

**A Phase II Study to Evaluate the Safety and Efficacy of
Rigosertib (ON 01910) plus Pembrolizumab
in Patients with Metastatic Melanoma Refractory to Immune Checkpoint Blockade**

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1.0 TRIAL SUMMARY

Abbreviated Title	Rigosertib plus pembrolizumab in unresectable/metastatic melanoma refractory to PD-1 inhibition
Trial Phase	II
Clinical Indication	Unresectable/metastatic melanoma
Trial Type	Two-stage, single arm trial
Type of control	None
Route of administration	Oral (rigosertib) Intravenous (pembrolizumab)
Treatment Groups	Rigosertib 560mg twice daily on days 1-21 of 28-day cycle plus pembrolizumab 400mg every six weeks
Number of trial sites	1
Number of trial participants	3-29
Estimated enrollment period	24 months
Estimated duration of trial	36 months
Duration of Participation	6 months
Estimated average length of treatment per patient	4 months

2.0 TRIAL DESIGN

2.1 Trial Design

This is an open-label, two-stage, single-arm study of oral (PO) rigosertib in combination with intravenous (IV) pembrolizumab in patients with metastatic melanoma that is refractory to PD-1 inhibitor therapy. The primary endpoint of the study will be overall

response rate (ORR). Secondary endpoints include progression-free survival (PFS), overall survival (OS), safety and tolerability, and correlation of response rate with biomarkers (change in tumor infiltrating lymphocytes).

This study will enroll 6 patients in the lead-in phase of stage I of this two-stage design; toxicity will be assessed, with potential down titration of rigosertib. Description of toxicity assessment is outlined in Section 6.1.3, “Clinical Safety Laboratory Assessments.” After toxicity assessment, an additional 4 patients will be enrolled in stage I. The sample size was designed to test whether rigosertib plus pembrolizumab has a $\geq 30\%$ response rate in PD-1 refractory metastatic melanoma with a clinically uninteresting response rate of 10%. If ≥ 2 patients experience disease response, then the study may proceed to stage II if the sponsors providing financial and/or drug support and Investigator are in agreement.

The primary objective of the study is to evaluate the activity of rigosertib in combination with pembrolizumab in terms of ORR. The overall type I error rate for this study is strictly controlled at 5% (one-sided) and the study has a power of 80%. The study is considered to be positive if at least 6 patients treated with rigosertib plus pembrolizumab experience an objective response (of 29 subjects enrolled). All patients receiving study drugs will receive rigosertib at 560mg po twice daily on days 1-21 of a 28-day cycle as well as pembrolizumab 400mg by IV infusion every six weeks. Patients are intended to receive study drugs until confirmed disease progression, intolerable toxicity, confirmed complete response, withdrawal of consent, completion of two years of therapy, or until they require another form of antineoplastic therapy as determined by the Investigator. We anticipate an accrual rate of 2 to 4 patients per month from one participating center.

After the baseline tumor evaluation, tumor assessment during the study will be performed by radiological scans every eight weeks starting from week 8 to week 24. Patients who remain on study after 24 weeks and are clinically stable may decrease imaging frequency to every 12 weeks in the following schedule:

- First scheduled disease assessment: week 8
- Disease assessments every 8 week from week 16-24
- Disease assessment every 12 weeks from week 24-48

Patients will be evaluated for tumor response based on the iRECIST criteria by the treating physician review. Guidelines for iRECIST are described in Appendix 4. On-study assessments by iRECIST take into account the observation that some patients with melanoma can experience a transient tumor flare in the first few months after immunotherapy treatment with subsequent disease

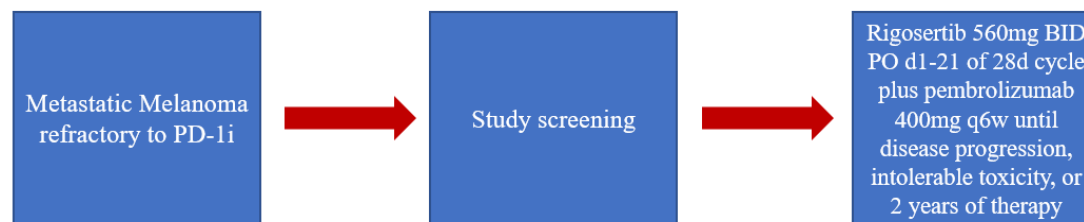
response. Clinical decisions will be based on the interpretation of the Investigator treating the patient in real time using the iRECIST criteria.

All patients must have at least one baseline measurable lesion by iRECIST 1.1 definition on CT or MRI (as assessed by Investigator). The timing for tumor assessments should be based on calendar and not adjusted for delays or variation in cycle starts.

Patients will be monitored regularly for safety and efficacy throughout the study, as per Section 2.3, Schedule of Activities.

2.2 Trial Schema

Figure 1. Trial Schema



2.3 Schedule of Activities

Table 1 Study Schedule of Activities

Trial Period		Screening Phase		Treatment Cycle														End of Treatment		Post-Treatment	
Treatment Cycle/Title	Screening visit	C1		C2		C3		C4		C5		C6		C7,C9, C11, 13, 15, 17, 19, 21, 23		C8, C10, C12, 14, 16, 18, 20, 22, 24		discontinuation	Safety follow-up	Follow up	Survival follow up
		D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15				
Week (approximate)		0	2	4	6	8	10	12	14	16	18	20	22	24, 32, 40, 48, 56, 64, 72, 80, 88	26, 34, 42, 50, 58, 66, 74, 82, 90	28, 36, 44, 52, 60, 68, 76, 84, 92	30, 38, 46, 54, 62, 70, 78, 86, 94				
Scheduling window¹ (days)	-28 to -1	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	At time of discount	30day post-discon²	Q12w post-discon	Q12w
Administrative Procedures																					
Informed Consent	X																				
Inclusion/Exclusion Criteria³	X																				
Demographics, Medical History, Prior Medications⁴	X																				
Subsequent Anti-neoplastic Therapy Status																		X	X	X	X
Survival Status		←-----→																X	X	X	X

Trial Period		Screening Phase		Treatment Cycle												End of Treatment				Post-Treatment			
Treatment Cycle/Title	Screening visit	C1		C2		C3		C4		C5		C6		C7,C9, C11, 13, 15, 17, 19, 21, 23		C8, C10, C12, 14, 16, 18, 20, 22, 24		discontinuation	Safety follow-up	Follow up	Survival follow up		
		D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15						
Week (approximate)		0	2	4	6	8	10	12	14	16	18	20	22	24, 32, 40, 48, 56, 64, 72, 80, 88	26, 34, 42, 50, 58, 66, 74, 82, 90	28, 36, 44, 52, 60, 68, 76, 84, 92	30, 38, 46, 54, 62, 70, 78, 86, 94						
Scheduling window ¹ (days)	-28 to -1	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	At time of discount	30day post-discon ²	Q12w post-discon	Q12w		
Clinical Procedures/Assessments																							
Review AEs ^{5, 13}		X	X	X	X	X	X	X	X	X	X	X		C7, 13, 19	C11, 15, 23	C10, 16, 22	C8, 14, 20	X	X	X ⁵			
ConMed Review	X	X	X	X	X	X	X	X	X	X	X	X		C7, 13, 19	C11, 15, 23	C10, 16, 22	C8, 14, 20	X					
Vital Signs & Weight ^{6, 13}	X	X	X	X	X	X	X	X	X	X	X	X		C7, 13, 19	C11, 15, 23	C10, 16, 22	C8, 14, 20	X					
ECOG PS ¹³	X	X	X	X	X	X	X	X	X	X	X	X		C7, 13, 19	C11, 15, 23	C10, 16, 22	C8, 14, 20	X					
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X		C7, 13, 19	C11, 15, 23	C10, 16, 22	C8, 14, 20	X					
Laboratory Procedures/Assessments																							
Pregnancy Test ⁷	X							X						X		X		X					

Trial Period		Screening Phase		Treatment Cycle												End of Treatment				Post-Treatment	
Treatment Cycle/Title	Screening visit	C1		C2		C3		C4		C5		C6		C7,C9, C11, 13, 15, 17, 19, 21, 23		C8, C10, C12, 14, 16, 18, 20, 22, 24		discontinuation	Safety follow-up	Follow up	Survival follow up
		D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15				
Week (approximate)		0	2	4	6	8	10	12	14	16	18	20	22	24, 32, 40, 48, 56, 64, 72, 80, 88	26, 34, 42, 50, 58, 66, 74, 82, 90	28, 36, 44, 52, 60, 68, 76, 84, 92	30, 38, 46, 54, 62, 70, 78, 86, 94				
Scheduling window ¹ (days)	-28 to -1	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	At time of discont	30day post-discon ²	Q12w post-discon	Q12w
CBC with differential ⁸	X	X	X	X	X	X		X		X	X	X		C7, 13, 19	C11 , 15, 23	C10 , 16, 22	C8, 14, 20	X			
Blood chemistry (CMP)	X	X	X	X	X	X	X	X	X	X	X	X		C7, 13, 19	C11 , 15, 23	C10 , 16, 22	C8, 14, 20	X			
Urinalysis	X	X		X		X		X						C7, 13, 19		C10 , 16, 22					
Magnesium, phosphorus	X	X	X	X	X	X	X	X	X	X	X	X		C7, 13, 19	C11 , 15, 23	C10 , 16, 22	C8, 14, 20	X	X		
Coagulation studies (PT, PTT)	X																				
Troponin	X					X															
Thyroid testing (TSH)	X					X				X	X	X			C11 , 15, 23		C8, 14, 20	X	X		
LDH	X																	X	X		

