ-at-risk to ensure safety of RT. Exceeding these dose tolerances by more than 2.5% constitutes a minor protocol violation. Exceeding these dose tolerances by more than 5% constitutes a major protocol violation.

#### **Three pulses**

Serial Tissue	Volume (cc)	Volume Max (Gy)	Max Point Dose (Gy)**	Endpoint ( $\geq$ Grade 3)
Optic Pathway	$< 0.2$	15.3	17.4	neuritis
Cochlea	-	-	14.4	hearing loss
Brainstem (not medulla)	$< 0.5$	15.9	23.1	cranial neuropathy
Spinal Cord and medulla	$< 0.35$	15.9	22.5	myelitis
Cauda Equina	$< 5$	21.9	25.5	neuritis
Sacral Plexus	$< 5$	22.5	25.5	neuropathy
Esophagus*	$< 5$	27.9	32.4	esophagitis
Brachial Plexus	$< 3$	22	26	neuropathy
Heart/Pericardium	$< 15$	24	30	pericarditis
Great vessels	$< 10$	39	45	aneurysm
Trachea and Large Bronchus*	$< 5$	39	43	impairment of pulmonary toilet
Bronchus- smaller airways	$< 0.5$	25.8	30	stenosis with atelectasis
Rib	$< 5$	40	50	pain or fracture
Skin	$< 10$	31	33	ulceration
Stomach	$< 5$	22.5	30	ulceration/fistula
Bile duct	-	-	36	stenosis
Duodenum*	$< 5$	22.5	30	ulceration
Jejunum/Ileum*	$< 30$	20.7	28.5	enteritis/obstruction

Colon*	< 20	28.8	45	colitis/fistula
Rectum*	< 3.5 < 20	43 30.3	47	proctitis/fistula
Ureter	-	-	40	stenosis
Bladder wall	< 15	17	33	cystitis/fistula
Penile bulb	< 3	25	-	impotence
Femoral Heads	< 10	24	-	necrosis
Renal hilum/vascular trunk	15	19.5	-	malignant hypertension
Parallel Tissue	Critical Volume (cc)	Critical Volume Dose Max (Gy)	Avoid Pneumonitis	Endpoint (≥ Grade 3)
Lung (Right & Left)	1500 for males; 950 for females***	10.8	-	basic lung function
Lung (Right & Left)	-	-	V-11.4 Gy < 37%	pneumonitis
Liver	700***	17.7	-	basic liver function
Renal cortex (Right & Left)	200***	14.7	-	basic renal function

\* Avoid circumferential irradiation

\*\* “point” defined as 0.035 cc or less

\*\*\* or one third of the “native” total organ volume (prior to any resection or volume reducing disease), whichever is greater

## 8.2 DOSING AND ADMINISTRATION OF IMSA101

IMSA101 is a sterile, nonpyrogenic solution containing 5 mg of IMSA101 in 1.0 mL of a

Composition of IMSA101 is presented in Table 3.

**Table 3 Composition of IMSA101 for Injection**

Ingredients	Grade	Function	Composition (1.0 mL per vial)

NF: National Formulary; USP: United States Pharmacopeia

## 8.2.1 Preparation of IMSA101

Prior to dosing, IMSA101 will be thawed and diluted in [REDACTED] as detailed in a separate pharmacy manual in order to be delivered via intra-tumoral injection. The following dose levels will be administered to the patients in the study:

Selected Phase 2 dose minus 1 level: 800 mcg

Selected Phase 2 dose: 1200 mcg

This drug is **NOT SAFE** to be administered without proper dilution.

No dose modification of IMSA101 is allowed.

A single pre-defined progressing lesion/lesion site per patient will be selected and injected via intra-tumoral injection throughout study participation. Injections of tumors that are not superficial will be performed under image guidance.

## 8.2.2 Administration of IMSA101

IMSA101 will be administered to the patients in the experimental arm only. IMSA101 will be part of the combination therapy with PULSAR-ICI from Cycle 1 to Cycle 3. IMSA101 will be administered to the patients on Day 1 of Cycles 1, 2, and 3 following the PULSAR treatment on the same day or the day after (Day 2).

In the experimental arm, a safety run-in component will be applied to initial patients enrolled in the treatment arm to establish safety of the combination therapy at the dose levels of Selected Phase 2 dose -1 (800 mcg) and Selected Phase 2 dose (1200 mcg) (see [Section 3.1](#)). A total volume of 1 mL will be administered each week for 3 weeks in Cycle 1 (Days 1, 8, and 15). For Cycle 2 and Cycle 3, IMSA101 will be given via intra-tumoral injection on Day 1 only.

