STATISTICAL ANALYSIS PLAN

Study Title:	Lerapolturev (formerly known as PVSRIPO) with and without Immune Checkpoint Blockade in Advanced PD-1 Refractory Melanoma
Phase:	II
Protocol No.:	LUMINOS-102
Protocol Date(s):	Protocol Amendment 4.0: 14 January 2022
Analysis Plan Version and Date:	Final Version 1.0: 03 August 2022 Final Version 2.0: 19 November 2024
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CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

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1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the planned data summary and analysis of data from Protocol LUMINOS-102. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection.

1.1. STUDY OVERVIEW

This multi-center, open-label, randomized, Phase 2 study will investigate the efficacy and safety of lerapolturev alone (Arm 1) or in combination with an anti-programmed cell death 1 (PD-1) inhibitor (Arm 2) in participants with unresectable, advanced anti-PD-1/L1 refractory melanoma. Following a 6-participant safety run-in period, up to approximately 50 participants with unresectable cutaneous melanoma who previously failed an anti-PD-1/L1-based therapy will be randomized 1:1 to receive either lerapolturev or lerapolturev plus an anti-PD-1.

As of December 10, 2021, the safety run-in was completed and a total of 17 participants had been enrolled. Upon review of the safety profile for lerapolturev administered as monotherapy or in combination with anti-PD-1 therapy, and in agreement with the Data Safety Monitoring Committee (DSMC), the protocol was amended to allow the total lerapolturev dose to be increased from 6 x 10^8 $TCID_{50}$/visit to a maximum of 1.6 x 10^9 $TCID_{50}$/visit, with up to 6 lesions injected per visit. The lerapolturev dosing schedule (referred to hereafter as once weekly (QW)) was also updated in this amendment to include weekly injections x 7 followed by either dosing every three weeks (Q3W) (lerapolturev monotherapy [Arm 1] or in combination with pembrolizumab [Arm 2]) or dosing every four weeks (Q4W) (combination with nivolumab [Arm 2]).

In Arm 2, anti-PD-1 therapy will be administered per the manufacturer's prescribing information concurrently with lerapolturev beginning Day 1. Participants enrolled in the safety run-in, or those randomized to Arm 1 (lerapolturev only), are allowed to crossover to Arm 2 for the following reasons: (1) disease progression per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, (2) once a partial response (PR) lasts at least 6 months, (3) after 26 weeks on study without RECIST-defined progression (ie, stable disease (SD) or unconfirmed PR or complete response (CR)). Those participants who crossover to Arm 2 may be required to repeat or continue the QW dosing, depending on when the crossover occurs, as shown in Table 1 (See Section 3.1.1 of the Study Protocol for additional information).

Table 1. Lerapolturev Injection Schedule After Crossover

Schedule of lerapolturev monotherapy injections at the time of crossover	Timing of when criteria for crossover are met	Recommended lerapolturev dosing schedule for combination
Participant is receiving weekly injections	< 6 months from Cycle 1 Day 1	Continue QW injections for a total of 7 (monotherapy + combination) followed by Q3W dosing (pembrolizumab) or Q4W dosing (nivolumab)*
Participant is receiving injections Q3W (pembrolizumab) or Q4W (nivolumab)	< 6 months from Cycle 1 Day 1	Continue concurrent dosing schedule

Schedule of lerapolturev monotherapy injections at the time of crossover	Timing of when criteria for crossover are met	Recommended lerapolturev dosing schedule for combination
Participant is receiving injections Q3W (pembrolizumab) or Q4W (nivolumab)	≥ 6 months from Cycle 1 Day 1	Weekly x 7 followed by every Q3W (pembrolizumab) or Q4W dosing (nivolumab)

After 12 participants have been treated under Study Protocol Amendment 4 (amendment that increased the lerapolturev dose and changed to QW injection schedule) and on study approximately 21 days (ie, once n=6 participants per treatment arm receiving lerapolturev QW have completed the dose-limiting toxicity (DLT) evaluation period), an additional safety review will be performed by the DSMC to confirm the safety of lerapolturev with or without anti-PD-1 and/or to make recommendations related to lerapolturev dose and/or schedule adjustments.

Participants receiving the Q3/4W schedule of injections are required to receive the increased lerapolturev dose and will be given the option to change to the QW schedule once Study Protocol Amendment 4 is open at their respective site.

1.2. SCHEDULE OF EVENTS

Table 2. Schedule of Assessments for Lerapolturev Monotherapy or Lerapolturev + Pembrolizumab

NOTE: Cycle length for lerapolturev monotherapy or lerapolturev + pembrolizumab is 3 weeks. Lerapolturev is administered weekly during Cycles 1 & 2 and every 3 weeks thereafter on the days indicated in the table below. Refer to the table below for the timing of other study assessments to be completed within each cycle.

Study Procedure[3]	Screening Period	Treatment			EOT Visit[15]	Survival Follow-up[16]
		Cycle 1	Cycle 2	≥ Cycle 3		
	(≤ 28D prior to C1D1)		+3W (+7D)	Q3W (+7D)	≤28D after last treatment	
Informed Consent[1]	X					
Medical History	X					
Physical Exam [2,3]	X	*C1D1*	*C2D1*	*Day 1 of each Cycle*	X	
Vital Signs[3]	X	*C1D1, C1D8, C1D15*	*C2D1, C2D8, C2D15*	*Day 1 of each Cycle*	X	
ECOG Performance Status[3]	X	*C1D1*	*C2D1*	*Day 1 of each Cycle*	X	
PV Immunization Booster[1]	*≥1W, but ≤6W before C1D1*					
Adverse Events	*Continuous from signing ICF until 30 days after last dose of study therapy*					
Concomitant Medications	*Continuous from signing ICF until 30 days after last dose of study therapy*					
Subsequent Anticancer Therapy					X	X
AESI, irAEs and SAEs	*Continuous from signing ICF until 90 days after last dose of study therapy or resolution/stabilization*					
Hematology [3,4]	X	*C1D1*	*C2D1*	*C3D1 then Q6W (ie, at every other visit) and as clinically indicated*	X	
Chemistry[3,4]	X	*C1D1*	*C2D1*	*C3D1 then Q6W (ie, at every other visit) and as clinically indicated*	X	
INR, PT, PTT (or aPTT)	X	*As clinically indicated*				
Thyroid Monitoring [3,5]	X	*Q6W (±7D) and as clinically indicated*				
Pregnancy Test[3,6]	*≤2D before C1D1*	*Q12W (±14D)*				
Cutaneous, Subcutaneous and Nodal Lesion Measurement and Photographs[3,7]	X	*C1D1, C1D8, C1D15*	*C2D1, C2D8, C2D15*	*Day 1 of each Cycle*	X	*per SOC*
Tumor Imaging[8]	*≤6W before C1D1*	*6 & 12W after C1D1, then Q12W thereafter. Crossover participants must have re-baseline imaging within 28D prior to administration of crossover C1D1 (ie, first dose of anti-PD-1 therapy)*				*per SOC*
Tissue Biopsy[9] *All samples to be collected prior to dosing at the given timepoint*	*Prior to PV Immunization Booster*	*C1D8*	*C2D1*	*At the time of PD ± 1 week (per RECIST)* ***Crossover Only:*** *within 1 week prior to crossover C1D1, 1 week after crossover C1D1 (pre-dose, if applicable), 3 weeks (+7d; pre-dose) after crossover C1D1, and at the time of PD ± 1 week (per RECIST) on the crossover regimen*		
Blood Collection[10] *All samples to be collected prior to dosing at the given timepoint*	*Prior to PV Immunization Booster*	*C1D1, C1D8*	*C2D1*	*C3D1 and at the time of PD ± 1 week (per RECIST)* ***Crossover Only:*** *within 1 week prior to crossover C1D1, 1 week after crossover C1D1 (pre-dose, if applicable), 3 weeks (+7d; pre-dose) after crossover C1D1, and at the time of PD ± 1 week (per RECIST) on the crossover regimen*		

Study Procedure[3]	Screening Period	Treatment			EOT Visit[15]	Survival Follow-up[16]
		Cycle 1	Cycle 2	≥ Cycle 3		
	(≤ 28D prior to C1D1)		+3W (+7D)	Q3W (+7D)	≤28D after last treatment	
Lerapolturev Administration[12]		*C1D1, C1D8, C1D15*	*C2D1, C2D8, C2D15*	*C3D1 and Q3W thereafter*		
ARM 2: Anti-PD-1 Administration (pembrolizumab) [11]		*C1D1*	*C2D1 (if given Q3W)*	*C3D1 and Q3W or Q6W thereafter per pembrolizumab package insert*		
Crossover from Arm 1 to Arm 2[13]		*If participant meets protocol-defined criteria*				
Lerapolturev Shedding: Injected Lesion[14]		*C1D1 (post-injection), C1D4, C1D8, C1D15 (post-injection), C1D18*	*C2D1, C2D15 (post-injection), C2D18*	*C3D1*		
Lerapolturev Shedding: Stool			*C2D8 (±3D)*			