Trial Period		Screening Phase		Treatment Cycle														End of Treatment		Post-Treatment	
Treatment Cycle/Title	Screening visit	C1		C2		C3		C4		C5		C6		C7,C9, C11, 13, 15, 17, 19, 21, 23		C8, C10, C12, 14, 16, 18, 20, 22, 24		discontinuation	Safety follow-up	Follow up	Survival follow up
		D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15	D 1	D 15				
Week (approximate)		0	2	4	6	8	10	12	14	16	18	20	22	24, 32, 40, 48, 56, 64, 72, 80, 88	26, 34, 42, 50, 58, 66, 74, 82, 90	28, 36, 44, 52, 60, 68, 76, 84, 92	30, 38, 46, 54, 62, 70, 78, 86, 94				
Scheduling window ¹ (days)	-28 to -1	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	+/- 4	At time of discont	30day post-discon ²	Q12w post-discon	Q12w
Tumor Biopsies/Archival Tissue Collection/Correlative Studies from Peripheral Blood																					
Archival or Newly Obtained Tissue	X																				
Correlative Blood ⁹		X	X	X	X	X		X			X			C7, 13, 19	C11, 15, 23	C10, 16, 22	C8, 14, 20				
Correlative Tissue	X*					X*				X*											
Efficacy measurements																					
Tumor Imaging ¹⁰	X					X				X				C7, 13, 19		C10, 16, 22					
Treatment																					
Rigosertib cycle D1 ¹¹		X		X		X		X		X		X		X		X					
Pembrolizumab ¹²		X			X			X			X			C7, 13, 19	C11, 17, 23	C10, 16, 22	C8, 14, 20				

¹ Routine laboratory tests (serum chemistry; hematology) for screening should be performed within 10 days of first dose of study treatment.

- 2 The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anti-cancer treatment, whichever comes first. See Section 6.1.7.3.
- 3 Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g. within 28 days prior to Cycle 1, Day 1).
- 4 Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment, and best response to prior systemic treatments. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator. Report complete medication history for 30 days prior to the screening visit (Visit 1).
- 5 Adverse experiences and laboratory safety measurements will be graded per NCI CTCAE Version 5.0. All adverse experiences, whether gradable by CTCAE or not, will also be evaluated for seriousness. See Section 6.2 for guidance.
- 6 Vital signs to include temperature, pulse, respiratory rate, and blood pressure; height required only at screening.
- 7 For women of reproductive potential, a urine pregnancy test will be performed within 72 hours of the first dose. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy testing will be obtained q3m on study and at discontinuation.
- 8 Routine laboratory tests including items listed in Appendix 2 (e.g., CBC with differential; comprehensive serum chemistry panel) will be performed by the local study site laboratory or their contract laboratory.
- 9 Up to 10mL of blood for research to be collected at indicated time points.
- 10 Tumor imaging will be performed within 30 days prior to first dose of study treatment. CT scans are the required modality for measurable disease unless a patient has a clinical condition e.g. severe contrast allergy, or the lesions are significantly better visualized through the use of an MRI. The same imaging technique must be used in a patient throughout the study. Patients with an objective response should have repeat imaging at least 4 weeks later to confirm the objective response. In addition, patients with progressive disease should undergo a second scan at least 4 weeks later to confirm progression and exclude the possibility of a tumor flare reaction, according to iRECIST guidelines (see Section 6.1.4.5). Response status will be assessed by the investigator. Tumor imaging will be performed every 8 weeks starting at Week 8 through Week 24. Following Week 24, tumor imaging may be performed approximately every 12 weeks (or whenever clinically indicated) while the patient remains on study therapy at the discretion of the investigator (Weeks 36, 48). Timing of imaging scans should follow the calendar and not be adjusted for treatment delays.
- 11 Rigosertib oral tablets scheduled for administration twice daily on Days 1-21 of 28-day cycles (3 weeks-on, 1 week-off) in a fasting state. The first daily dose should be taken on an empty stomach after an overnight fast, and patients should wait 1hr after dosing to eat breakfast. The second daily rigosertib dose should be administered at approximately 3pm (+/- 1 hour), at least 2 hours after lunch, on an empty stomach, and patients should wait at least 1 hour before next meal..
- 12 Pembrolizumab scheduled as a 30-minute IV infusion every 6 weeks. Pembrolizumab infusions intended on C1D1, C2D15, C4D1, C5D15, C7D1, C8D15, C10D1, C11D15, C13D1, C14D15, C16D1, C17D15, C19D1, C20D15, C22D1, C23D15. (Note: As overall treatment cycles on this study are considered to be 28 days, pembrolizumab q6w scheduled to be absent from every 3rd cycle in this study – i.e. no scheduled pembrolizumab in Cycles 3, 6, 9, 12, etc.). There are no restrictions regarding the sequential dosing of rigosertib and IV pembrolizumab, though rigosertib should be taken in a fasting state as described in (11).
- * On-treatment biopsy is required for at least 10 patients on study, including 5 patients in the Stage 1. Preference for on-treatment biopsy will be given to those patients whose tumor is easily accessible (ie, cutaneous lesion, subcutaneous nodules). A maximum of three biopsies per patient will be obtained.
- 13 Vital signs, labs, ECOG PS will be evaluated every 2 weeks through week 14, then will move to every 6 weeks with pembrolizumab infusions. Patients who are having treatment related toxicities or complications will be seen more frequently as per protocol. If there are concerns we can potentially increase the frequency of visits, but every 6 week assessments were deemed reasonable in patients who are tolerating therapy.

3.0 OBJECTIVE(S), HYPOTHESIS(ES), AND ENDPOINT(S)

3.1 Primary Objective(s), Hypothesis(es), and Endpoint(s)

Objective: To determine the efficacy of rigosertib plus pembrolizumab in patients with metastatic melanoma who are refractory to treatment with a PD-1 inhibitor.

Hypothesis: Response rate to rigosertib plus pembrolizumab in patients with metastatic melanoma refractory to PD-1 inhibitor will experience a response rate of 30%.

Primary Endpoint: Overall response rate (ORR)

3.2 Secondary Objective(s), Hypothesis(es), and Endpoint(s)

Objective:

- (1) To evaluate progression-free survival (PFS) in patients with PD-1 inhibitor refractory metastatic melanoma receiving rigosertib plus pembrolizumab.
- (2) To evaluate safety, tolerability and adverse event profile of rigosertib plus pembrolizumab in patients with PD-1 inhibitor refractory metastatic melanoma.
- (3) To evaluate overall survival (OS) in patients with PD-1 inhibitor refractory metastatic melanoma receiving rigosertib plus pembrolizumab.

Secondary Endpoint:

- (1) Progression-free survival.
- (2) Rate of any-grade toxicity.
- (3) Overall Survival.

3.3 Exploratory Objective(s)

Objective: To evaluate change in tumor-infiltrating lymphocytes (TILs) upon treatment with rigosertib plus pembrolizumab in patients with metastatic melanoma that is refractory to PD-1 inhibitor.

4.0 BACKGROUND & RATIONALE

4.1 Background

Rigosertib sodium (ON 01910.Na) is the sodium salt of (E)-2,4,6-trimethoxystyryl-3-carboxymethylamino-4-methoxybenzyl sulfone, a member of the broader class of styrylbenzyl sulfones proprietary to the Sponsor, Onconova Therapeutics, Inc. Rigosertib is being developed as an anticancer agent in advanced solid tumors. The compound is available in both intravenous and oral formulations and is under evaluation as both monotherapy and in combination with other anti-cancer therapies.

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda[®] (pembrolizumab) is indicated for the treatment of patients across a number of indications because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator brochure (IB).

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 Rigosertib Background

In vitro studies during the development of rigosertib suggest that the drug induces arrest of cancer cells at the G2-M stage, prompting apoptosis after dispersion of chromosomes in the cytoplasm. When tested against 25 cancer cell lines (including one melanoma cell line and four multidrug resistant cancer cell lines), IC₅₀ values for rigosertib range from 50-250nM. A panel of normal (non-cancer) human cell lines demonstrated resistance to rigosertib, with IC₅₀ values >10,000nM¹.

The cytotoxic effect of rigosertib on tumor cells results from inhibition of kinase pathways involved in cell cycle control, cancer cell growth and survival. Rigosertib binds directly to the Ras binding domain (RBD) found in Ras effector proteins, including Raf and P13K kinases. Alternatively, rigosertib activates the JNK pathway, resulting in the disruption of RAF/RAS activation and its downstream signaling². In addition, rigosertib has been shown to inhibit the PLK-1 pathway in multiple cell types. This specific binding disrupts the protein-protein interactions between Ras and its effector molecules, preventing their activation. Because the majority of malignant human cells exhibit aberrant Ras signaling (either through intrinsic Ras mutations, mutations of growth factor receptors, regulatory proteins or effect molecules), blocking the transmission of Ras pathway signaling is thought to be important for the anti-tumor activity of rigosertib. In addition, rigosertib has been shown to induce the formation of reactive oxygen species (ROS), resulting in the activation of apoptotic pathways

in tumor cells ³. There has been controversy in the scientific community regarding a potential microtubule destabilizing effect of rigosertib observed by some preclinical investigators. However, definitive analysis demonstrated that this inhibition of tubulin polymerization was related to a contaminant (ON01500), which was present at levels of 5% in commercially-sourced rigosertib.

Pharmacokinetic evaluation of rigosertib in vivo (including mice, rats and dogs) indicates achievement of plasma concentrations that are higher than that necessary for the anti-tumor activities predicted by cell culture models in both intravenous and oral administration. These studies demonstrated a biliary-predominant elimination, with minor urinary excretion ⁵.