IMSA101 is injected directly into the selected tumor. Patients will be observed for 1 hr following each intra-tumoral injection.

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 (ie, 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 intra-tumoral 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  $\geq 5$  mm and  $\leq 50$  mm

- Be fully efficacy evaluable per RECIST Version 1.1 ([Appendix 13.2](#)) and iRECIST ([Appendix 13.3](#))

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 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.

### **8.2.3 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 Flurotec coated lyophilization stopper, and sealed with a 13 mm flip-off overseal and 13 mm cap.

The product (IMSA101 for Injection) is stored at  $-20 \pm 5^{\circ}\text{C}$ . Clinical trial sites will be provided specific expiry and stability updates via memoranda as new data become available.

## **8.3 ADMINISTRATION OF ICI DRUG**

ICI drug (pembrolizumab or nivolumab) is part of the combination therapy in both the control arm and experimental arm from Cycle 1 to Cycle 3. The initial dose of the prescribed ICI will be administered to the patients on Cycle 1 Day 2 (following PULSAR [for both treatment arms] and IMSA101 [for experimental arm only] on C1D1). If IMSA101 is administered on C1D2, then ICI may be administered same day following IMSA101, or on C1D3. Thereafter, the ICI drug will be administered to the patients at frequencies per product labels (every 3 weeks or every 6 weeks for pembrolizumab; every 2 weeks or every 4 weeks for nivolumab).

ICI drug will be administered to the patients in both treatment arms as monotherapy from Cycle X onwards and at frequencies according to the product labels.

## **8.4 RESCUE MEDICATIONS AND CONCOMITANT TREATMENTS**

All medications administered from the beginning of study treatment (C1D1) through EOS will be recorded on the eCRF. Any change in medication dosage will also be noted.

Necessary supportive care (ie, anti-emetic and/or anti-diarrheal medications, pre-infusion medications for ICI treatment per local guidelines, corticosteroid and analgesic pre-medication during PULSAR, etc.) will be allowed. Prophylactic pre-treatment for headache, nausea, and vomiting is permitted ([Section 6.2](#)).

The following medications are prohibited during the study:

- **Additional anticancer therapy, other investigational agents, and immunotherapy**  
During the study treatment period, patients are not to receive any additional anticancer therapy, except for palliative radiotherapy to relieve symptoms if approved by sponsor, other investigational agents, or other immunotherapy not specified in this protocol. Non-protocol specified radiotherapy may not be given to treat a new lesion or progressive disease. If the investigator determines that a patient requires any additional anti-cancer treatment, except for palliative radiation for symptomatic control, all study treatment must be discontinued.
- **Herbal therapies**  
Concomitant use of herbal therapies/traditional Chinese medicine with anti-cancer activity included in the product label is prohibited.
- **Corticosteroids**  
Corticosteroids used as an anti-cancer therapy (eg, > 10 mg/day prednisone or equivalent) are not permitted; however, they are allowed as a pre-medication, as physiologic replacement, or for symptomatic management.
  - Systemic corticosteroids are permitted for the following purposes:
    - To modulate symptoms of an AE that is suspected to have an immunologic etiology
    - As needed for the prevention of emesis
    - Pre-medication for IV contrast allergies
  - In addition, the following glucocorticoid use is allowed:
    - For topical use or ocular use
    - Intra-articular joint use
    - For inhalation in the management of asthma or chronic obstructive pulmonary disease

Note: Inhaled steroids are allowed for the management of asthma.

The investigator should also refer to the prescribing information or other known sources for the prohibited concomitant medications that should be avoided during an ICI treatment.

#### **8.4.1 COVID-19 Vaccination**

The current study will be conducted amidst the coronavirus disease 2019 (COVID-19) pandemic. As mass vaccination campaign of COVID-19 vaccine is ongoing worldwide, the patients enrolled in the study may receive COVID-19 vaccine prior to or concurrently during the study.

The current COVID-19 vaccines available to the public is considered to have no interaction with IMSA101 that necessitate advice on vaccine timing or other precautions.