AESI = adverse event of special interest; aPTT = activated partial thromboplastin time; C= cycle; CBC = complete blood count; CMP = comprehensive metabolic panel; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; ICF = Informed consent form; IgG = immunoglobulin G; INR = international normalized ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PD-1 = Programmed cell death protein 1; PT = prothrombin time; PTT = partial thromboplastin time; PV = poliovirus; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; SAE = serious adverse event; W = weeks

1. Informed Consent must be signed prior to initiation of screening activities.
2. Physical Exam: The screening physical examination should be a complete physical exam of major body systems and include the general appearance of the participant, height and weight, vital signs (temperature, respiratory rate, blood pressure (systolic and diastolic [mmHg]), and heart rate [bpm]), examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. During treatment and at the end of treatment (EOT) visit, weight assessment and limited symptom-directed physical examination are required. An evaluation of all skin lesions, including those injected with lerapolturev at the previous treatment visit, should be performed prior to subsequent lerapolturev injection.
3. Procedures and/or Assessments unless otherwise specified should occur on D1 of each Cycle. Any assessment or procedure scheduled on the same day as lerapolturev and/or anti-PD-1 administration should always precede receipt of study treatments. Note that laboratory assessments (eg, hematology, chemistry, thyroid monitoring) may be done up to 2 calendar days prior to Day 1 of the cycle.
4. Hematology and Chemistry: Blood draws for hematology and chemistry occurring on the same day as study treatment should be collected prior to lerapolturev injection and/or prior to anti-PD-1 infusion (as applicable). Hematology should include hemoglobin, white blood cell (WBC) count with differential and platelet count. Chemistry measured in serum should include the following: LDH, glucose, calcium, sodium, potassium, bicarbonate, chloride, BUN, creatinine, total protein, albumin, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, amylase, and lipase.
5. Thyroid Monitoring: Should include TSH, free T4, and free T3.
6. Pregnancy Test: A pregnancy test (urine-based allowed) must be performed for all female participants of childbearing potential during Screening (≤ 2 days of lerapolturev injection) and approximately every 12 weeks while on study. If a urine-based test produces an equivocal result, a serum-based test should be performed.
7. Measurement of Cutaneous, Subcutaneous and Nodal Lesions: Measurement by ruler or caliper (along with photographs) should occur prior to lerapolturev administration to determine/verify lerapolturev injection volumes for each lesion. For timepoint response assessment of target lesions not visible by radiography, ruler/caliper measurement with photographs should be performed prior to lerapolturev injection.

8. Tumor Imaging: Baseline imaging assessments should include CT of the chest, abdomen, and pelvis, a brain MRI, as well as photography of all cutaneous/visible lesions. Participants without evidence of central nervous system (CNS) disease at screening are not required to have brain imaging on study, provided clinical evidence of CNS disease does not emerge. All imaging should be performed with and without IV contrast (oral contrast can be used per institutional guidelines), provided participant can tolerate contrast agent (brain CT—preferably with IV contrast--is acceptable for those who cannot tolerate MRI). Photographic evaluation of visible lesions should precede lerapolturev injection, if occurring in the same visit. All qualifying scans prior to and during screening used to determine enrollment eligibility (ie, baseline scans prior to initiating anti-PD-1, as well as initial and confirmatory scans demonstrating disease progression per immune Response Evaluation Criteria in Solid Tumors (iRECIST) prior to enrollment) should be provided to the central imaging vendor, where possible. Imaging should be performed using identical techniques and equipment, where possible.
9. Tissue Biopsy for Biomarker Assessment: Participants are required to provide a qualifying biopsy. Archival tissue collected ≤4 months prior to Day 1 is allowed in lieu of the qualifying biopsy, provided the participant has not received intervening systemic/intratumoral anti-cancer therapy since the biopsy was performed; if not available, the participant should have a qualifying biopsy taken during the Screening Period prior to polio boost vaccination. Biopsy of a previously irradiated lesion is not allowed unless there is documented disease progression in that lesion.
    - NOTE: At all timepoints, biopsies from all three sites (injected lesion, noninjected lesions and draining lymph nodes) should be collected if the biopsy is technically feasible and does not put the participant at significant risk. Examples of sites considered to be of significant risk include, but are not limited to, the following: biopsies of the brain, lung, mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel wall. For situations where the investigator determines biopsy of a lesion would (1) result in a significant decrease in the size of the lesion such that RECIST 1.1 response assessment would be confounded, or (2) increase the risk of lerapolturev leakage from the lesion, the mandatory biopsy for that timepoint can be waived. In addition, complete resection of target lesions is prohibited unless necessary for participant's safety as determined by the investigator.
    - Tissue from additional biopsies taken as part of standard of care may also be collected for analysis.
10. Blood Collection: Participants who experience an AE of Special Interest (AESI) of cytokine release syndrome (CRS) or immune effector cell associated neurotoxicity syndrome (ICANS) should have a blood sample drawn as soon as possible upon learning of the AESI, in order to allow for the profiling of cytokine changes related to the event.
11. Arm 2 Anti-PD-1 Administration: Participants randomized to Arm 2 should receive anti-PD-1 concurrently with lerapolturev while on study. Administration of the first anti-PD-1 dose should begin on C1D1 (+2 days). Where possible, participants should receive the same anti-PD-1 therapy that they previously failed prior to enrollment, dosed according to manufacturer's prescribing information.
12. Lerapolturev Administration: Up to 6 lesions may be injected with lerapolturev injection volume proportional to lesion size as determined from protocol Table 7. The same or different lesion(s) may be injected at each treatment visit, as described in protocol Section 5.3. The lerapolturev treatment cycle is Q3W for participants on Arm 1 and for Arm 2 or crossover participants receiving pembrolizumab, whether pembrolizumab is given Q3 or Q6W.
    - After Cycle 3, lerapolturev should be administered Q3W. If pembrolizumab is administered Q6W, lerapolturev should be continued Q3W.
    - NOTE: Participants previously treated with the Q3/4W lerapolturev schedule are allowed to receive the QW lerapolturev schedule per the guidance in protocol Section 3.1.2.
    - Where possible, at least one target lesion should remain uninjected for as long as feasible while on study to facilitate the anti-tumor response assessment of non-injected target lesions
13. Crossover from Arm 1 to Arm 2: Participants enrolled in the safety run-in or randomized to Arm 1 are allowed to crossover to Arm 2 following radiologic disease progression (per RECIST criteria), once a PR lasts ≥ 6 months, or after 36 weeks on study without progression or confirmed PR (per RECIST criteria). Where possible, participants should receive the same anti-PD-1 therapy on which they had disease progression prior to enrollment, which should be administered according to manufacturer's prescribing information. The below assessments should be completed for participants at the time of crossover:
    - Tumor Imaging: All participants crossing over to Arm 2 should have a complete tumor assessment (ie, scans and ruler/caliper measurement of skin lesions with photography) within 28 days prior to the first cycle of the lerapolturev/anti-PD-1 combination. Scans and photographic ruler/caliper assessments performed to document disease progression prior to crossover are acceptable, provided they occur within 28 days prior to the initial treatment with the lerapolturev/anti-PD-1 combination.
    - Cutaneous and Subcutaneous Measurements and Imaging: For participants crossing over from Arm 1 to Arm 2, ruler/caliper measurement with photographs should be performed within 28 days prior to their first treatment with the lerapolturev/anti-PD-1 combination (along with scans).

- Lerapolturev Administration: See protocol Section 3.1.2 for guidance.
- Tissue Biopsy: Prior to crossover, a mandatory tissue biopsy (injected lesions, noninjected lesions and draining lymph nodes) should be performed, within 1 week prior to the first cycle of the lerapolturev/anti-PD-1 combination (see protocol Section 7.4); the biopsy taken at the time of PD can be used as the biopsy prior to the first crossover treatment cycle. Additional mandatory biopsies (injected lesions, noninjected lesions, and draining lymph nodes) should be performed 1 week (±2days) and 3 weeks (+7d) after Day 1 of crossover, and within 7 days of confirmed crossover PD. Any biopsy scheduled on same day as lerapolturev injection should be collected prior to treatment.