4.1.1.2 Pembrolizumab Background

Pembrolizumab (MK-3475; previously known as SCH 900475) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab contains the S228P stabilizing mutation and has no antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity. Pembrolizumab strongly enhances T lymphocyte immune responses in cul in cultured blood cells from healthy human donors, cancer patients, and primates. In T- cell activation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM. Pembrolizumab also modulates the level of interleukin-2 (IL-2), tumor necrosis factor alpha (TNF α), interferon gamma (IFN γ), and other cytokines. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T- cells. A one-month repeat dose GLP-toxicity study with four months observation post dosing revealed no major safety findings. The no observed adverse event level (NOAEL) was ≥ 200 mg/kg. Pembrolizumab was first approved for use in metastatic melanoma in September 2014, with approval in the adjuvant setting in February 2019. In addition to melanoma, pembrolizumab is approved in 17 other malignancies, including NSCLC, head & neck cancer, Hodgkin Lymphoma, urothelial cell carcinoma, renal cell, gastric and GEJ, cervical cancer, endometrial cancer, hepatocellular carcinoma, Merkel cell carcinoma, cutaneous squamous cell carcinoma, triple-negative breast cancer primary mediastinal B cell lymphoma. Pembrolizumab is also the only anti-cancer medication approved in the tumor-agnostic setting for mismatch repair deficient (dMMR)/ microsatellite instability high (MSI-H) as well as tumor mutational burden-high (TMB) solid tumors.

4.1.1.3 Melanoma Background

Melanoma is the fifth most common malignancy in men and the seventh most common malignancy in women ⁶. The incidence of melanoma is increasing worldwide, with a growing fraction of patients with advanced disease for which prognosis remains poor. The median survival for patients with metastatic melanoma has traditionally been under 1 year; the 5-year survival rate of patients with visceral involvement has been under 10% ⁷. Treatment options for

metastatic melanoma have been limited to chemotherapeutic agents such as dacarbazine and high-dose interleukin-2 immunotherapy in a small percentage of patients. In the past few years there has been steady progress in the development of targeted therapy and immunotherapy for metastatic melanoma. Vemurafenib, a BRAF inhibitor, was approved in 2011 for the treatment of patients with unresectable or metastatic melanoma with *BRAF*^{V600E} mutation⁸. Ipilimumab, an anti-CTLA4 monoclonal antibody, was also approved in 2011 for the treatment of patients with unresectable or metastatic melanoma⁹. In spite of these newly approved therapies, overall outlook for patients with metastatic melanoma remains dismal and the development of new effective therapy is still needed.

4.1.1.4 PD-1/PD-L1 Signaling Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades¹⁰. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8⁺ T-cells and the ratio of CD8⁺ effector T-cells/FoxP3⁺ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded *ex vivo* and reinfused, inducing durable objective tumor responses in cancers such as melanoma^{11, 12}.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *Pdcd1*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2)^{13, 14}.

The structure of murine PD-1 has been resolved¹⁵. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable-type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade^{14, 16-18}. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins^{19, 20}. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in melanoma.

4.1.2 Preclinical Data

Rigosertib is a small molecule that binds to a key regulatory domain contained in all rat sarcoma (Ras) effector proteins. Binding to this domain, also called the Ras-binding domain (RBD), prevents the interaction of effector molecules with Ras, thus blocking their activation.

Similarities in the tertiary structures of the RBD of various proteins suggest that rigosertib may inhibit multiple Ras-driven signaling pathways. In summary, recent studies continue to demonstrate that rigosertib acts as a Ras mimetic and disrupts Ras signaling by binding to RBDs.

Consequently, interactions with phosphatidyl-inositol 3 kinase (PI3K), protein kinase B (PKB, also known as Akt), and mitogen-activated proteins (MAPK) such as c-Jun N-terminal kinases (JNK) and extracellular-signal-regulated kinase (ERK) were found. Rigosertib was also shown to induce the formation of reactive oxygen species (ROS), resulting in the activation of apoptotic pathways in cancer cells.

Rigosertib has a differential effect on cell cycle progression in tumor cells versus normal cells. In tumor cells, rigosertib selectively induces mitotic arrest at the GM-M stage, leading to apoptosis after dispersion of chromosomes in the cytoplasm, whereas in normal cells, the cell cycle progression is arrested reversibly at the G1 stage and cells are temporarily prevented from progressing in the cell cycle.

In *in vitro* nonclinical pharmacology studies, rigosertib was evaluated against a broad spectrum of human tumor cell lines and exhibited potent cytotoxicity, with concentrations of compound required to inhibit activity by 50% (IC50) ranging from 50 to 250 nM. Studies on drug-resistant human tumor cell lines demonstrated that rigosertib is cytotoxic to many drug-resistant tumor cells and does not induce resistance in tumor cells. In studies on normal human bone marrow (BM) and leukemic cells, rigosertib was shown to have low BM toxicity and to effectively inhibit human hematopoietic tumor cell lines. This difference in rigosertib effects on normal BM cells compared to leukemic cells may be due to the above mentioned effects of rigosertib on apoptosis in leukemic cells. These effects may also explain the limited occurrence of myelosuppression observed with rigosertib administration.

In *in vitro* studies, when used in combination with other anti-cancer agents, rigosertib displayed an additive or synergistic effect; in particular, the compound has shown a high degree of synergism with azacitidine (AZA). In *in vivo* nonclinical pharmacology studies, rigosertib used as a single agent inhibited the growth of a variety of tumors implanted subcutaneously (SC) in mice and showed potentiating activity when combined with oxaliplatin, paclitaxel, irinotecan, or vincristine. In addition to an anti-tumor benefit, rigosertib showed a significant protective effect against doxorubicin-induced weight loss, cardiotoxicity, and death in mice. Screening safety pharmacology assays did not reveal any adverse effects of rigosertib.

In cardiovascular safety studies, the human-ether-à-go-go related gene (hERG) potassium ion channel assay was negative, and no electrocardiogram (ECG) abnormalities or cardiac adverse effects were observed in dogs treated once daily for 28 days at high doses of rigosertib or

treated for 6 cycles with 72-hour continuous intravenous infusions (CIV) in 14-day dose cycles at supraphysiological high doses of rigosertib.

4.1.3 Clinical Trial Data

Rigosertib has not yet been studied in patients with melanoma. However, it has been evaluated in hematologic malignancy including myelodysplastic syndrome, acute lymphocytic leukemia, acute myeloid leukemia, transformed myeloproliferative neoplasms, chronic lymphocytic leukemia, mantle cell lymphoma and multiple myeloma as well as in pancreatic cancer and other solid tumors. Pembrolizumab has been well-studied in patients with advanced and metastatic melanoma and is FDA approved in melanoma, in both the unresectable/metastatic and adjuvant settings.

Clinical Efficacy of Rigosertib in Hematologic Malignancy

Early clinical trials of rigosertib in hematologic malignancy showed promising efficacy results. A phase I trial of oral rigosertib plus standard-dose azacitadine in an 18-patient cohort revealed an overall response rate of 56%, with ORR 78% among patients with myelodysplastic syndrome and 29% among patients with acute myeloid leukemia ²¹. This led to an expanded Phase II study of rigosertib plus standard-dose azacitadine in the first-line setting in patients with higher-risk myelodysplastic syndromes. Rigosertib dosing in this study was increased to either 840mg/day (as 560mg morning/ 280mg evening) or 1120mg/day (as 560mg BID or 840mg morning/ 280mg evening), again on days 1-21 of a 28-day cycle. Overall response rate of oral rigosertib plus azacitadine in this Phase II study was 90%, with 34% of patients exhibiting CR. Toxicity was primarily hematologic (26% febrile neutropenia, 21% thrombocytopenia) and urinary (51% hematuria, 14% dysuria). Ten of 39 patients discontinued therapy due to toxicity, including dysuria, urinary retention, hematuria, hydronephrosis, osteolysis, cerebral hemorrhage, leukopenia, neutropenia, and abdominal pain ²².

Clinical Efficacy of Rigosertib in Non-Melanoma Solid Tumors

A phase II/III study of 160 patients with previously untreated pancreatic cancer who were randomized to receive either rigosertib plus gemcitabine versus gemcitabine alone. In this study, rigosertib was administered as IV infusion (rather than PO formulation described herein). This study was negative, with no significant difference in PFS or OS between the groups.

A phase I study of advanced solid tumor patients was conducted to evaluate dosing and toxicity of oral rigosertib. Notably, this trial did not include any patients with melanoma. Among 46 patients with evaluable efficacy data, one patient experienced CR and one patient experienced partial response (PR, with an overall response rate of 4.3%. Both responding patients had squamous cell head & neck tumors. An additional 8 patients experienced stable disease (SD), resulting in a clinical benefit rate (defined as CR+PR+SD) of 21.7% ²³.

Two Phase II studies of rigosertib monotherapy are ongoing in patients with recessive dystrophic epidermolysis bullosa-associated squamous cell carcinoma in the United States and Europe (NCT04177498, NCT03786237).

Ongoing Clinical Trials of Rigosertib in combination with anti-PD-1 agents

One study of rigosertib in combination with an anti-PD-1 agent is ongoing. This is a Phase I/IIa trial of oral rigosertib in combination with the PD-1 inhibitor nivolumab in KRAS-positive lung adenocarcinoma after progression on standard first-line therapy (NCT04263090); preliminary results from the first 7 patients (all of whom progressed on first-line anti-PD-1 therapy) with evaluable response demonstrates a 43% rate of clinical benefit to this combination (2 PRs, 1 SD). Manageable safety was observed as well in this population. Subjects 1 and 2 were dosed with 280mg bid and 560mg/280mg daily, followed by 10 patients dosed at 560mg bid in combination with nivolumab 240mg q14 days. In these 12 patients, 1 DLT was observed (hyponatremia). Table X lists the toxicities observed thus far in this study.