## 8.5 TREATMENT COMPLIANCE

Patients will receive the combination therapy directly from the investigator or designee, under medical supervision. The investigator or other study staff will supervise each study treatment given at the study site. The date and time of each treatment administered at the study site will be recorded in the eCRF. The dose of study drugs and patient identification will be confirmed at the time of dosing by the study site staff.

The investigator and/or the study staff will administer IMSA101 only for use in patients enrolled in the experimental arm as described in this protocol. The study drugs are not to be used for reasons other than those described herein.

Study personnel associated with the sponsor will monitor the treatment compliance of PULSAR, IMSA101, and ICI.

## 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 study treatment, whether or not related to the study treatment. AE reporting begins from the start of study treatment and continues until the EOS visit.

#### 9.1.2 Serious Adverse Events

An SAE is any untoward medical event that occurs at any dose from the start of study treatment until the EOS visit:

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

<sup>1</sup> “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.

<sup>2</sup> 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.

<sup>3</sup> “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.

<sup>4</sup> 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 IRB/IEC according to IRB/IEC policies (to include annual Continuing Review Reports), to the SRC as required, and to the US FDA as required for the annual report.

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 4.

**Table 4 Definitions of Adverse Events Severity**

<b>Grade 1 (Mild)</b>	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. The AE does not interfere with routine activities. The patient may experience slight discomfort.
<b>Grade 2 (Moderate)</b>	Moderate; minimal, local or noninvasive intervention indicated; The AE interferes with routine activities. The patient may experience significant discomfort.
<b>Grade 3 (Severe)</b>	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.
<b>Grade 4 (Life-Threatening)</b>	Life-threatening consequences; urgent intervention indicated.
<b>Grade 5 (Fatal)</b>	Death related to AE

Based on the CTCAE Version 5.0

The term “severe” is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (eg, ‘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 Treatment

Determination of the relationship between an AE and any component of the study treatment will be made using the guidelines presented in Table 5.

**Table 5 Guidelines for Determining the Relationship (if any) Between Adverse Event and the Study Treatment**

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

Pregnancy or lactation is an exclusion criterion for this study. Pregnancy per se is not considered an AE unless there is cause to believe that the study treatment 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 sponsor, 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 the sponsor 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.

### **9.1.6 Dosing Errors**

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

Subsequent dosing shall be discontinued until the investigator and sponsor have both determined that it is 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](#).

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.

The female patients/pregnant female partner of male patients will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the female patients/pregnant female partner of male patients and the neonate and the information will be forwarded to the sponsor.

## **9.2 SERIOUS ADVERSE EVENT REPORTING**

### **9.2.1 Reporting Requirements**

Any SAE made known to the investigator during the study must be reported in the EDC within 24 hours by the investigator to the sponsor, whether or not the SAE is considered to be related to any component of the study treatment (PULSAR/IMSA101/ICI).

If the EDC is not available, complete the paper SAE form and send to CRO Pharmacovigilance.

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 treatment and linked by the investigator to this study, should be reported to the sponsor's 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.

The sponsor or delegate has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

The sponsor or delegate will notify the regulatory authorities of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after sponsor's first knowledge of the event. A complete report should be provided within 15 calendar days after sponsor's first knowledge of the event and must include an assessment of the importance and implication of the findings and/or previous experience on the same or similar medical products.

Any suspected unexpected serious adverse reaction (SUSAR) that is not fatal or life-threatening must be filed as soon as possible but no later than 15 calendar days after sponsor's first knowledge of the event. Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

## 10 STATISTICAL METHODS

The statistical analysis plan (SAP) will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section.

### 10.1 ANALYSIS DATASETS

Analysis dataset	Description
Enrolled	All patients who have signed the informed consent.
Full Analysis Set (FAS)	All enrolled patients.  Randomized patients will be classified according to the treatment to which they are randomized.
Safety Analysis Set (SAF)	All patients receiving at least one dose of study treatment.  The patients will be analyzed according to the group corresponding to the treatment that they actually receive.
Intention-to-Treat (ITT)	All patients who receive at least one dose of study treatment.  Randomized patients will be classified according to the treatment to which they are randomized.  The ITT set will be used for efficacy analyses.
Per Protocol Set (PPS)	All patients who receive at least one dose of study treatment and either undergo at least one post-baseline assessment or withdraw due to death or disease progression before any evaluation and have no major protocol violations, as defined by the sponsor prior to database lock.  The PPS will be used for efficacy analyses.