14. Lerapolturev Viral Shedding:
    - The individual lesion receiving the largest injection volume of lerapolturev at C1D1, C1D15, and C2D15 should be designated for swabbing during that treatment cycle on the days indicated above (ie, the same lesion should be swabbed at each timepoint within a given cycle). Separate swabs should be used to test each area in triplicate (ie, samples are not to be combined or pooled), as described. Following sample collection, the swabbed lesion should be wiped with alcohol, and redressed with an occlusive dressing as required.
    - The lesion injected with lerapolturev at C1D1, C1D15, and C2D15 should be swabbed at least 15 minutes, but less than 4 hours, after the injection site has been cleaned and bandaged post-lerapolturev injection, as described in protocol Section 3.2. All other lesion swabbing timepoints have a ±1D window for collection, but those scheduled on the same day of a given treatment cycle must be collected prior to lerapolturev administration.
    - The injection site, as well as the inside and outside of the occlusive dressing should be swabbed independently (ie, samples are not to be combined or pooled into a single collection tube) in triplicate (ie, 3 swabs collected per area of interest), with the corresponding swab for each tested area labeled and placed into its own container of viral transport medium, according to the laboratory manual. The swabbed lesion should be cleaned and redressed with a new occlusive dressing once lesion swabbing has been completed, as described in protocol Section 5.3.
    - Stool samples may be collected at the participant's home up to 3 days prior to or after the C2D8 clinic visit, per the lab manual.
15. End of Treatment Visit should be performed within 28 days after the last dose of study drug(s). The visit should include a focused and symptom directed physical assessment, cutaneous, subcutaneous, and nodal tumor measurements (including photographs), as well as radiographic tumor imaging.
16. Survival Follow-up: Scans and cutaneous, subcutaneous, and nodal lesion measurements performed per SOC should still be collected for participants in post-EOT survival follow-up who discontinued study treatments for reasons other than disease progression. The collection of lesion measurement (cutaneous, subcutaneous, and nodal, and scans) performed per standard of care should continue until confirmed progression or the start of the next anti-cancer therapy. Sites should continue to collect post-study therapies and survival status for follow-up duration.

Table 3. Schedule of Assessments for Lerapolturev + Nivolumab

NOTE: Cycle length for lerapolturev + nivolumab is 4 weeks. Lerapolturev is administered weekly during Cycles 1 & 2 and every 4 weeks thereafter on the days indicated in the table below. Refer to the table below for the timing of other study assessments to be completed within each cycle.

Study Procedure[3]	Screening Period	Treatment			EOT Visit[15]	Survival Follow-up[16]
		Cycle 1	Cycle 2	≥ Cycle 3		
	(≤ 28D prior to C1D1)		+4W (+7D)	Q4W (+7D)	≤28D after last treatment	
Informed Consent[1]	X					
Medical History	X					
Physical Exam [2,3]	X	*C1D1*	*C2D1*	*Day 1 of each Cycle*	X	
Vital Signs[3]	X	*C1D1, C1D8, C1D15 C1D22*	*C2D1, C2D8, C2D15*	*Day 1 of each Cycle*	X	
ECOG Performance Status[3]	X	*C1D1*	*C2D1*	*Day 1 of each Cycle*	X	
PV Immunization Booster[1]	*≥1W, but ≤6W before C1D1*					
Adverse Events	*Continuous from signing ICF until 30 days after last dose of study therapy*					
Concomitant Medications	*Continuous from signing ICF until 30 days after last dose of study therapy*					
Subsequent Anticancer Therapy					X	X
AESI, irAEs and SAEs	*Continuous from signing ICF until 90 days after last dose of study therapy or resolution/stabilization*					
Hematology [3,4]	X	*C1D1*	*C2D1*	*C3D1 then Q8W (ie, at every other visit) and as clinically indicated*	X	
Chemistry[3,4]	X	*C1D1*	*C2D1*	*C3D1 then Q8W (ie, at every other visit) and as clinically indicated*	X	
INR, PT, PTT (or aPTT)	X	*As clinically indicated*				
Thyroid Monitoring [3,5]	X		X	*Day 1 of each Cycle*	X	
Pregnancy Test[6]	*≤2D before C1D1*	*Q12W (±14D)*				
Cutaneous, Subcutaneous, and Nodal Lesion Measurement and Photographs[3,7]	X	*C1D1, C1D8, C1D15 C1D22*	*C2D1, C2D8, C2D15*	*Day 1 of each Cycle*	X	*per SOC*
Tumor Imaging[8]	*≤6W before C1D1*	*6 & 12W after C1D1, then Q12W thereafter. Crossover participants must have re-baseline imaging within 28D prior to administration of crossover C1D1 (ie, first dose of anti-PD-1 therapy)*				*per SOC*
Tissue Biopsy[9] *All samples to be collected prior to dosing at the given timepoint*	*Prior to PV Immunization Booster*	*C1D8, C1D22*		*At the time of PD ± 1 week (per RECIST)* ***Crossover Only:*** *within 1 week prior to crossover C1D1, 1 week after crossover C1D1 (pre-dose, if applicable), 3 weeks (+7d; pre-dose) after crossover C1D1, and at the time of PD ± 1 week (per RECIST) on the crossover regimen*		
Blood Collection[10] *All samples to be collected prior to dosing at the given timepoint*	*Prior to PV Immunization Booster*	*C1D1, C1D8, C1D22*	*C2D15*	*At the time of PD ± 1 week (per RECIST)* ***Crossover Only:*** *within 1 week prior to crossover C1D1, 1 week after crossover C1D1 (pre-dose, if applicable), 3 weeks (+7d; pre-dose) after crossover C1D1, and at the time of PD ± 1 week (per RECIST) on the crossover regimen*		

Study Procedure[3]	Screening Period	Treatment			EOT Visit[15]	Survival Follow-up[16]
		Cycle 1	Cycle 2	≥ Cycle 3		
	(≤ 28D prior to C1D1)		+4W (+7D)	Q4W (+7D)	≤28D after last treatment	
Lerapolturev Administration[12]		*C1D1, C1D8, C1D15 C1D22*	*C2D1, C2D8, C2D15*	*C3D1 and Q4W thereafter*		
ARM 2: Anti-PD-1 Administration (nivolumab) [11]		*C1D1 (C1D15 if nivolumab Q2W)*	*C2D1 (C2D15 if nivolumab Q2W)*	*C3D1 and Q2W or Q4W thereafter per nivolumab package insert*		
Crossover from Arm 1 to Arm 2 [13]		*If participant meets protocol-defined criteria*				
Lerapolturev Shedding: Injected Lesion[14]		*C1D1 (post-injection), C1D4, C1D8, C1D15 (post-injection), C1D18 C1D22*	*C2D8 (post-injection), C2D11, C2D15*			
Lerapolturev Shedding: Stool			*C2D1 (±3D)*			

AESI = adverse event of special interest; aPTT = activated partial thromboplastin time; C= cycle; CBC = complete blood count; CMP = comprehensive metabolic panel; CT = computed tomography; D= day; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; ICF = Informed consent form; IgG = immunoglobulin G; INR = international normalized ratio; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PD-1 = Programmed cell death protein 1; PT = prothrombin time; PTT = partial thromboplastin time; PV = poliovirus; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; SAE = serious adverse event; W = weeks

1. Informed Consent must be signed prior to initiation of screening activities.
2. Physical Exam: The screening physical examination should be a complete physical exam of major body systems and include, the general appearance of the participant, height and weight, vital signs (temperature, respiratory rate, blood pressure (systolic and diastolic [mmHg]), and heart rate [bpm]), examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. During treatment and at the end of treatment (EOT) visit, weight assessment and limited symptom-directed physical examination are required. An evaluation of all skin lesions, including those injected with lerapolturev at the previous treatment visit, should be performed prior to subsequent lerapolturev injection.
3. Procedures and/or Assessments unless otherwise specified should occur on D1 of each Cycle. Any assessment or procedure scheduled on the same day as lerapolturev and/or anti-PD-1 administration should always precede receipt of study treatments. Note that laboratory assessments (eg, hematology, chemistry, thyroid monitoring) may be done up to 2 calendar days prior to Day 1 of the cycle.
4. Hematology and Chemistry: Blood draws for hematology and chemistry occurring on the same day as study treatment should be collected prior to lerapolturev injection and/or prior to anti-PD-1 infusion (as applicable). Hematology should include hemoglobin, white blood cell (WBC) count with differential and platelet count. Chemistry measured in serum should include the following: LDH, glucose, calcium, sodium, potassium, bicarbonate, chloride, BUN, creatinine, total protein, albumin, ALP, AST, ALT, total bilirubin, amylase, and lipase.
5. Thyroid Monitoring: Should include TSH, free T4, and free T3.
6. Pregnancy Test: A pregnancy test (urine-based allowed) must be performed for all female participants of childbearing potential during screening (≤ 2 days of lerapolturev injection) and approximately every 12 weeks while on study. If a urine-based test produces an equivocal result, a serum-based test should be performed.