Treatment-Related Adverse Events (TRAEs) – n (%)	Entire Cohort: N=12	
	Grade 1-2	Grade 3
Dysuria	7 (58)	1 (8)
Hematuria	7 (58)	1 (8)*
Urinary Frequency	2 (17)	
Abdominal Pain	4 (33)	
Fatigue	6 (50)	
Anemia	10 (83)	
Lymphopenia	3 (25)	
Thrombocytopenia	2 (17)	
Hyponatremia*	3 (25)	
Hyperglycemia	11 (92)	
AST elevation	3 (25)	
ALT elevation	3 (25)	
ALK elevation	2 (17)	
Nausea/Vomitting	4 (33)	
Constipation	4 (33)	
Diarrhea	2 (17)	
Anorexia	2 (17)	
Pruritis	1 (8)	
Infusion-related Reaction	1 (8)	
*Dose Limiting Toxicity		

4.2 Rationale

4.2.1 Preclinical Rational for Rigosertib plus Pembrolizumab

Rigosertib has shown promising antitumor activity in both in vitro and in vivo melanoma models. Evaluation of melanoma cell death upon rigosertib treatment in vitro revealed sensitivity at IC50 of

0.1-1 μ M in a panel of ten human and murine melanoma cell lines of varying mutational status (including NRASQ^{61R}, BRAF^{V600E}, PTEN^{null}, TP53^{mut} and/or CDKN2A^{null}), with dose-dependent cytotoxic effects validated on both CellTiter Blue and crystal violet assays. Pathway interrogation of melanoma cells demonstrated that treatment with rigosertib rapidly and durably suppressed PI3K-AKT^{T308}-mTORC1 and mTORC2-AKT^{S473} activation in melanoma cells, while also inducing cleaved-caspase3 and formation of reactive oxygen species. This suggests that in vitro treatment of melanoma cell lines with rigosertib inhibits cell viability and promotes both apoptotic (non-immunogenic) and inflammatory cell death.

Evaluation of rigosertib treatment (delivered by oral gavage) of mice subcutaneously implanted with BRAF^{mut} murine melanoma cell lines revealed that sensitivity to rigosertib requires an intact immune system, as melanoma tumors in athymic mice (lacking mature T cells) were near-completely resistant to rigosertib treatment. However, when melanoma tumors were implanted into C57Blk/6 mice, rigosertib was effective in inhibiting tumor growth. Dose escalation cohorts (150, 200, 300, 400mg/kg) demonstrated comparable effects of the 300 and 400mg/kg dosing regimens, which both resulted in ~60% inhibition of tumor volume. This effect was confirmed in an NRAS^{wt}/BRAF^{wt} model, suggesting that rigosertib efficacy is mutant-independent. Immune profiling by FACS analysis revealed that treatment with rigosertib induced increase the total number and density of tumor-infiltrating leukocytes (TILs). Profiling of the immune effector cell infiltrate showed that rigosertib increased the frequency of both CD4⁺ T helper and CD8⁺ cytotoxic T cells within the tumor microenvironment, both of which demonstrated increased levels of activation as compared to control-treated mice (as assayed by CD69 positivity). This finding was confirmed on immunohistochemical staining of tumor sections.

Based on the increased activated TILs seen in the tumor-immune microenvironment upon rigosertib treatment, it was hypothesized that combination treatment with checkpoint inhibitor may function synergistically to further inhibit tumor growth. This was similarly evaluated in mouse models. Treatment with anti-PD-1/anti-CTLA-4 checkpoint inhibitor therapy alone induced only marginal inhibition of tumor growth, but concurrent treatment with rigosertib resulted in significant 70% inhibition of tumor growth. Notably, tumor growth inhibition induced by combination checkpoint inhibitor plus rigosertib treatment was significantly greater than that induced by rigosertib alone.

Preclinical mouse models of both *BRAF*-mutant and *BRAF*-wild type melanoma exhibit high frequency and density of CD4⁺ and CD8⁺ T cells. However, these T cells have very low levels of activation in the tumor microenvironment, thus limiting their anti-tumor activity. Treatment with rigosertib strongly activates CD8⁺ T cells in the tumor-draining lymph nodes compared to activation under vehicle treatment, suggesting a potent immunosuppressive effect mediated by tumor microenvironment. Furthermore, the combination of immune checkpoint inhibition with rigosertib resulted in a significant decrease in tumor growth as compared to either rigosertib or immune checkpoint inhibition alone. Combination treatment did not cause any significant weight loss or change in liver function tests of treated mice as compared to vehicle treated controls, suggesting low toxicity. These preliminary data suggest a strong therapeutic basis for the use of immune checkpoint inhibitors in combination with rigosertib to enhance anti-tumor immunity, providing a potential treatment option for patients whose tumors exhibit primary or secondary resistance to PD-1 inhibition.

For preclinical data regarding pembrolizumab monotherapy, please refer to the Investigator's Brochure for Preclinical and Clinical data.

4.2.2 Rationale for the Trial and Selected Population

Therapies targeting the programmed cell death 1 (PD-1) pathway have dramatically improved outcomes for patients with metastatic melanoma over the last decade, producing 5-year overall survival (OS) rates from 31-44%^{24, 25}. A minority of patients experience durable complete response (CR). However, 40-60% of patients will experience only limited or no clinical benefit from PD-1 inhibitors due to acquired or primary resistance to these drugs^{26, 27}. While myriad of mechanisms underlie resistance to PD-1 inhibitors, a major contributor to the failure of these drugs involves inadequate tumor-infiltrating lymphocytes within the tumor-immune microenvironment²⁸. A “cold” immune microenvironment is thought to be less receptive to treatment with PD-1 inhibitors, while and inflamed “hot” tumor-immune microenvironment is better primed for tumor cell targeting as directed by PD-1/L1 inhibitors²⁹. As discussed above, preclinical evaluation of rigosertib in mouse studies suggests that rigosertib treatment increased tumor-infiltrating leukocyte invasion into the tumor microenvironment and induces activation state of CD4+ and CD8+ T cells. The combination of immune checkpoint inhibition with rigosertib resulted in a significant decrease in tumor growth as compared to either rigosertib or immune checkpoint inhibition alone. This preclinical data suggests that concurrent treatment with rigosertib functions to increase immunogenicity of the tumor microenvironment and may function to “prime” a patient for the anti-tumor effect of PD-1 inhibitor pembrolizumab.

Presently, treatment options for melanoma patients depend on the presence or absence of specific driver mutations. About half of patients with metastatic melanoma have tumors which harbor activating mutations at the BRAF V600 locus, rendering them sensitive to targeted therapy with BRAF/MEK inhibitors. These patients have FDA-approved treatment options with good response rates beyond checkpoint inhibitors. Mutually exclusive of BRAF driver mutations, another 30% of patients with metastatic melanoma have tumors which are driven by activating mutations in NRAS. The remaining 20% of melanoma patients have tumors without either of these driver mutations. In current practice, most patients with unresectable/metastatic melanoma are treated initially with checkpoint inhibitor therapy (barring contraindication) regardless of underlying BRAF mutation, as ICI therapy is associated with a greater potential for durable response³⁰. Upon disease progression, patients whose disease has an underlying BRAF mutation are eligible for targeted therapy, but approximately half of all patients with metastatic melanoma lack effective treatment options after progression on checkpoint inhibitor therapy.

Once disease progresses on PD-1/L1 inhibitor, effective treatment options are limited. One strategy is to continue PD-1/L1 inhibitor and add ipilimumab; this has resulted in objective response rates of 31% in the PD-1/L1-refractory setting. Transition to single-agent ipilimumab is associated with a much lower ORR of 13%, despite similar rates of G3+ toxicity³¹. A similar study also demonstrated improved ORR with the addition of ipilimumab to PD-1/L1 inhibitor upon disease progression; 19.5% versus 4.2% with transition to single-agent ipilimumab³².

Early preclinical data suggested that BRAF inhibitors induce TIL invasion into the tumor-immune environment, providing rationale for clinical evaluation of BRAF-targeted therapy/checkpoint inhibitor therapy combinations³³. This led to Phase III clinical trial of combination therapy with PD-L1 inhibitor atezolizumab plus BRAF inhibitor vemurafenib and MEK inhibitor cobimetinib, which demonstrated a 5-month progression-free survival benefit with triple therapy compared to BRAF/MEK inhibition alone³⁴. The combination of atezolizumab plus vemurafenib/cobimetinib was FDA approved in the first-line setting for use in patients with unresectable for metastatic melanoma whose disease harbors activating BRAF V600 mutations. However, approximately half of melanoma patients are ineligible for this combination treatment due to lack of BRAF driver mutation, and as a first-line trial, this study did not evaluate the PD-1 refractory setting.

4.2.3 Justification for Dose of Experimental Agents

The planned dose of rigosertib for this study is 560mg BID on days 1-21 of a 28-day cycle. Rigosertib has been used in the clinical trial setting in both IV and PO formulations. For this trial, a PO formulation has been selected. An oral formulation has the advantage of ease of administration with demonstrated equivalency to the IV formulation. See Investigator's Brochure for additional information.

The planned dose of pembrolizumab for this study is 400 mg Q6W. The current approved dosing regimens of pembrolizumab for IV administration are 200 mg Q3W and 400 mg Q6W for adults [³⁵, ³⁶]. A 400 mg Q6W dosing regimen of pembrolizumab is expected to have a similar benefit-risk profile as 200 mg Q3W, in all treatment settings in which 200 mg Q3W pembrolizumab is currently appropriate. Specifically, the dosing regimen of 400 mg Q6W for pembrolizumab is considered adequate based on M&S analyses, given the following rationale:

PK simulations demonstrating that in terms of pembrolizumab exposures:

- C_{avg} (or AUC) at 400 mg Q6W is similar to the approved 200 mg Q3W dose, thus bridging efficacy between dosing regimens.
- Trough concentrations (C_{min}) at 400 mg Q6W are generally within the range of those achieved with 2 mg/kg or 200 mg Q3W in the majority (>99%) of patients.
- Peak concentrations (C_{max}) at 400 mg Q6W are well below the C_{max} for the highest clinically tested dose of 10 mg/kg Q2W, supporting that the safety profile for 400 mg Q6W should be comparable to the established safety profile of pembrolizumab
- Exposure Response (E-R) for pembrolizumab has been shown to be flat across indications, and OS predictions in melanoma and NSCLC show that efficacy at 400 mg Q6W is expected to be similar to 200 mg or 2 mg/kg Q3W, given the similar exposures; thus, use of 400 mg Q6W is not expected to alter efficacy across indications

4.2.4 Rationale for Endpoints

4.2.4.1 Efficacy Endpoints

The primary endpoint for this study is the overall response rate, with the hypothesis that the ORR will be approximately 30% (and >10%) in patients with PD-1i-refractory metastatic melanoma. This ORR was chosen because meta-analysis data of two large phase III trials of PD-1 inhibitors in melanoma suggests that patients treated with PD-1 inhibitor beyond progression can expect a response rate of 28%³⁷; as such, ORR greater than 28% suggests benefit beyond that of what is expected.