## 10.2 DETERMINATION OF SAMPLE SIZE

The total number of patients in each treatment arm will be as follows:

- a. Approximately 15 patients in the control arm (PULSAR-ICI)
- b. Approximately 30 patients in the experimental arm (PULSAR-ICI + IMSA101), including 24 randomized patients and 6 patients in the safety run-in who are treated at the dose level selected for the experimental arm.

The primary evaluation for efficacy is based on the proportion of patients remaining progression-free at 12 months after the start of the study treatment. The study is initially designed to enroll 45 patients. If the proportions of patients remaining progression-free at 12 months after commencement of therapy is assumed to be 20% in the control arm and 40% in the experimental arm, a total of 45 subjects will provide 53% power, assuming a two-sided hypothesis test with a significance level of 20%.

This study is designed for signal detection. A sample size adaptation may be considered in order to acquire adequate power under the control of type I error. A larger full-powered randomized trial may also be considered if the provocative signal of efficacy is detected in this study, even if the efficacy is not statistically significant.

## 10.3 DATA PRESENTATION

### 10.3.1 General Considerations

All measured variables and derived parameters will be listed and tabulated. Summary descriptive statistics will be provided for all safety, efficacy, and baseline/demographic variables. Data of all study sites and regions will be pooled for statistical analysis. Tabulation of results will be displayed by visit and by treatment/dose cohort and overall.

Continuous variables will be summarized descriptively with number of patients, mean, median, standard deviation (SD), Q1, Q3, minimum and maximum. Categorical variables will be summarized with number and percentage of patients.

For all endpoint measurements, the last non-missing values before the first administration of study treatment will be used as the baseline for the respective endpoints.

Protocol deviations, including what generally constitutes major (important) or minor protocol deviations, are detailed in the SAP in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. All protocol deviations will be reviewed and classified as either important or minor by the clinical team.

### **10.3.2 Disposition of Patients**

A tabulation of patient disposition will be presented by treatment arm, including the number in each analysis set, the number that withdrew prior to completing the study, and reason(s) for withdrawal.

### **10.3.3 Demographic and Baseline Characteristics**

Demographic and baseline characteristics will be summarized by treatment arm in appropriate tables with descriptive statistics.

Demographic and baseline characteristics to be captured include (but not necessarily limited to):

- Age, gender, race
- Smoking history
- Tumor type
- Body weight
- Height
- ECOG performance status
- Disease history

### **10.3.4 Prior and Concomitant Medications**

All medications will be classified as follows:

- Prior use ended before the first day of study treatment
- Concomitant use on or after the first dose of study treatment

The number and percentage of patients taking prior and concomitant medication will be summarized by treatment arm.

### **10.3.5 Safety Data**

All safety summaries will be provided for the SAF.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

All safety variables will be presented in by-patient listings. Safety data will be listed by patient and treatment. Listings of all AEs will contain information of seriousness, severity, relationship, sequelae, and onset date and resolved date.

Study treatment exposure (treatment duration, number of cycles, dose intensity, and dose adjustment) will be summarized with descriptive statistics. All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to CTCAE v5.0. All AEs, SAEs, AEs leading to death, grade  $\geq 3$  AEs, and AEs leading to study treatment discontinuation or interruption that occur on or after the initiation of study treatment will be summarized by system organ class and preferred terms, and by severity grade if necessary. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be summarized.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate.

Additional analyses may be performed as indicated.

### **10.3.6 Primary Efficacy Data**

The primary efficacy analysis will be conducted on the ITT population, using the ITT principle: with patients grouped according to the study arm assigned at randomization, regardless of whether they receive any assigned study drug, cause of treatment discontinuation, etc. The number and proportion of subjects remaining progression-free at 12 months after the start of the study treatment will be descriptively summarized by treatment group. The difference in progression-free rate at 12 months between treatment groups will be compared using Fisher's exact test with the type I error controlled at a two-sided significance level of 0.2. The null and alternative hypotheses regarding the proportion of subjects remaining progression-free at 12 months after the start of the study treatment can be phrased in terms of  $P_E$  and  $P_C$  for experimental arm and control arm, respectively:

$H_0: P_E = P_C$  versus  $H_1: P_E \neq P_C$

If a patient withdraws from the study before disease progression or death, and the disease progression status at 12 month is missing, this patient will be treated as PD.

In addition, for the descriptive purpose, the point estimate of proportion of subjects remaining progression-free at 12 months after the start of the study treatment and its 95% Clopper-Pearson confidence interval (CI) will be provided for each treatment group.