7. Measurement of Cutaneous, Subcutaneous, and Nodal Lesions: Measurement by ruler or caliper (along with photographs) should occur prior to lerapolturev administration to determine/verify lerapolturev injection volumes for each lesion. For timepoint response assessment of target lesions not visible by radiography, ruler/caliper measurement with photographs should be performed prior to lerapolturev injection.
8. Tumor Imaging: Baseline imaging assessments should include CT of the chest, abdomen, and pelvis, a brain MRI, as well as photography of all cutaneous/visible lesions. Participants without evidence of central nervous system (CNS) disease at screening are not required to have brain imaging on study, provided clinical evidence of CNS disease does not emerge. All imaging should be performed with and without IV contrast (oral contrast can be used per institutional guidelines), provided participant can tolerate contrast agent (brain CT—preferably with IV contrast--is acceptable for those who cannot tolerate MRI). Photographic evaluation of visible lesions should precede lerapolturev injection, if occurring in the same visit. All qualifying scans prior to and during screening used to determine enrollment eligibility (ie, baseline scans prior to initiating anti-PD-1, as well as initial and confirmatory scans demonstrating disease progression per iRECIST prior to enrollment) should be provided to the central imaging vendor, where possible. Imaging should be performed using identical techniques and equipment, where possible.
9. Tissue Biopsy for Biomarker Assessment: Participants are required to provide a qualifying biopsy. Archival tissue collected ≤4 months prior to Day 1 is allowed in lieu of the qualifying biopsy, provided the participant has not received intervening systemic/intratumoral anti-cancer therapy since the biopsy was performed; if not available, the participant should have a qualifying biopsy taken during the Screening Period prior to polio boost vaccination. Biopsy of a previously irradiated lesion is not allowed unless there is documented disease progression in that lesion.
    - NOTE: At all timepoints, biopsies from all three sites (injected lesion, noninjected lesions and draining lymph nodes) should be collected if the biopsy is technically feasible and does not put the participant at significant risk. Examples of sites considered to be of significant risk include, but are not limited to, the following: biopsies of the brain, lung, mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel wall. For situations where the investigator determines biopsy of a lesion would (1) result in a significant decrease in the size of the lesion such that RECIST 1.1 response assessment would be confounded, or (2) increase the risk of lerapolturev leakage from the lesion, the mandatory biopsy for that timepoint can be waived. In addition, complete resection of target lesions is prohibited unless necessary for participant's safety as determined by the investigator.
    - Tissue from additional biopsies taken as part of standard of care may also be collected for analysis.
10. Blood Collection: Participants who experience an AE of Special Interest (AESI) of cytokine release syndrome (CRS) or immune effector cell associated neurotoxicity syndrome (ICANS) should have a blood sample drawn as soon as possible upon learning of the AESI, in order to allow for the profiling of cytokine changes related to the event.
11. Arm 2 Anti-PD-1 Administration: Participants randomized to Arm 2 should receive anti-PD-1 concurrently with lerapolturev while on study. Administration of the first anti-PD-1 dose should begin on C1D1 (+2 days). Where possible, participants should receive the same anti-PD-1 therapy that they previously failed prior to enrollment, dosed according to manufacturer's prescribing information. The lerapolturev treatment cycle is Q4W for participants receiving nivolumab, whether nivolumab is given Q2 or Q4W.
12. Lerapolturev Administration: Up to 6 lesions may be injected with lerapolturev injection volume proportional to lesion size as determined from protocol Table 7. The same or different lesion(s) may be injected at each treatment visit, as described in protocol Section 5.3.
    - After Cycle 3, lerapolturev should be administered Q4W in Arm 2 participants receiving nivolumab. If nivolumab is administered Q2W, lerapolturev should be continued Q4W.
    - NOTE: Participants previously treated with the Q3/4W lerapolturev schedule are allowed to receive the QW lerapolturev schedule per the guidance in Section 3.1.2.
    - Where possible, at least one target lesion should remain uninjected for as long as feasible while on study to facilitate the anti-tumor response assessment of non-injected target lesions
13. Crossover from Arm 1 to Arm 2: Participants enrolled in the safety run-in or randomized to Arm 1 are allowed to crossover to Arm 2 following radiologic disease progression (per RECIST criteria), once a PR lasts ≥ 6 months, or after 26 weeks on study without progression or confirmed PR (per RECIST criteria). Where possible, participants should receive the same anti-PD-1 therapy on which they had disease progression prior to enrollment, which should be administered according to manufacturer's prescribing information. The below assessments should be completed for participants at the time of crossover:
    - Tumor Imaging: All participants crossing over to Arm 2 should have a complete tumor assessment (ie, scans and ruler/caliper measurement of skin lesions with photography) within 28 days prior to the first cycle of the lerapolturev/anti-PD-1 combination. Scans and photographic ruler/caliper assessments performed to document disease progression prior to crossover are acceptable, provided they occur within 28 days prior to the initial treatment with the lerapolturev/anti-PD-1 combination.

- Cutaneous and Subcutaneous Measurements and Imaging: For participants crossing over from Arm 1 to Arm 2, ruler/caliper measurement with photographs should be performed within 28 days prior to their first treatment with the lerapolturev/anti-PD-1 combination (along with scans). Lerapolturev Administration: See Section 3.1.1 for guidance.
- Tissue Biopsy: Prior to crossover, a mandatory tissue biopsy (injected lesions, noninjected lesions and draining lymph nodes) should be performed, within 1 week prior to the first cycle of the lerapolturev/anti-PD-1 combination (see protocol Section 7.4); the biopsy taken at the time of PD can be used as the biopsy prior to the first crossover treatment cycle. Additional mandatory biopsies (injected lesions, noninjected lesions, and draining lymph nodes) should be performed 1 week (±2days) and 3 weeks (+7d) after Day 1 of crossover, and within 7 days of confirmed crossover PD. Any biopsy scheduled on same day as lerapolturev injection should be collected prior to treatment.

14. Lerapolturev Viral Shedding:
    - The individual lesion receiving the largest injection volume of lerapolturev at C1D1, C1D15, and C2D8 should be designated for swabbing during that treatment cycle on the days indicated above (ie, the same lesion should be swabbed at each timepoint within a given cycle). Separate swabs should be used to test each area in triplicate (ie, samples are not to be combined or pooled), as described. Following sample collection, the swabbed lesion should be wiped with alcohol, and redressed with an occlusive dressing as required.
    - The lesion injected with lerapolturev at C1D1, C1D15, and C2D8 should be swabbed at least 15 minutes, but less than 4 hours, after the injection site has been cleaned and bandaged post-lerapolturev injection, as described in Section 3.2. All other lesion swabbing timepoints have a ±1D window for collection, but those scheduled on the same day of a given treatment cycle must be collected prior to lerapolturev administration.
    - The injection site, as well as the inside and outside of the occlusive dressing should be swabbed independently (ie, samples are not to be combined or pooled into a single collection tube) in triplicate (ie, 3 swabs collected per area of interest), with the corresponding swab for each tested area labeled and placed into its own container of viral transport medium, according to the laboratory manual. The swabbed lesion should be cleaned and redressed with a new occlusive dressing once lesion swabbing has been completed, as described in protocol Section 5.3.
    - Stool samples may be collected at the participant's home up to 3 days prior to or after the C2D1 clinic visit, per the lab manual.
15. End of Treatment Visit should be performed within 28 days after the last dose of study drug(s). The visit should include a focused and symptom directed physical assessment, cutaneous, subcutaneous, and nodal tumor measurements (including photographs), as well as radiographic tumor imaging.
16. Survival Follow-up: Scans and cutaneous, subcutaneous, and nodal lesion measurements performed per SOC should still be collected for participants in post-EOT survival follow-up who discontinued study treatments for reasons other than disease progression. The collection of lesion measurement (cutaneous, subcutaneous, and nodal and scans) performed per SOC should continue until confirmed progression or the start of the next anti-cancer therapy. Sites should continue to collect post-study therapies and survival status for follow-up duration.

1.3. GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
BPM	Beats per minute
CBC	Complete blood count
CI	Confidence interval
CMP	Comprehensive metabolic panel
CNS	Central nervous system
CR	Complete response
CRF	case report form(s) (paper or electronic as appropriate for this study)
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DLT	Dose limiting toxicity
DOR	Duration of response
DRR	Durable response rate
DSMC	Data safety monitoring committee
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of treatment
FDA	Food and Drug Administration
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICE	Intercurrent events
ICF	informed consent form
ICH	International Council for Harmonization
IgG	Immunoglobulin G
INR	International normalized ratio
irAE	Immune-related adverse event
iRECIST	Immune response evaluation criteria in solid tumors
ISR	Injection site reaction
ITT	Intent-to-treat
LDH	Lactose dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging

Abbreviation	Definition
NCI	National Cancer Institute
NE	Not evaluable
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-1	Program death receptor - 1
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PR	Partial response
PT	Prothrombin time
PT	Preferred term
PTT	Partial thromboplastin time
PV	Poliovirus
QW	Once weekly
Q3W	Every three weeks
Q4W	Every four weeks
RECIST	Response evaluation criteria in solid tumors
SAE	serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System Organ Class
T3	triiodothyronine
T4	thyroxine
TCID	Tissue culture infectious dose
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary

2. OBJECTIVES

Objective	Endpoint
Primary	
To evaluate the antitumor activity of lerapolturev with and without anti-PD-1, in participants who have failed anti-PD-1/L1based therapy	• Overall Response Rate (ORR): the proportion of participants achieving confirmed complete (CR) or partial response (PR), per RECIST 1.1 criteria.
To evaluate the safety/tolerability of lerapolturev with and without anti-PD-1, in participants who have failed anti-PD-1/L1based therapy	• The frequency and severity of treatment-emergent adverse events (TEAEs) via National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, v5.0) • Changes in laboratory (hematology, chemistry) parameters • Changes in vital sign parameters • The frequency and severity of lerapolturev AESI • The frequency and severity of anti-PD-1 immune-related AE (irAE) • Study treatment discontinuation due to AEs
Secondary	
To evaluate survival and disease control outcomes of lerapolturev with and without anti-PD1, in participants who have failed anti-PD-1/L1based therapy	• Overall survival (OS): time from treatment group assignment until death from any cause • Duration of Response (DOR): time from confirmed objective response (CR or PR per RECIST 1.1) until unequivocal disease progression or death, whichever occurs first • Disease control rate (DCR): the proportion of participants achieving confirmed CR, confirmed PR, or SD per RECIST 1.1, as best response • Disease control rate-6months (DCR-6mo): the proportion of participants achieving confirmed CR (any duration), confirmed PR (any duration), or SD (≥ 6 months) per RECIST 1.1 as best response • Durable Response Rate (DRR): the proportion of participants with confirmed CR or PR (per RECIST 1.1) lasting at least 6 months • Progression-free survival (PFS): time (number of months) from treatment group assignment until date of documented radiologic disease progression per RECIST 1.1 or death due to any cause, whichever comes first

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. SAMPLE SIZE AND POWER

The determination of sample size in this two-arm, randomized open-label Phase 2 trial was based on feasibility and logistical considerations. As discussed in Protocol Section 1.1, the Sponsor estimates that the true activity of anti-PD-1 re-challenge in the anti-PD-1 refractory population eligible for this study is less than 10%. Therefore, lerapolturev administered in combination with anti-PD-1 therapy using the QW injection schedule, will be considered to have anti-tumor activity in the anti-PD-1 refractory melanoma population if the lower bound of the 95% CI is above 10%. We estimate the sample size for participants receiving lerapolturev (QW schedule) ± anti-PD-1 therapy to be approximately 30 participants (n=15 per arm). Therefore, 5 of 15 participants (ie, 33%) in Arm 2 treated with the lerapolturev/anti-PD-1 combination (QW schedule) must have an objective response for the 95% CI to be greater than 10% (95% CI: 11.8% to 61.6%).

3.2. HANDLING OF DATA

3.2.1. Strata and Covariates

Participants receiving lerapolturev injections using the Q3/4W schedule ± anti-PD-1 therapy will be stratified based on time since prior anti PD1/L1 exposure (≤ 6 weeks versus > 6 weeks) and baseline LDH (normal versus > upper limit of normal [ULN]).

Participants receiving lerapolturev injections using the QW schedule ± anti-PD-1 therapy will be stratified based on type of anti-PD-1/L1 resistance (primary versus secondary as defined in Kluger et al) and baseline LDH (normal versus > ULN).

For statistical summary presentation, summaries, for the following subgroups will be presented:

- lerapolturev monotherapy on the QW schedule
- lerapolturev monotherapy on the Q3/4W schedule
- lerapolturev + anti-PD-1 on the QW schedule
- lerapolturev + anti-PD-1 on the Q3/4W schedule
- all crossover to lerapolturev + anti-PD-1 participants
- lerapolturev + anti-PD-1 plus crossover participants (all lerapolturev + anti-PD-1)
- overall treated participants

3.2.2. Multiple Testing and Comparisons

All analyses will be conducted without adjustments for multiple comparisons.

3.2.3. Missing Data and Outliers

Every effort will be made to obtain required data at each scheduled evaluation from all participants who have been enrolled. In situations where it is not possible to obtain all data, it may be necessary to impute missing data. These situations are described below. Unless otherwise specified, all other missing data will not be imputed.

3.2.3.1. Missing Severity or Relationship for Adverse Events

AEs with missing severity will have the severity imputed as “Grade 3” for the AE tabulations. AEs with missing relationship to study drug will have the relationship imputed as ‘Definite’ for the AE tabulations if the AE started after initiation of study drugs.

3.2.3.2. Imputation of Incomplete Dates

An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a participant. The database contains data fields for month, day, and year. A date is incomplete if at least one of these three fields is not known. For many of the planned analyses, a complete date is necessary to determine if the event should be included in the analysis (ie, if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

For the purposes of handling partially reported start and stop dates for an event the following algorithm will be applied:

1) For onset date:
   a) If only the day part of the onset date is missing and occurs in the same month and year as the date of dose of study drug, the date of dose of study drug will be used as the onset date. Otherwise, the first day of the month will be used to complete the onset date.
   b) If the day and month parts of the onset date are missing and occur in the same year as the dose of study drug, the date of the dose of study drug will be used as the onset date. Otherwise, January 1st will be used to complete the onset date.
   c) If the onset date is completely missing, the date of the dose of study drug will be used as the onset date.
2) For end date:
   a) If only the day part of the end date is missing, the last day of the month will be used to complete the end date.
   b) If the day and month parts of the end date are missing, December 31st will be used to complete the end date.
   c) If the end date is completely missing, the maximum of the participant's study discontinuation date or date of last contact will be used as the end date.

If any imputed start date causes the start date to occur after the end date, the end date will be used for the imputation of the start date. If any imputed end date causes the end date to occur prior to the start date of the event, the start date of the event will be used for the imputation of the end date.

3.2.4. Presentations by Study Visit

When data are collected serially over time, individual data presentations may include by-study visit displays. By-study visit displays will only be summarized up to 30 days after last treatment. Visits will be presented according to the nominal visit as obtained from the eCRF. If multiple observations are collected at a scheduled visit, the closest observation to the target day will be chosen. If two observations have equal distance from the target day but one is earlier and the other is later than the target day, the earlier observation will be chosen. Unscheduled assessments will be included in the listings.

3.2.5. Presentations by Worst Case

When data are collected serially over time, individual data presentations may include "worst case on study" displays. In those situations, both scheduled and unscheduled assessments up to 30 days after last treatment will be included.

3.2.6. Definitions and Terminology

Age
Age is age at informed consent and is as captured on the eCRF.

Baseline Value
For purposes of analysis, the baseline value is defined as the last non-missing value obtained prior to initiation of study drug.

Cycle 1, Day 1 (Baseline)
Cycle 1, Day 1 is the earliest day that study drug is initiated.

Study Day
Study Day is defined relative to Baseline (Cycle 1, Day 1). Thus, the study day of an event is calculated as:

Study Day = event date – date of Cycle 1, Day 1 (+ 1, if event date ≥ date of Cycle 1, Day 1).

Study Visit
Study Visit is the nominal visit as recorded on the eCRF.

Change from Baseline
Change from baseline for a given endpoint is defined as the Study Day X value minus the Baseline Value.

Days on Study
Days on study is the number of days from Cycle 1, Day 1 to the date of study completion as recorded on the End of Study eCRF page.

Adverse Event (AE)
An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study drug(s), whether or not considered related to the study drug(s). An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug(s).

Treatment-emergent Adverse Event (TEAE)
A TEAE is an AE that occurred during the study on or after the initiation of study drug through 30 days after last dose of study drugs. Additionally, it is assumed that an AE which was reported to have started on Cycle 1, Day 1 without an associated onset time occurred on or after initiation of study drug. Treatment-emergent serious adverse events (TESAEs) are collected through 90 days post last dose of study drug.

Adverse Event of Special Interest (AESI)
Any AE (serious or non-serious) of scientific and medical concern for which ongoing monitoring and communication by the investigator to the Sponsor or designee may be appropriate. Such events may require further investigation to characterize and understand them.

Because lerapolturev is an immunotherapeutic administered by intratumoral injection, AESIs fall into 2 categories: (1) AEs related to lerapolturev administration (ie, injection site reaction [ISR]), and (2) AEs related to cytokine release syndrome [CRS] and immune effector cell-associated neurotoxicity syndrome [ICANS], which can occur when the body's immune cells release a bolus of inflammatory cytokines in response to an immunotherapy.

AESIs are collected through 90 days post last dose of study drug.

Immune-Related Adverse Events (irAEs)
Any adverse event affecting an organ system through an autoimmune or inflammatory mechanism, whereby the immune system is acting against normal tissue. The list of terms to identify irAEs is as

follows: (1) high level term (HLT): Colitis (excl infective); (2) HLT: Lower respiratory tract inflammatory and immunologic conditions; (3) HLT: Hepatocellular damage and hepatitis NEC; (4) HLT: Hypothalamic and pituitary disorders NEC; (5) HLT: Adrenal cortical hypofunctions; (6) HLT: Diabetes mellitus (incl subtypes); (7) HLT: Nephritis NEC; (8) HLT: Encephalitis NEC; (9) Preferred term (PT): Toxic epidermal necrolysis; (10) PT: Severe cutaneous adverse reaction; (11) PT: SJS-TEN overlap; (12) PT: Stevens-Johnson syndrome. Recommendations for study drug management in the event of an irAE are described in Protocol Section 5.5.

irAEs are collected through 90 days post last dose of study drug.