PFS and OS will also be assessed as secondary endpoints. These metrics are clinically relevant, although this Phase II study is not powered to assess these endpoints.

4.2.4.1 Planned Exploratory Biomarker Research

Blood samples (10mL each) will be collected as indicated in the Time and Events Table (see Section 2.3). Blood will be processed to isolate both PBMCs and serum for future biomarker analyses at the conclusion of the study, as to be determined by the Investigator based on the state of knowledge at that time and available molecular analysis platforms. Possible analyses include, but are not limited to, immune cell populations, circulating free DNA (cfDNA), circulating miRNA and protein/cytokine arrays.

On-treatment biopsies will be mandatory for 10 of the 29 patients enrolled, including 5 patients from the stage I of study. On-treatment biopsy will be preferentially obtained from those patients with accessible tumors (ie, cutaneous lesions, subcutaneous nodules). On-treatment biopsies will be obtained with patient consent. A maximum of three on-treatment biopsies will be obtained per individual patient. These samples will be interrogated to determine change in T-cell infiltration induced by rigosertib plus pembrolizumab (as compared to archival pre-treatment tumor biopsies). RNA sequencing will also be performed on biopsy specimens to evaluate T-cell receptor evolution.

5.0 METHODOLOGY

5.1 Study Population

5.1.1 Participant Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Male/female participants who are at least 18 years of age on the day of signing informed consent with histologically confirmed diagnosis of unresectable or metastatic cutaneous melanoma will be enrolled in this study.

Male participants:

A male participant must agree to use a contraception as detailed in Appendix 3 of this protocol during the treatment period and for at least 6 days (140 hours) plus an additional 90 days (a spermatogenesis cycle) after the last dose of study treatment and refrain from donating sperm during this period.

Female participants:

A female participant is eligible to participate if she is not pregnant (see Appendix 3), not breastfeeding, and at least one of the following conditions applies:

- a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 3
- OR
- b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 during the treatment period and for at least 6 days (140 hours) plus 120 days after the last treatment dose of study.
2. Participants must have progressed on treatment with an anti-PD-1/L1 mAb administered either as monotherapy or in combination with other checkpoint inhibitors or other therapies. PD-1 inhibitor treatment progression is defined by meeting the following criteria:
 - a. For patients treated with anti-PD-1/L1 mAb in the unresectable/metastatic setting:
 1. Has received at least 2 doses of an approved anti-PD-1/L1 mAb.
 2. Has demonstrated disease progression after anti-PD-1/L1 as defined by iRECIST. The initial evidence of PD is to be confirmed by a second assessment no less than 4 weeks from the date of the first documented disease progression, in the absence of rapid clinical progression (as defined in 2c).
 3. Progressive disease has been documented within 12 weeks from the last dose of anti-PD-1/L1 mAb.
 - b. For patients treated with anti-PD-1/L1 mAb in the adjuvant setting:
 4. Has received at least 2 doses of an approved anti-PD-1/L1 mAb.

5. Develops recurrent disease during active adjuvant treatment with anti-PD-1/L1 mAb, OR
 6. Develops recurrent disease within 6 weeks of last dose of anti-PD-1/L1 mAb.
 - c. Progressive disease is determined according to iRECIST (ie, progression by RECIST v1.1 on first imaging, confirmed with repeat imaging performed at least 4 weeks later). Once disease progression is confirmed, the initial date of disease progression documentation will be considered the date of disease progression OR
 - d. The determination of clinical progression is made by the investigator.
3. Participants whose disease harbors BRAF V600 mutation must have been exposed to BRAF-targeted therapy, with BRAF-targeted treatment discontinued for either progressive disease or intolerable toxicity.
 4. The participant (or legally acceptable representative if applicable) provides written informed consent for the trial.
 5. Have measurable disease based on iRECIST . Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
 6. Have provided archival tumor tissue sample or newly obtained (within 3 months of enrollment) core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.
 7. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Evaluation of ECOG is to be performed within 7 days prior to the first dose of study intervention.
 8. Have adequate organ function as defined in the following table (Table 2). Laboratory values must be collected within 10 days prior to the start of study intervention (ie, first dose of study treatment).

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
White blood cell (WBC)	$\geq 3,000/\mu\text{L}$
Absolute neutrophil count (ANC)	$\geq 1,500/\mu\text{L}$
Platelets	$\geq 75,000/\mu\text{L}$
Hemoglobin ^a	$\geq 9 \text{ g/dL}$ or $\geq 5.6 \text{ mmol/L}$
Renal	
Serum creatinine OR Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	$\leq 1.5 \times$ upper limit of normal (ULN) OR $\geq 30 \text{ mL/min}$ for subject with creatinine levels $> 1.5 \times$ institutional ULN
Hepatic	
Serum total bilirubin	$\leq 1.5 \times \text{ULN}$ OR $\leq 3.0 \text{ mg/dL}$ for patients with Gilbert syndrome
AST (SGOT) and ALT (SGPT)	$\leq 2.5 \times \text{ULN}$ for subjects without liver metastases OR $\leq 5 \times \text{ULN}$ for subjects with liver metastases
Coagulation	
International normalized ration (INR) OR prothrombin time (PT) AND Activated partial thromboplastin time (aPTT)	$\leq 1.5 \times \text{ULN}$ unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
Urinary Function	
Urinalysis	Negative for hematuria with negative blood AND $< 10 \text{ RBCs}$. Note: if blood is known to be coming from a renal source, the patient may be enrolled after discussion with the PI.
ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal. ^a Criterion must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks. ^b Creatinine clearance (CrCl) should be calculated per institutional standard.	

5.1.2 Participant Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Has a diagnosis of primary uveal or mucosal melanoma.

2. A WOCBP who has a positive urine pregnancy test within 72 hours of the first dose of study intervention (see Appendix 3). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. In the event that 72 hours have elapsed between the screening pregnancy test and the first dose of study treatment, another pregnancy test (urine or serum) must be performed and must be negative in order for subject to start receiving study medication. Pregnancy testing will be obtained every three months while on study treatment; patients will be withdrawn from the study if pregnancy occurs.
3. Has received prior systemic anti-cancer therapy including investigational agents within 4 weeks (for immunotherapeutic agents) or within 2 weeks (for targeted therapeutics) prior to the first dose of study drug. If a subject has experienced AE from prior treatment, he/she must have recovered from all AEs to <Grade 1 or baseline. Patients with <Grade 2 neuropathy may be eligible. Patients with endocrine-related AEs <2 requiring treatment or physiologic steroid replacement may be eligible.
4. Has received prior radiotherapy within 2 weeks of the first dose of study drug. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.
5. If participant has had recent major surgery, the participant must have recovered adequately from the procedure and/or any complications from the surgery prior to the first dose of study drug.
6. Has received a live vaccine or live-attenuated vaccine within 30 days prior to the first dose of study drug. Administration of killed vaccines is allowed.
7. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study drug. Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.
8. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
9. Has a known additional malignancy that is progressing or has required active treatment within the past 2 years. Participants with non-melanoma skin cancer (eg, basal cell carcinoma of the skin, squamous cell carcinoma of the skin) or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
10. Subjects with untreated active central nervous system (CNS) metastases, active brain metastases or leptomeningeal metastatic foci. For the subjects with brain metastases, if they have received treatment and have no evidence of progressive disease on

magnetic resonance imaging (MRI) at least 4 weeks after completion of the treatment and within 30 days prior to the first dose, they are eligible to participate in the study.

11. Has a history of severe hypersensitivity ($\geq$ Grade 3), specifically infusion reaction or anaphylaxis to pembrolizumab and/or any of its excipients.
12. Has a history of severe hypersensitivity ($\geq$ Grade 3 reactions including wheezing, rash, or hypotension) to rigosertib and/or any of its excipients (including polyethylene glycol), or anaphylaxis.
13. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment and is allowed.
14. Has a history of (non-infectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
15. Has an active infection requiring systemic therapy.
16. Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Note: no testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.
17. Has a known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
18. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
19. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
20. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of trial treatment.
21. Has had an allogenic tissue/solid organ transplant.

5.1.3 Lifestyle Considerations

5.1.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting. Participants should ensure excellent hydration status with at least 2 liters of oral fluid intake per day to minimize risk of urinary toxicity from rigosertib. Rigosertib should be administered in the fasting state between meals (ie, at least two hours after meals and one hour before next meal).. Please see Section 5.2.1, Timing of Dose Administration for further detail.

5.1.3.2 Contraception

Rigosertib is classified as Pregnancy Category C (potential evidence of risk). Preclinical studies in animal models suggest that rigosertib has potential for fetotoxicity and teratogenicity (including lower fetal weights and craniofacial malformation). Pembrolizumab may have adverse effects on a fetus in utero. Strict contraception rules should be followed (See Appendix 3 for approved methods of contraception).

For this study, male participants will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

5.1.4 Pregnancy

Women of childbearing potential will undergo period pregnancy testing as described in the study protocol and will be withdrawn from the study if they become pregnant. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Coordinating Center, Onconova and Merck within 2 working days if the outcome is a serious adverse experience (e.g. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Coordinating Center (which will subsequently inform Onconova and Merck). If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Coordinating Center (which will subsequently inform Onconova and Merck) and followed as described in Section 6.2.