For the sensitivity analysis, if a patient withdraws from the study before disease progression or death, or any other reason causes the disease progression status at 12 month is missing, this patient will be excluded from the analysis. The Fisher's exact test will be applied using the similar approach mentioned above. The point estimate of the proportion and its 95% CI will be provided as well.

All these analyses will also be performed on PPS.

### **10.3.7 Secondary Efficacy Data**

All efficacy summaries will be provided for the ITT and PPS.

The proportion of patients remaining progression-free at 8-week intervals from 6 months to 22 months after the start of the study treatment will be summarized by treatment group and be analyzed using the similar approaches for the primary efficacy endpoint.

TTP, defined as the time from commencement of therapy to progression based on RECIST Version 1.1 and iRECIST. Patients who are not progressed at the time of the analysis will be censored at the time of last tumor assessment on or prior to the clinical cutoff date. TTP will be estimated using Kaplan-Meier methods by treatment arm and displayed graphically. Median event times and two-sided 95% CI for each median will be provided based on the Brookmeyer-Crowley method.

PFS is defined as the time from commencement of therapy to progression or any cause of death based on RECIST Version 1.1 and iRECIST. Patients who have not experienced progression or died at the time of analysis will be censored at the date of the last evaluable assessment. PFS will be estimated using Kaplan-Meier methods by treatment arm and displayed graphically. Median event times and two-sided 95% CI for each median will be provided based on the Brookmeyer-Crowley method. A two-sided log-rank test might be used to compare PFS between the two arms, if needed.

DOR is defined as the time from the first occurrence of a documented objective response to disease progression or death from any cause (whichever occurs first), based on RECIST Version 1.1 and iRECIST. Patients who have not progressed and who have not died at the time of the analysis will be censored at the time of last tumor assessment on or prior to the clinical cutoff date. The analysis methods are similar to those described for TTP.

Objective response (OR) is defined as a complete or partial response based on RECIST Version 1.1 and iRECIST. Patients not meeting these criteria, including patients without any post-baseline tumor assessment, will be considered non-responders. ORR, defined as the percentage of patients who have an objective response, will be estimated for each treatment arm. The respective 95% CIs will be calculated using the Clopper-Pearson method.

The ORR via RECIST Version 1.1 and iRECIST will be presented with exact 2-sided 95% CIs using the Clopper-Pearson method.

### **10.3.8 Quality of Life Data**

The QoL summary will be provided for the ITT and PPS.

QoL data will be summarized using descriptive statistics.

### **10.3.9 Missing Data**

Missing values will be regarded as missing. No imputation method will be applied for missing data transformation. Analyses will be performed using the available data points.

The missing components of incomplete dates will be assumed as the most conservative value possible. For example, if the start date has a missing day value, the first day of the month will be imputed for study day computations. If day is missing for an end date, the last day of the month will be imputed. Similar logic will be assumed for missing month and year components.

Missing severities of AEs will not be imputed and will be considered missing in any tabulations of AE severity. If an AE is missing relationship to treatment, the event will be considered to be related.

Actual values, as they appear in the original eCRFs, will be presented in the patient data listings.

### **10.3.10 Futility Analysis**

A futility analysis for the experimental arm is planned when the tenth (10<sup>th</sup>) patient treated at the selected dose level has had the opportunity to reach 6 months. If 7 out of 10 patients have progressed or died, the study will be declared futile. Additional details will be described in the SAP.

## **10.4 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS**

Any changes 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 regulatory 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 ICH for GCP in clinical studies ([ICH E6\(R2\), 2016](#)).

### **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 (eg, 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 ICF (date, version).

The investigator is responsible for supplying the IRB/IEC with a copy of the current 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 (or by the legally authorized representatives) and by the physician (or qualified delegate) 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. Patients must be reconsented to the most current version of the ICF(s) during their participation in the study.

## 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 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 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 (eg, 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 (ie, 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 eCRFs, 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 the 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 E6\(R2\), 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 (ie, Master Service Agreement).

The IRB/IEC should retain all relevant records (eg, 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 the sponsor 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 the sponsor 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 sponsor may terminate the investigator's participation in this study after submission of a written notice. The sponsor 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/research ethics board 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

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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, eg, 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

Source: [Oken et al., 1982](#)

## 13.2 RECIST VERSION 1.1 GUIDELINE

All tumor assessment findings will be evaluated for response according to RECIST Version 1.1 ([Eisenhauer et al., 2009](#)) at the scheduled time points in [Table 1](#) and Table 2.