Concomitant Medications

Concomitant medications are those medications taken on or after the initiation of study drugs through 30 days post last dose of study drug. This definition includes medications started prior to initiation of study drugs and continuing concomitantly with study drugs.

Prior Medications

Prior medications are those medications taken and discontinued prior to initiation of study drugs.

Complete Response (CR)

A CR is defined by:

- disappearance of all target lesions AND
- disappearance of all non-target lesions AND
- all lymph nodes must be non-pathological in size (< 10 mm short axis) AND
- no appearance of new unequivocal lesions.

Partial Response (PR)

A PR is defined by:

- ≥ 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters AND
- non-CR / non-PD *or* not evaluated non-target lesions AND
- no appearance of new unequivocal lesions.

Stable Disease (SD)

Stable disease (SD) is defined by:

- non-PR / non-PD of target lesions AND
- non-PD or not all evaluated of non-target lesions AND
- no appearance of new unequivocal lesions.

Progressive Disease (PD)

Progressive disease (PD) is defined by:

- ≥ 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study) *and* an absolute increase of at least 5 mm OR
- unequivocal progression of non-target lesions OR
- appearance of one or more new lesions.

Duration of Response (DOR)

DOR is defined as time since a confirmed objective response (CR or PR) is first observed (ie, the scan date when the response originally occurred prior to confirmation) until unequivocal disease

progression (PD) or death, whichever occurs first. Participants will be censored at the date of the last imaging, if there is no date for PD or death.

Objective Response Rate (ORR)
ORR is defined as the proportion of participants achieving confirmed CR or confirmed PR.

Durable Response Rate (DRR)
DRR is defined as the proportion of participants with confirmed CR or confirmed PR lasting ≥ 6 months.

Overall Survival (OS)
OS is defined as time from start of treatment until death from any cause or last follow-up if participant is alive. Participants who are lost to follow-up will be censored at the last date of contact. The primary analysis will include the following subgroups:

- Participants who received lerapolturev monotherapy
- Participants who received lerapolturev + anti-PD-1
- Participants who crossed over from lerapolturev monotherapy to lerapolturev + anti-PD-1 from treatment group assignment until death from any cause or last follow-up, if participant is alive
- Participants who crossed over from lerapolturev monotherapy to lerapolturev + anti-PD-1 from time of crossover until death from any cause or last follow-up if participant is alive

Progression Free Survival (PFS)
PFS is defined as time (number of months) from start of treatment until date of documented radiologic disease progression or death due to any cause, whichever comes first. Participants not meeting this definition will be censored at the date of the last imaging. The primary analysis will include the following subgroups:

- Participants who received lerapolturev monotherapy
- Participants who received lerapolturev + anti-PD-1
- Participants who crossed over from lerapolturev monotherapy to lerapolturev + anti-PD-1 from treatment group assignment until death from any cause or last imaging, if participant is alive
- Participants who crossed over from lerapolturev monotherapy to lerapolturev + anti-PD-1 from time of crossover until death from any cause or last imaging if participant is alive

Disease Control Rate (DCR)
DCR is defined as the proportion of participants achieving confirmed CR, confirmed PR, or SD as best response.

Disease Control Rate-6 Months (DCR-6mo)
DCR is defined as the proportion of participants achieving confirmed CR for any duration, confirmed PR for any duration, or SD for ≥ 6 months as best response.

Treatment Period
Treatment period is defined as Cycle 1, Day 1 of study to the EOT.

3.3. TIMING OF ANALYSES

The final analysis will be completed after the last participant completes or discontinues the study and the resulting clinical database has been cleaned, quality checked, and locked.

4. ANALYSIS POPULATIONS

Data analyses will be based on the intent-to-treat (ITT), efficacy, safety, and screening analysis sets.

4.1. INTENT-TO-TREAT ANALYSIS SET (ITT)

All participants who sign the ICF and are randomized. The participants in the ITT population will be analyzed based on treatment assigned.

4.2. EFFICACY

Participants receiving at least one lerapolturev injection and at least 1 post-baseline assessment. If a participant crosses over from monotherapy to combination therapy, then the treatment analyzed will be based on the treatment for that participant at the time of the assessment for the efficacy set.

4.3. SAFETY

Participants receiving at least one lerapolturev injection. If a participant crosses over from monotherapy to combination therapy, then the treatment analyzed will be based on the treatment for that participant at the time of the assessment.

4.4. SCREENING ANALYSIS SET

A screening analysis set will include all participants who signed the ICF and includes screen failures who failed up until randomization. This will be the primary population for the disposition tables and listings. Participants in the screening analysis set will be analyzed based on the treatment assigned.

5. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study. Unless stated otherwise, the term “descriptive statistics” refers to number of participants (n), mean, median, standard deviation, minimum and maximum for continuous data and frequencies and percentages for categorical data.

Survival endpoints will be analyzed with Kaplan-Meier method and summarized with median, twenty-fifth and seventy-fifth percentiles, and 95% confidence intervals (CI), if applicable.

All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by treatment, participant, and then by date within each participant number.

All summary tables and figures will be presented by treatment group and overall. The term "treatment group" refers to the following subgroups:

- lerapolturev monotherapy on the QW schedule
- lerapolturev monotherapy on the Q3/4W schedule
- lerapolturev + anti-PD-1 on the QW schedule
- lerapolturev + anti-PD-1 on the Q3/4W schedule
- all crossover to lerapolturev + anti-PD-1 participants
- lerapolturev + anti-PD-1 plus crossover participants (all lerapolturev + anti-PD-1)
- overall treated participants

Analyses will be implemented using SAS® 9.4 or higher (SAS Institute, Cary, North Carolina, USA). The International Conference on Harmonization (ICH) numbering convention (ie, ICH-E3) will be used for all tables and listings. Upon completion, all SAS® programs will be validated by an independent programmer within the staff of the third-party vendor doing the primary analysis. The validation process will be used to confirm that statistically valid methods have been implemented and that all data transformations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

5.1. PARTICIPANT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Participant disposition will be presented for the screening analysis set. A summary table will be generated for the overall population. The number of participants who were screened, screen failures, and the reason for screen failure will be summarized. Additionally, the number of participants in each analysis population will be summarized. The end of treatment and reason for treatment discontinuation for each drug in the treatment combination (ie, lerapolturev and anti-PD-1) will be provided; the end of study status and reason the participant discontinuation from study will also be provided. The survival status and primary reason for death will be presented. Additionally, the number of days on treatment and number of days on study will be summarized. Participant disposition including treatment group, analysis population, end of treatment study and reasons, end of study status and reason, and death date and reason will be listed.

Demographic data and baseline characteristics including age at informed consent, gender, race, ethnicity, time since most recent prior anti-PD-1 exposure, type of anti-PD-1 resistance and baseline LDH levels and vital signs (height, weight and ECOG status) will be summarized using descriptive statistics. Demographic data and baseline characteristics will be listed.

5.2. MEDICAL, MELANOMA AND BIOMARKER HISTORY

Medical history will be coded to system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) Version 24.0 and presented in a listing.

Melanoma history will be summarized by treatment group and overall, for the following variables. A separate listing will also be provided.

- Initial diagnosis stage
- Current disease stage with T, N, M
- Site(s) of metastatic disease

Initial diagnosis and current disease are collected for both pathological and clinical stages. If both are non-missing, then the pathological stage will be presented for summaries. Otherwise, the non-missing stage will be used.

Biomarker history will be summarized by treatment group and overall. Unless the mutation is specified below under the mutational analysis, the mutation will be grouped into the "Other, specify" category under each mutational analysis. A separate listing will also be provided.

- BRAF mutational analysis
  - V600E
  - V600K
  - V600R
  - V600D
  - Other, specify
- NRAS mutational analysis
  - NRAS Q61R
  - NRASQ61K
  - NRASQ61L
  - NRASQ61H
  - NRASG12R
  - NRASG12S
  - NRASG12D
  - NRASG12V
  - NRASG13R
  - NRASG13S
  - Other, specify
- KIT mutational analysis
  - KIT L576P
  - KIT K642E
  - KIT V559A
  - KITW557R
  - Other, specify
- Other, specify

5.3. CONCOMITANT MEDICATIONS

All medication verbatim terms collected will be coded to Anatomical Therapeutic Classification (ATC) and PT using the World Health Organization Drug Dictionary (WHO-DD) Version 24.0.

Concomitant medications will be summarized by presenting the number and percentage of participants by PT and ATC. Participants taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC class and PT within each ATC class. Concomitant medications will be presented in a participant listing.