5.2 Trial Intervention(s)

The intervention(s) to be used in this trial is outlined below in **Table 3:**

Table 3 Trial Intervention(s)

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	400 mg	Q6W	IV infusion	Day 1 of each 6-week cycle	Study Provided
Rigosertib	560 mg	BID	oral	Days 1-21 of 28-day cycle	Investigational

Trial interventions should begin as close as possible to the date on which study eligibility is confirmed by the Coordinating Center.

5.2.1 Timing of Dose Administration

Trial interventions should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Schedule of Activities, Section 2.3. Trial interventions may be administered up to 2 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial interventions will be administered on an outpatient basis.

Rigosertib will be administered as 560 mg (2x 280 mg tablets) taken twice daily (1,120 mg total daily dose) on days 1-21 on a 28 day cycle. Rigosertib should be taken in a fasting state twice daily as follows:

- Patients will be instructed to take their morning dose after an overnight fast, on an empty stomach, and wait 1 hr after dosing to have breakfast.
- The afternoon dose should be taken at approximately 3 PM (± 1 hr) at least 2 hours after lunch, on an empty stomach, and patients should wait 1 hr before the next meal.

Water is permitted during the fasting period. Any vomited dose will be reported as a missed dose. Good hydration (ie, at least 2 liters of water per day) is recommended for all patients.

All study drug should be maintained in its original container and brought to all clinic appointments for usage review by study administrator.

Pembrolizumab 400 mg will be administered as a 30 minute IV infusion every 6 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

5.2.2 Dose Modification and toxicity management for immune-related AEs associated with pembrolizumab and AEs associated with rigosertib therapy

5.2.2.1 Pembrolizumab Toxicity and Management

AEs associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in Table 4.

Table 4 Dose modification and toxicity management guidelines for AEs (immune and non-immune) associated with pembrolizumab monotherapy and IO combinations

General instructions:				
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids. 2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤ 10 mg/day within 12 weeks of the last study intervention treatment. 3. The corticosteroid taper should begin when the irAE is $\leq$ Grade 1 and continue at least 4 weeks. 4. If pembrolizumab has been withheld, it may resume after the irAE decreased to $\leq$ Grade 1 after corticosteroid taper.				

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
			Add prophylactic antibiotics for opportunistic infections	
Diarrhea/Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	- Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) - Participants with $\geq$Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis - Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT Elevation or Increased Bilirubin	Grade 2 ^a	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 ^b or 4 ^c	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β -cell failure	Withhold ^d	- Initiate insulin replacement therapy for participants with T1DM - Administer antihyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue ^d		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue ^d		
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event ^e		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

- ^a AST/ALT: >3.0 to 5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal
- ^b AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal
- ^c AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal
- ^d The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.
- ^e Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Infusion reactions related to pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 5.

Table 5 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
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Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug intervention.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

5.2.2.2 Rigosertib Toxicity and Management

In a Phase I study of oral rigosertib plus azacitadine in patients with myelodysplastic syndrome or acute myeloid leukemia, rigosertib was well-tolerated. Maximal tolerated dose was not reached, with the final cohort of patients treated at rigosertib dosing of 560mg morning/ 280mg evening for the first 21 days of a 28-day cycle. The most frequent toxicities observed were diarrhea (50%), constipation (44%), fatigue (44%), nausea (44%), pneumonia (33%) and back pain (33%) ²¹. In the expanded Phase II study of rigosertib plus azacitadine in first-line treatment of patients with higher-risk myelodysplastic syndromes, rigosertib dosing was increased to either 840mg/day (as 560mg morning/ 280mg evening) or 1120mg/day (as 560mg BID or 840mg morning/ 280mg evening), again on days 1-21 of a 28-day cycle. Toxicity was primarily hematologic (26% febrile neutropenia, 21% thrombocytopenia) and urinary (51% hematuria, 14% dysuria). Ten of 39 patients discontinued therapy due to toxicity, including dysuria, urinary retention, hematuria, hydronephrosis, osteolysis, cerebral hemorrhage, leukopenia, neutropenia, and abdominal pain ²².

In patients with previously untreated metastatic pancreatic cancer, rigosertib was administered as IV infusion with pyrimidine antimetabolite gemcitabine. The most frequently reported treatment-related adverse events included fatigue. When compared to the gemcitabine monotherapy arm, toxicities with higher incidence in the rigosertib plus gemcitabine arm included hyponatremia (any grade, 25% versus 6%; grade 3+, 17% v 4%) and grade 3+ anemia (8% v 4%) ³⁸.

In contrast to the intravenous form of rigosertib, the dosing and safety of the oral formulation of rigosertib was evaluated in a Phase I study in adult patients with advanced solid tumors. A total of 48 patients (including gastrointestinal, head & neck, genitourinary, gynecologic, breast, lung, and sarcoma) were treated with increasing dosing regimens; safe dosage of the oral formulation was determined to be 560mg twice daily. Dose-limiting toxicities were observed in 2 of 47 evaluable patients (4.3%); these toxicities included one case of hematuria and one case of dysuria. No grade 4+ toxicities were observed. Any-grade toxicities seen in this study included: dysuria, cystitis, urinary urgency, hematuria, urinary hesitancy, abdominal discomfort/distension, nausea, fatigue, hypertonic bladder, pelvic pain, and hyponatremia ²³. Notably, risk of urinary toxicity may be reduced with urinary management strategies including maintenance of good hydration status (at least 2L per day), afternoon dosing of second daily dose, and emptying bladder before bedtime. By minimizing bladder dwell of rigosertib, these strategies mitigate risk of urinary toxicity. Table 6 includes suggested management strategies for rigosertib toxicities, although investigator discretion is permitted.

Table 6 Adverse Events associated with oral rigosertib

AEs	Toxicity Grade (CTCAE v5.0)	Suggested Action With Rigosertib	Therapies	Monitoring and Follow-up
Urinary toxicity: dysuria, hematuria, pollakiuria, proteinuria, urinary retention, cystitis	Grade 2, initial episode	delay dose for up to 4 weeks, until toxicity resolves to $\leq$ Grade 1, then resume at 560mg BID (full starting dose)	Supportive care per investigator discretion. Supportive care options may include oral and/or intravenous hydration, urinary alkalinization, and/or bladder anti-spasmodics such as mirabegron, darifenacin, oxybutynin	• Monitor participants for signs and symptoms of renal dysfunction (serum creatinine, renal ultrasound) • Monitor serial urinalysis, consider urine cytology, urology consultation
	Recurrent Grade 2, second episode or Grade 3, initial episode	delay dose for up to 4 weeks, until toxicity resolves to $\leq$ Grade 1, then resume at 560mg AM / 280mg PM (first dose reduction)		
	Recurrent Grade 2, third episode or Recurrent Grade 3, second episode	delay dose for up to 4 weeks, until toxicity resolves to $\leq$ Grade 1, then resume at 280mg BID (second reduced dose)		
	Recurrent Grade 3, third episode Or Grade 4	Permanently discontinue		

AEs	Toxicity Grade (CTCAE v5.0)	Suggested Action With Rigosertib	Therapies	Monitoring and Follow-up
Hyponatremia	Grade 2, first episode	delay dose for up to 4 weeks, until toxicity resolves to $\leq$ Grade 1, then resume at 560mg BID (full starting dose)	Supportive care Consider general or ICU admission for symptomatic or significant derangement	• Monitor participants with serial electrolyte evaluations • Supportive care as indicated
	Recurrent Grade 2, second episode Or Grade 3, first episode	delay dose for up to 4 weeks, until toxicity resolves to $\leq$ Grade 1, then resume at 560mg Am/ 280mg PM (first dose reduction)		
	Recurrent Grade 2, third episode Or Recurrent Grade 3, second episode	delay dose for up to 4 weeks, until toxicity resolves to $\leq$ Grade 1, then resume at 280mg BID (second dose reduction)		
	Recurrent Grade 3, third episode Or Grade 4	Withhold or permanently discontinue		
All Other AEs	Grade 2, first episode	delay dose for up to 4 weeks, until toxicity resolves to $\leq$ Grade 1, then resume at	Supportive care Consider general or ICU admission for symptomatic or significant derangement	• Ensure adequate evaluation to confirm etiology or exclude other causes

AEs	Toxicity Grade (CTCAE v5.0)	Suggested Action With Rigosertib	Therapies	Monitoring and Follow-up
		560mg BID (starting dose)		
	Recurrent Grade 2, second episode Or Grade 3, first episode	delay dose for up to 4 weeks, until toxicity resolves to $\leq$ Grade 1, then resume at 560mg Am/ 280mg PM (first dose reduction)		
	Recurrent Grade 2, third episode Or Recurrent Grade 3, second episode	delay dose for up to 4 weeks, until toxicity resolves to $\leq$ Grade 1, then resume at 280mg BID (second dose reduction)		
	Recurrent Grade 3, third episode Grade 4* (excluding neutropenia, thrombocytopenia, nausea, vomiting, diarrhea)	Permanently discontinue		
	Grade 4 neutropenia, thrombocytopenia, nausea, vomiting, diarrhea	delay dose for up to 4 weeks, until toxicity resolves to $\leq$ Grade 1, then resume at reduced dose		

AEs	Toxicity Grade (CTCAE v5.0)	Suggested Action With Rigosertib	Therapies	Monitoring and Follow-up
	Confirmed SJS, TEN, or DRESS	Permanently discontinue	Supportive care Dermatology consultation Consider general or ICU admission for symptomatic or significant derangement	

*Grade 4 toxicity EXCLUDING neutropenia, thrombocytopenia, nausea/vomiting/diarrhea. See below Section 5.2.2.2.1, Rigosertib Dose Modification for detail.