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

<b>RECIST Version 1.1 Lesion Response</b>	
<b>Evaluation of target lesions</b>	
Complete response (CR):	Disappearance of all extranodal target lesions. All pathological lymph nodes must have decreased to < 10 mm in short axis
Partial response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the Baseline sum of diameters
Progressive disease (PD):	At least a 20% increase in the sum of diameters of target lesions from the smallest value on trial (including Baseline, if that is the smallest). The sum of diameters must also demonstrate an absolute increase of at least 5 mm. Or, the appearance of one or more new lesions
Stable disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD
<b>Evaluation of nontarget lesions</b>	
Complete response (CR):	Disappearance of all extranodal nontarget lesions, all lymph nodes must be nonpathological in size (< 10 mm in short axis), and normalization of tumor marker level
Non-CR/Non-PD:	Persistence of 1 or more nontarget lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive disease (PD):	Unequivocal progression of existing nontarget lesions. Or, the appearance of one or more new lesions

Note: Evaluations for target, nontarget, and new lesions are to be considered together to assess an overall response status.

Source: [Eisenhauer et al., 2009](#)

### **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 on study (including baseline).

### **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 sum on study (including baseline). **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	Not Evaluable	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	Not Evaluable
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	Not Evaluable
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 the study. All lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the “merged lesion”.

### **CT / MRI**

CT and MRI might be the best currently available and reproducible methods to measure target lesions selected for response assessment. CT and MRI should be performed with cuts of 5 mm or less in slice thickness contiguously.

### 13.3 IMMUNE-BASED RECIST (IRECIST) GUIDELINE

All tumor assessment findings will also be evaluated for response according to iRECIST (reviewed in [Seymour et al., 2017](#)) at the scheduled time points in [Table 1](#) and Table 2.

Immunotherapy may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST Version 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Note: “i” indicates immune responses assigned using iRECIST.

iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST Version 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
  - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
  - Continued unequivocal progression in non-target disease with an increase in tumor burden
  - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST Version 1.1 criteria are met in lesion types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). The prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response providing that iCPD is not documented at the next assessment after iUPD.

The same definitions of *Response Duration* and *Stable Disease Duration* applied for RECIST Version 1.1 also apply for iRECIST.

## Time Point Response of iRECIST

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last time point	iUPD with no change OR decrease from last time point	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size ( $\geq 5$ mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last time point, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST Version 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: <ul style="list-style-type: none"> <li>further increase in SOM of at least 5 mm, otherwise remains iUPD</li> </ul>
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: <ul style="list-style-type: none"> <li>previously identified T lesion iUPD SOM <math>\geq 5</math> mm and / or</li> <li>NT lesion iUPD (prior assessment - need not be unequivocal PD)</li> </ul>
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: <ul style="list-style-type: none"> <li>previously identified T lesion iUPD <math>\geq 5</math> mm and / or</li> <li>previously identified NT lesion iUPD (need not be unequivocal) and /or</li> </ul>

				<ul style="list-style-type: none"> <li>size or number of new lesions previously identified</li> </ul>
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Abbreviations: iCPD = confirmed progression; iCR = complete response; iPR = partial response; iSD = stable disease; iUPD = unconfirmed progression; NA = not applicable; NL = new lesion; NT = non-target; SOM = sum of measures

\* Using RECIST Version 1.1 principles. If no PSPD occurs, RECIST Version 1.1 and iRECIST categories for CR, PR and SD would be the same.

\*\* in any lesion category.

\*\*\* previously identified in assessment immediately prior to this time point.

Source: [Seymour et al., 2017](#)

All patients will have their Best Overall Response from the start of study treatment until the end of treatment classified as outlined below.

### Best Overall Responses of iRECIST

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, iCPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

Table assumes a randomized study where confirmation of CR or PR is not required.

BOR = best overall response; NE = not evaluable that cycle; TPR = response at that time point.

For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

Source: [Seymour et al., 2017](#)

The same Method of Measurement applied for RECIST Version 1.1 also apply for iRECIST.

## 13.4 CREATININE CLEARANCE

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

### **Females:**

*For serum creatinine concentration in mg/dL:*

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

### **Males:**

*For serum creatinine concentration in mg/dL:*

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

## 13.5 CONTACT LIST

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