5.4. PRIOR SYSTEMIC AND INTRATUMORAL ANTI-CANCER THERAPY, PRIOR RADIOTHERAPY AND PRIOR/CONCOMITANT PROCEDURES

All verbatim terms collected of systemic and intratumoral anti-cancer therapy will be coded to ATC and PT using the WHO-DD Version March 2021 B3.

The prior systemic and intratumoral anti-cancer therapy will be summarized by presenting the number and percentage of participants by PT and ATC. Participants taking the same medication multiple times will only be counted once for that PT or ATC. Each summary will be ordered by descending order of incidence of ATC class and PT within each ATC class. If a participant experiences more than one prior systemic therapy, all unique therapies will be presented for the categorical summaries. In addition, the number of prior lines of therapy a patient received will be summarized. A participant will only be included in a single category once. All prior and subsequent systemic therapies will be presented in a participant listing.

The prior radiotherapy will be listed. The number and percentage of participants with prior radiotherapy will be summarized. If a participant experiences more than one prior radiotherapy, the total dose will be used for numerical summaries and the highest total dose delivered across the prior radiotherapies will be presented for categorical summaries. A participant will only be included in a single category once.

A listing of the number of prior systemic and intratumoral anti-cancer therapy and prior radiotherapy will be presented by each subject.

All prior procedures specific to melanoma will be summarized by SOC and PT as well as presented in a separate listing.

All concomitant procedures will be summarized by SOC and PT and will be presented in a separate listing. All concomitant procedures will be presented in a separate listing.

5.5. EXPOSURE AND STUDY DRUG COMPLIANCE

The number of participants who received lerapolturev and the total dose received will be summarized.

The following exposure variables will be summarized for lerapolturev:

- Number of cycles received
- Number of lesions injected
- Mean/median/Min, Max of TCID50 per cycle
- Mean/median/Min, Max of number of lesions per cycle
- Mean/median/Min, Max of sum of diameters (SOD) of injected lesions per cycle
- Mean/median/Min, Max of individual injected size (mm) per cycle
- Total TCID 50 received

The overall exposure to anti-PD-1 will be summarized and exposures to pembrolizumab and nivolumab will be summarized separately for the following variables:

- Number of cycles received
- Mean/median/Min, Max of dose received per cycle
- Mean/median/Min, Max of proportion of planned dose received (%)

5.6. EFFICACY

5.6.1. Primary Efficacy Endpoints

The primary efficacy endpoint is ORR which is the overall number and percentage of participants in each treatment arm with confirmed CR or confirmed PR. The primary analysis for the safety run-in and Arm 1 will include participant response prior to crossover to Arm 2. ORR will be analyzed by treatment arm, dosing schedule and overall.

5.6.1.1. Statement of Estimand

The **population for the trial** is defined through appropriate inclusion/exclusion criteria to reflect the targeted participant population for approval. The analysis population is based on the efficacy population.

The **treatments** of interest are lerapolturev alone or lerapolturev + an FDA-approved anti-PD-1 therapy by dosing schedule.

The **variable** of interest for ORR is the binary response value for a participant.

The ability to evaluate treatment effect using the variables may be impacted by **intercurrent events** (ICEs). Death and use of additional cancer treatments may all impact the interpretation of treatment effect. For ORR, a composite strategy will be used to address intercurrent events (ICEs) of potential death, and start of additional cancer treatments, meaning occurrence of any of these events prior to a participant achieving CR or PR will mean the participant is considered a non-responder.

The **population level summary measures** are the ORR and associated confidence intervals in each treatment arm and lerapolturev dosing schedule.

5.6.1.2. Primary Efficacy Analysis

The number of participants in each category of best overall response per RECIST v1.1 (confirmed CR, confirmed PR, SD, unconfirmed CR, unconfirmed PR, PD, non-evaluable (NE)) and ORR along with the associated exact 95% two-sided CIs using Clopper Pearson method will be computed within each treatment group and dosing schedule. A participants BOR will be determined based on Table 4.

Supportive data listings will also be provided.

Table 4 Best Overall Response When Confirmation of CR and PR are Required

First Timepoint Response	Second Timepoint Response	Best overall response for ORR
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD
CR	PD	SD
CR	NE or NA	SD
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD
PR	NE or NA	SD
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.
[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes "CR" may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

5.6.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints for the study are:

- OS
- PFS by RECIST v1.1
- DOR by RECIST v1.1
- DCR by RECIST v1.1
- DCR-6mo by RECIST v1.1
- DRR by RECIST v1.1

5.6.2.1. Secondary Efficacy Analysis

OS, PFS, and DOR will be summarized using Kaplan-Meier method to estimate the median, 25% and 75% percentiles along with their 95% CIs. OS, PFS and DOR survival curve will be estimated using Kaplan-Meier method. PFS and DOR will use RECIST v1.1 definitions for response and progression of disease.

DRR will be presented as the number and percentage of participants with confirmed CR or confirmed PR (by RECIST v1.1) lasting ≥ 6 months along with the 95% CI.

Analysis of DCR and DCR-6mo will be summarized. The associated exact 95% two-sided CIs using Clopper Pearson method will be computed within each treatment group and dosing schedule. DCR and DCR-6mos will use RECIST v1.1 definitions for response and SD.

5.6.3. Translational Analysis

Summaries of translational data are not covered by this SAP.

5.7. SAFETY

Participants receiving at least one lerapolturev injection will be analyzed for safety. Values for all safety variables will be listed by participant and visit (as applicable). Safety summaries by visit will use scheduled visits up to 30 days after the last dose of study drugs.

If a participant crosses over from monotherapy to combination therapy, then the treatment analyzed will be based on the treatment for that participant at the time of the assessment.

5.7.1. Adverse Events

AE will be mapped to a MedDRA version 24.0 by SOC and PT. If a participant experiences multiple events that map to a single PT, the greatest severity and strongest assessment of relation to a study drug will be assigned to the PT for the appropriate summaries. AE severity will be assessed according to the NCI CTCAE version 5. If CTCAE grading does not exist for an AE, the severity of the AE will be graded as mild (1), moderate (2), severe (3), life-threatening (4), or death (5).

AESIs will be identified within the EDC by the investigator.

The number of participants for the following groups will be summarized by treatment group and overall:

- Any TEAE
- Any TEAE related to
  - lerapolturev

  - anti-PD-1 therapy
- Any TESAE
- Any TESAE related to
  - lerapolturev
  - anti-PD-1 therapy
- Any treatment-emergent lerapolturev AESIs
- Any treatment-emergent irAEs
- Any TEAE with CTCAE grade ≥ 3
- Any TEAE related to
  - lerapolturev with CTCAE grade ≥ 3
  - anti-PD1 therapy with CTCAE grade ≥ 3
- Any Grade 5 TEAE
- Any Grade 5 TEAE related to lerapolturev or anti-PD1 therapy

The occurrence of TEAEs and TEAEs related to lerapolturev, or anti-PD-1 therapy will be summarized by PT, SOC, and severity. Additionally, TEAEs will be summarized by PT in descending frequency. All AEs reported will be listed for individual participants showing both verbatim and PT. All AEs that occurred prior to initiation of study drugs will be excluded from the tables but will be included in the listings.

Adverse events occurring during screening due to lerapolturev-related procedures that are not standard of care (eg, PV booster) will be considered related to lerapolturev and summarized separately.

Additional analysis may be conducted to investigate rates of TEAE based on lerapolturev dose and/or schedule. Should there be a difference, we may perform additional analyses to discern whether there is a relationship between dose and occurrence of AEs.

Missing onset dates will be imputed as previously outlined in Section 3.2.3.2 as required to determine TEAE.

5.7.2. Clinical Laboratory Assessments

AEs for clinical labs will be characterized according to NCI CTCAE version 5 (when possible) and shift in grade from baseline to the worst post-baseline value will be summarized. Both scheduled and unscheduled assessments will be used to identify the worst post-baseline values.

The following categories of abnormal hepatic laboratory values will be evaluated for any occurrence among all post baseline assessments.

- Alanine Aminotransferase (ALT) and/or Aspartate Aminotransferase (AST) > 3 x ULN, Alkaline Phosphatase (ALP) < 2 x ULN, and Total Bilirubin ≥ 2 x ULN
- AST > 3, 5, 8, 10, and 20 x ULN, and 5 x ULN for more than 5 weeks
- ALT > 3, 5, 8, 10, and 20 x ULN, and 5 x ULN for more than 5 weeks
- Total Bilirubin > 1.5 or ≥ 2 x ULN

Listings of all laboratory data with normal reference ranges and NCI CTCAE grades (when possible) will be provided.

5.7.3. Vital Signs

For vital sign parameters (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, body temperature, and weight), the observed values and change from baseline will be

summarized using descriptive statistics at each visit. The maximum post-baseline values and the change from baseline will also be summarized. Both scheduled and unscheduled assessments will be used to identify the worst post-baseline values.