5.2.2.2.1 Rigoseritib Dose Modification

Dose reduction in rigoseritib will be allowed. As described in Section 2.1 Trial Design, Stage 1 of the Simon Two-Stage design will allow for a Lead-in Phase to assess for treatment-related toxicity. During the Lead-in phase, 6 patients will be enrolled, evaluated for toxicity prior to initiation of cycle 2 (C1D2 of 28-day cycle) based on laboratory studies as described in Section 2.3 Schedule of Activities. Toxicity assessment will include blood and urine tests, including CBC, CMP, magnesium, phosphorus, and urinalysis.

Dose-limiting toxicities (DLTs) are defined as the following:

- Grade 3-4 febrile neutropenia
- Grade 4 neutropenia lasting longer than 5 days
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia with bleeding
- ALT/AST > 3xULN with bilirubin >2xULN without another explanation (e.g., cholestasis)
- Grade 4 nausea/vomiting/diarrhea of any duration
- Grade ≥ 3 non-hematologic toxicity **with the following exceptions:**
 - Grade 3 nausea managed with maximal medical therapy that has persisted < 72 hours
 - Grade 3 vomiting and/or diarrhea managed with maximal medical therapy that has persisted < 72 hours
 - Grade 3 fatigue < 7 days
- Any toxicity that delays administration of rigoseritib for more than 2 weeks
- Any toxicity that results in a patient receiving < 80% of the anticipated dose in the first 28-day cycle (DLT observation period)

If treatment-related toxicity (as defined above) is observed, rigoseritib will be held for up to 4 weeks until toxicity resolved to $\leq$ Grade 1, then rigoseritib will be resumed at reduced dosage. Two dose reductions are permitted on study for the individual patient: first dose reduction to 560mg AM / 280mg PM, and second dose reduction to 280mg BID. Re-assessment of toxicity will occur to ensure that toxicity has improved to $\leq$ Grade 1 prior to rigoseritib resumption, and after an additional 28-day cycle of treatment following dose reduction. If AE resolves to G1 or baseline at the reduced level, and no additional toxicities are seen at the reduced dose, the dose of rigoseritib may be increased in a step-wise manner (ie, second dose reduction [280mg BID] increased to first dose reduction [560mg AM/280mg PM], or first dose reduction [560mg AM/280mg PM] increased to full starting dose [560mg BID]). If toxicity persists as G2, rigoseritib will be continued at reduced dose. If toxicity persists for greater than four weeks as $G \geq 3$, rigoseritib will be withheld. If G4 toxicity is observed, rigoseritib will be permanently discontinued, except for G4 neutropenia, thrombocytopenia, nausea/vomiting, and diarrhea.

Dose Levels	Rigosertib dose
Full starting dose	560mg BID
First dose reduction	560mg AM /280mg PM
Second dose reduction	280mg BID

5.2.2.3 Attribution of Toxicity

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. If, in the clinical opinion of the Investigator a toxicity may be clearly attributed to either pembrolizumab [Table 4] or rigosertib [Table 6], then the offending drug may be held while the other is continued. In clinically ambiguous cases in which toxicity is not clearly attributable to rigosertib or to pembrolizumab alone, both interventions must be held according to the criteria in Table 4 and 6 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab.

Rigosertib (oral formulation) and anti-PD-1 mAb nivolumab are currently being evaluated in a clinical trial of KRAS-mutant, PD-1 inhibitor refractory non-small cell lung cancer. Preliminary results from the first 12 patients enrolled on this study demonstrate encouraging toxicity profile of rigosertib plus nivolumab in this cohort. Of note, all patients included in this trial experienced progressive disease on prior treatment with PD-1/L1 inhibition. Observed toxicities most classically associated with rigosertib include dysuria (58%), hematuria (58%) and urinary frequency (17%), with all cases being mild (grade 1-2). Other common toxicities included hyperglycemia (92%), anemia (83%), and fatigue (50%); all cases were similarly mild (grade 1-2). At rigosertib dose of 560mg BID, 1 patient experienced dose-limiting toxicity of hyponatremia. Importantly, no synergistic toxicities were observed for either rigosertib or nivolumab. These preliminary data in a heavily pre-treated cohort of NSCLC patients suggest that the combination of rigosertib plus pembrolizumab will be well-tolerated in melanoma patients.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, pembrolizumab should be held according to recommended dose modifications. If the AE is considered to be related to rigosertib, it may be dose-reduced (for G2 AEs) or held (for G_≥3 AEs) as described in Section 5.2.2.2.1 Rigosertib Dose Modification.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in [Table 6].

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from pembrolizumab.

Participants may have rigosertib dose modifications in this study, as described in Section 5.2.2.1.

- If, upon treatment with reduced dose of rigosertib, the toxicity does not improve or resolve to baseline, the participant must be discontinued from rigosertib.
- If, upon treatment with reduced dose of rigosertib for at least one 28-day cycle, the toxicity does improve to G1 or resolve to baseline, the participant may continue on reduced dose or resume full dose rigosertib at the discretion of the investigator.

If the toxicities do resolve and conditions are aligned with what is defined in Tables 4 and 6, the combination of rigosertib plus pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to [the combination or to rigosertib alone], re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion .

5.2.2.4 Allowable Interruptions

Other allowed dose interruption for rigosertib and pembrolizumab

Rigosertib may be interrupted for situations other than treatment-related AEs such as medical/surgical events and/or unforeseen circumstances not related to study intervention. However, intervention is to be restarted within 4 days of the originally scheduled dose and within 4 days of the previously administered dose (if interruption occurs during original day 1-21 of rigosertib treatment cycle) OR within 7 days of planned cycle initiation (if interruption occurs during original day 22-28 of rigosertib treatment cycle), unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the patient's study record.

Pembrolizumab must be discontinued if irAE does not resolve or improve to grade 1 within 12 weeks of last treatment. Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events and/or unforeseen circumstances not related to study intervention. However, intervention is to be restarted within 6 weeks (42 days) of the originally scheduled dose and within 84 days of the previously administered dose. The reason for study intervention interruption is to be documented in the participant's study record.

5.3 Randomization or Treatment Allocation

All patients are scheduled to receive rigosertib 560 mg BID on day 1-21 of a 28 day cycle plus pembrolizumab 400mg every six weeks. There is no randomization in this study.

5.4 Stratification

No treatment stratification will be performed.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

5.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 30 days prior to the first dose of trial intervention and up to 30 days after the last dose of trial intervention should be recorded. If participants experience an SAE or ECI, concomitant medications administered within 30 days after the last dose of trial intervention are to be recorded as defined in Section 6.2.

5.5.2 Prohibited Concomitant Medications

Participants are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than rigosertib and pembrolizumab
- Radiation therapy
 - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the discretion of the Investigator.
- Live vaccines within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed, as are

mRNA such as the COVID-19 vaccines. However, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
- Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.5.3 Rescue Medications & Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.2, Table 4 and Table 6. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines in Table 4 are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

If after the evaluation of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to Table 4 in Section 5.2.2 for guidelines regarding dose modification and supportive care.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

5.6 Participant Discontinuation Criteria

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 2.3 unless the participant has withdrawn from the study (Section 5.7).

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Intervention (pembrolizumab + rigosertib) will be given for a maximum of 24 months.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention
- After prolonged study intervention interruption that prohibits restarting study intervention if agreed upon with the Sponsor
- Radiographic disease progression outlined in Section 6.1.4.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 5.2.2.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or sponsor, placed the participant at unnecessary risk from continued administration of study treatment.
- The participant has a confirmed positive serum pregnancy test

Completion of intervention therapy includes 18 treatments of pembrolizumab Q6W plus 24 twenty-eight day cycles of rigosertib (approximately 2 years). Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 24 weeks (4 Q6W cycles of pembrolizumab plus 6 twenty-eight day cycles of rigosertib) and have been treated for at least two 28-day cycles of rigosertib plus at least one doses of pembrolizumab beyond the date when the initial CR was declared.

5.7 Participant withdrawal From Study

A participant must be withdrawn from the study if the participant or the participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specified details regarding procedures to be performed at the time of withdrawal from the study are outlined in Section 6.1.6.1.

5.8 Participant Replacement Strategy

If a patient withdraws consent or dies prior to receiving at least two doses of study regimen, an additional patient will be enrolled.

5.9 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to participants
4. Plans to modify or discontinue the development of the study drug rigosertib
5. Lack of efficacy as defined by <2 response in the first 10 patients enrolled at 17 weeks

In the event of a decision by Onconova and/or Merck to no longer supply study drug, adequate notification will be provided so that appropriate adjustments to participant treatment can be made.

6.0 TRIAL ASSESSMENTS AND PROCEDURES

6.1 Trial Procedures

- Study procedures and their timing are summarized in The Schedule of Activities, Section 2.3.
- Adherence to the study design requirements, including those specified in the Schedule of Activities is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria
- Additional evaluations/testing may be deemed necessary by the investigator, the Sponsor and/or Onconova and Merck for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

6.1.1 Administrative and General Procedures

6.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical trial. If there are changes to a participant's status during the study (e.g. health requirements) the investigator must ensure appropriate consent is in place.

6.1.1.2 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the participant must receive the IRB/ERC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may reasonably be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

6.1.1.3 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the participant qualifies for the trial.

6.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the participant has enrolled in this study may be recorded separately and not listed as medical history.

6.1.1.5 Prior and Concomitant Medications Review

6.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before participant's first dose of treatment in the trial. Treatment for the disease for which the participant has enrolled in this study may be recorded separately and not listed as a prior medication.

6.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the trial.

6.1.1.6 Disease Details and Treatments

6.1.1.6.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

6.1.1.6.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

6.1.1.6.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a participant initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the participant will move into survival follow-up. See Section 2.3 Schedule of Activities.