A listing of all vital sign data will be provided.

5.7.4. ECOG Status

ECOG status will be summarized at each visit. Summary statistics for change from baseline in ECOG score for post baseline visits will be provided. A summary of max post-baseline change in ECOG status will also be included.

A listing of ECOG status will be generated.

6. PROTOCOL DEVIATIONS

Protocol deviation summaries and listing are not covered by this SAP but will be presented in the clinical study report.

7. CHANGES IN THE PLANNED ANALYSES

The following exploratory analysis listed in protocol will no longer be conducted.

- ORR/DOR, DRR, DCR, and DCR-6mo based on iRECIST criteria
- ORR, DOR, DRR, DCR, and DCR-6mo in the following subgroups:
  - Acquired versus primary PD-1/L1 resistance, as defined by Kluger, et al
  - BRAF wild type and mutant
  - LDH levels at baseline
  - Time since last dose of anti-PD-1/L1 therapy prior to randomization (≤ or > 6 weeks)
  - Crossover to combination arm from lerapolturev monotherapy

- OS and PFS in the following subgroups:
  - According to treatment arm and AJCC stage at baseline
  - Acquired versus primary PD-1/L1 resistance, as defined by Kluger, et al
  - BRAF wild type and mutant
  - LDH levels at baseline
  - Time since last dose of anti-PD-1/L1 therapy prior to randomization (≤ or > 6 weeks)
  - Crossover to combination arm from lerapolturev monotherapy

8. REVISION HISTORY

Date	Revision	Rationale
10OCT2024	1. Update PFS definition to be censored at last imaging instead of death. 2. Update tables that were using the ITT Population to Safety Population.	1. Last imaging is more appropriate here since we are looking at Progression-free Survival. 2. ITT does not include Safety Run-ins since those subjects are not randomized.

9. REFERENCES

Kluger HM, Tawbi HA, Ascierto ML, et al. Defining tumor resistance to PD-1 pathway blockade: recommendations from the first meeting of the SITC Immunotherapy Resistance Taskforce. 2020;8(1): e000398. doi:10.1136/jitc-2019-000398

10. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1.0" boundary on the left and right edges. The top and bottom margins are 1.0" for tables and listings but may vary for figures. Output should be printed in Courier New with a point size of 8. Titles may be printed using a larger font (eg, Arial point size 10).
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all participants.
- Group headers: In the summary tables, the group headers will identify the summary group and the sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of participants summarized within any given summary module; some participants in the analysis population may have missing values and thus may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of participants contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of participants in the analysis population due to missing data.
    - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations. The number of missing observations, if any, will be noted.
    - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented to indicate clearly to a reviewer the method of calculation. The number of missing observations, if any, will be noted.
- Sorting: Listings will be sorted by treatment group, participant number and date, if applicable. If a listing is sorted in a different manner, a footnote will indicate as such.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- Numerical Values: The presentation of numerical values will adhere to the following guidelines:
    - Raw measurements will be reported to the number of significant digits as captured electronically or on the eCRFs.
    - Standard deviations will be reported to one decimal place beyond the number of decimal places the original parameter is presented.
    - Means will be reported to the same number of significant digits as the parameter.
    - Calculated percentages will be reported with no decimals.
- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on eCRFs.
    - Time will be presented according to the 24-hour clock (HH:MM).

11. PROPOSED TABLES, LISTINGS, AND FIGURES

Summary Tables

Accountability and Baseline Characteristics

14.1.1.1 Participant Disposition, Screening Analysis Set
14.1.2.1 Demographics and Baseline Characteristics, Safety Set
14.1.4.1 Melanoma History, Safety Set
14.1.4.2 Biomarker History, Safety Set
14.1.4.3 Prior Systemic and Intratumoral Anti-Cancer Therapy, Safety Set
14.1.4.4 Prior Radiotherapy for Melanoma, Safety Set
14.1.4.5 Prior Procedures, Safety Set
14.1.4.6 Concomitant Medications, Safety Set
14.1.4.7 Concomitant Procedures, Safety Set
14.1.4.8 Subsequent Anti-Melanoma Treatment, Safety Set
14.1.5.1 Summary of Study Drug Exposure, Safety Set

Efficacy

14.2.1.1 Summary of Best Overall Tumor Response Based on RECIST 1.1 Criteria, Efficacy Set
14.2.2.1 Summary of Overall Survival, Efficacy Set
14.2.3.1 Summary of Progression Free Survival, Efficacy Set

Safety

14.3.1.1 Overall Summary of Treatment-Emergent Adverse Events, Safety Set
14.3.1.2 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Greatest Severity, Safety Set
14.3.1.3 Treatment-Emergent Adverse Events by Preferred Term in Descending Frequency, Safety Set
14.3.1.4.1 Treatment-Emergent Adverse Events Related to Lerapolturev by System Organ Class, Preferred Term, and Greatest Severity, Safety Set
14.3.1.4.2 Treatment-Emergent Adverse Events Related to Anti-PD-1 by System Organ Class, Preferred Term, and Greatest Severity, Safety Set
14.3.1.5.1 Treatment-Emergent Adverse Events Related to Lerapolturev by Preferred Term in Descending Frequency, Safety Set
14.3.1.5.2 Treatment-Emergent Adverse Events Related to Anti-PD-1 by Preferred Term in Descending Frequency, Safety Set
14.3.2.1 Treatment-Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Greatest Severity, Safety Set
14.3.2.2.1 Treatment-Emergent Serious Adverse Events Related to Lerapolturev by System Organ Class, Preferred Term, and Greatest Severity, Safety Set
14.3.2.2.2 Treatment-Emergent Serious Adverse Events Related to Anti-PD-1 by System Organ Class, Preferred Term, and Greatest Severity, Safety Set
14.3.3.1 Treatment-Emergent Lerapolturev Adverse Event of Special Interest by System Organ Class, Preferred Term, and Greatest Severity, Safety Set
14.3.3.2 Treatment-Emergent Immune Related Adverse Event by System Organ Class, Preferred Term, and Greatest Severity, Safety Set
14.3.3.3 Treatment-Emergent Adverse Events Leading to Discontinuation of Study Treatment by System Organ Class, Preferred Term, and Greatest Severity, Safety Set
14.3.4.1 Summary of Grade Shifts in Laboratory Abnormalities – Hematology, Safety Set
14.3.4.2 Summary of Grade Shifts in Laboratory Abnormalities – Chemistry, Safety Set
14.3.4.3 Summary of Grade Shifts in Laboratory Abnormalities – Coagulation, Safety Set

14.3.4.4 Number of Participant with at Least One ALT, AST, or Total Bilirubin Above Upper Limit of the Normal Range Post-Baseline, Safety Set
14.3.4.5 Summary of Vital Signs by Visit, Safety Set
14.3.4.6 Summary of ECOG Performance Status by Visit, Safety Set

Summary Figures

Efficacy

14.2.1.2 Duration of Response – Kaplan Meier Curve, Efficacy Set
14.2.2.2 Overall Survival – Kaplan Meier Curve, Efficacy Set
14.2.3.2 Progression Free Survival – Kaplan Meier Curve, Efficacy Set

Data Listings

16.2.1.1 Participant Disposition, All Participants
16.2.1.2 Inclusion/Exclusion Criteria, All Participants
16.2.1.3 Participant Enrollment, Safety Set
16.2.4.1 Demographics and Baseline Characteristics, Safety Set
16.2.4.2 Medical History, Safety Set
16.2.4.3 Melanoma History, Safety Set
16.2.4.4 Biomarker History, Safety Set
16.2.4.5.1 Prior Systemic and Intratumoral Anti-Cancer Therapy, Safety Set
16.2.4.5.2 Subsequent Anti-Melanoma Treatment, Safety Set
16.2.4.5.3 Prior Radiotherapy for Melanoma, Safety Set
16.2.4.5.4 Prior and Concomitant Procedures, Safety Set
16.2.4.5.5 Prior and Concomitant Medications, Safety Set
16.2.5.1 Lerapolturev Injection, Safety Set
16.2.5.2 Anti-PD-1 Infusion, Safety Set
16.2.6.1 Target Lesion Description, Efficacy Set
16.2.6.2 Non-Target Lesion Description, Efficacy Set
16.2.6.3 New Lesion Description, Efficacy Set
16.2.6.4 Response Assessment for RECIST 1.1, Efficacy Set
16.2.6.5 Survival, Efficacy Set
16.2.7.1 Adverse Events, Safety Set
16.2.8.1 Laboratory Values – Hematology, Safety Set
16.2.8.2 Laboratory Values – Chemistry and Thyroid Function Test, Safety Set
16.2.8.3 Laboratory Values – Coagulation, Safety Set
16.2.8.4 COVID-19 Impact, Safety Set
16.2.9.1 Vital Signs and ECOG Performance Status, Safety Set