6.1.1.7 Trial Compliance (Medication/Diet/Activity/Other)

Patients will self-administer rigosertib in the fasting state as described in Section 5.2.1 (Timing of Dose Administration). Patients will receive extensive education on appropriate administration of rigosertib and will self-report any deviations during study visits.

6.1.2 Clinical Procedures/Assessments

6.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each participant to evaluate for potential new or worsening AEs as specified in Section 2.3 Schedule of Activities and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 5.0 (see Appendix 5). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to section 6.2 for detailed information regarding the assessment and recording of AEs.

6.1.2.2 Physical Exam

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard. Height (during screening) and weight will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

6.1.2.3 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 2.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

6.1.2.4 Directed Physical Exam

For cycles that do not require a full physical exam per the Section 2.3, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

6.1.2.5 Vital Signs

The investigator or qualified designee will take vital signs at screening, at cycle initiation (day 1) and mid cycle (day 15) for the first four cycles, then prior to each subsequent dose of pembrolizumab thereafter (ie, every six weeks), and at treatment discontinuation as specified in the Schedule of Activities (Section 2.3). Patients may be seen more often should symptoms

develop. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

6.1.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Appendix 1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Schedule of Activities (Section 2.3).

6.1.3 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Study Procedures Manual. Refer to the Study Schedule of Activities (Section 2.3) for the timing of laboratory assessments.

6.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

6.1.3.2 Pregnancy Testing

All women who are being considered for participation in the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of the first dose of study intervention. If a urine test is positive or not evaluable, a serum test will be required. Participants

must be withdrawn from the study in the event of a positive test result. Repeated pregnancy test will be performed every 3 months on study as well as at time of discontinuation.

6.1.4 Tumor Imaging and Assessment of Disease

Tumor imaging is strongly preferred to be acquired by computed tomography (CT). For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when local practice mandates it. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging. Imaging should include chest, abdomen and pelvis.

Expedited confirmation of measurable disease based on RECIST 1.1 at screening should be used to determine participant eligibility. Confirmation that the participant's imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 is highly recommended prior to fully screening for the study.

6.1.4.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 30 days prior to first dose of study treatment. The site study team must review screening images to confirm the participant has measurable disease and confirms patient's status as refractory to PD-1 inhibition per iRECIST.

Brain imaging, if performed to document the stability of existing metastases, should be by MRI if possible. If MRI is medically contraindicated, CT with contrast is an acceptable alternative.

6.1.4.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed 8 weeks (56 days $\pm$ 7 days) after the first dose of rigosertib or pembrolizumab (whichever is administered first). Subsequent tumor imaging should be performed every 8 weeks (56 days $\pm$ 7 days) after the previous imaging or more frequently if clinically indicated. After 24 weeks (168 days $\pm$ 7 days) since first dose of study treatment, participants who remain on treatment will have imaging performed every 12 weeks (84 days $\pm$ 7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression is identified by the Investigator.

Objective response should be confirmed by a repeat imaging assessment. Tumor imaging to confirm PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging every 8 weeks (or 12 weeks as outlined above), starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per iRECIST (Section 6.1.4.5), disease progression should be confirmed by the site 4 to 8 weeks after first radiologic evidence of PD in clinically stable participants. Participants who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 6.1.4.5. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 6.1.4.5.

6.1.4.3 End of Treatment and Follow-up Tumor Imaging

In participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. In participants who discontinue study treatment due to documented disease progression and the investigator elects not to implement iRECIST, this is the final required tumor imaging.

For participants who discontinue study treatment without documented disease progression, every reasonable effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 8 or 12 weeks as outlined in Section 6.1.4.2) to monitor disease status until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

6.1.4.4 iRECIST 1.1 Assessment of Disease

iRECIST 1.1 will be used as the initial measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study treatment). Although iRECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, the Sponsor allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

6.1.4.5 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the investigator, working with local radiology, according to the rules outlined in Appendix 4. This allowance to continue treatment despite initial radiologic disease progression takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

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

Any participant deemed clinically unstable should be discontinued from study intervention at first radiologic evidence of disease progression, and is not required to have repeat tumor imaging for confirmation of disease progression by iRECIST.

If the investigator decides to continue treatment, the participant may continue to receive study intervention and the tumor assessment should be repeated 4 to 8 weeks later to confirm disease progression by iRECIST, per investigator assessment.

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

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 4, study intervention should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study intervention may be considered following consultation with the Sponsor. In this case, if study intervention is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.

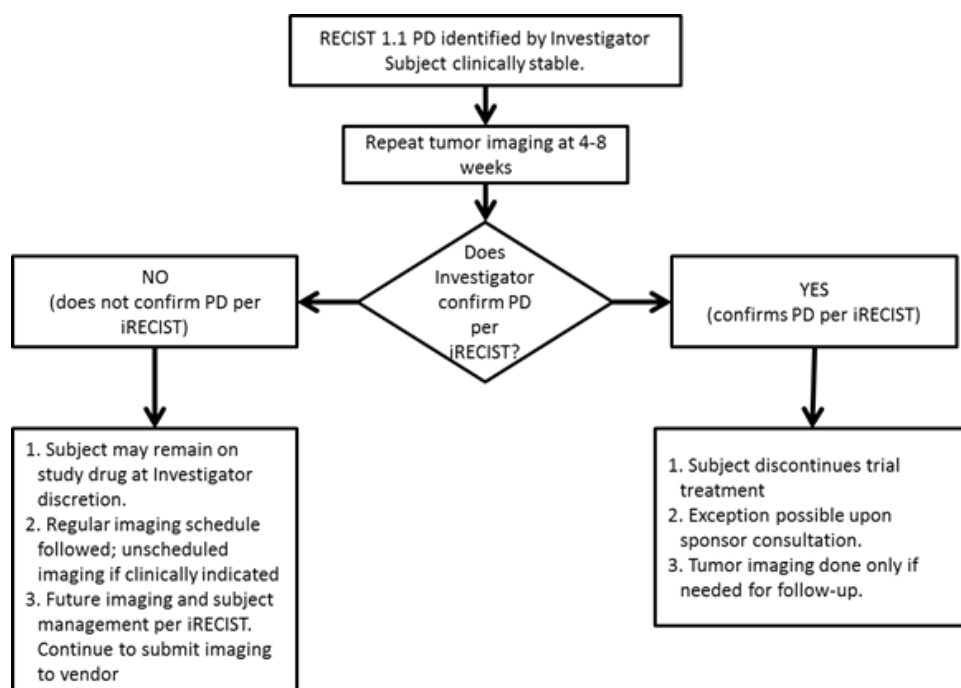
A description of the adaptations and iRECIST process is provided in Appendix 4. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 7 and illustrated as a flowchart in Figure 2.

Table 7 Imaging and Treatment After First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
First radiologic evidence of disease progression by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm disease progression	May continue study treatment at the assessment of the investigator and after the participant's consent	Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only.	Discontinue treatment
First radiologic evidence of disease progression by iRECIST	Repeat imaging at 4 to 8 weeks to confirm disease progression.	May continue study intervention at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only.	Discontinue treatment

	Clinically Stable		Clinically Unstable	
	Imaging	Treatment	Imaging	Treatment
First radiologic evidence of disease progression by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm disease progression	May continue study treatment at the assessment of the investigator and after the participant's consent	Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms disease progression (iCPD) by iRECIST per investigator assessment.	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment.	Repeat imaging at 4 to 8 weeks to confirm disease progression. May occur at next regularly scheduled imaging visit.	Continue study intervention at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm disease progression per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study intervention at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study intervention if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.
iCPD=iRECIST confirmed progressive disease; iCR=iRECIST complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD=iRECIST stable disease; iUPD=iRECIST unconfirmed progressive disease; RECIST 1.1=Response Evaluation Criteria in Solid Tumors 1.1; VOP=verification of progression				

Figure 2: Imaging and Treatment for Clinically Stable Participants after First Radiologic Evidence of PD Assessed by the Investigator



6.1.5 Tumor Tissue Collection and Correlative Studies Blood Sampling

Blood samples (up to 12mL) will be collected from all patients as indicated in the Schedule of Activities (see Section 2.3). Blood will be processed to isolate both PBMCs and serum for future biomarker analyses at the conclusion of the study, as to be determined by the Investigator based on the state of knowledge at that time and available molecular analysis platforms. Possible analyses include, but are not limited to, immune cell populations, circulating free DNA (cfDNA), circulating miRNA and protein/cytokine arrays. See **Laboratory Manual** for full processing instructions.

After processing, samples will be delivered to the laboratory of Ann Richmond, PhD, in Preston Research Building room 432. Both serum and PBMCs will be slow-frozen in ethanol before long-term storage in liquid nitrogen in secured freezers of room 443 of Preston Research Building. Banked serum will be used to perform cytokine array upon completion of collection. PBMCs will be used to perform bulk RNA sequencing for T-cell receptor (TCR) interrogation as well as fluorescence automated cell cytometry to characterize changes to peripheral immune milieu upon study treatment

On-treatment biopsies will be mandatory for at least 10 of 29 patients enrolled on study, including 5 patients from Stage 1. Preference for on-treatment biopsy will be given to those patients whose tumor is easily accessible (ie, cutaneous lesions, subcutaneous nodules). A maximum of three on-treatment biopsies will be obtained per patient. These samples will be interrogated to determine change in T-cell infiltration induced by rigosertib plus pembrolizumab (as compared to archival pre-treatment tumor

biopsies). RNA sequencing will also be performed on biopsy specimens to evaluate T-cell receptor evolution.

Upon collection, tumor specimens will be delivered to the laboratory of Ann Richmond, PhD, in Preston Research Building room 432. Tumor samples will be transported in DMEM or equivalent culture media sufficient to submerge sample. Richmond lab staff will process tissue for future use by isolating tumor as indicated below. Processed tumor tissue will be stored in secured liquid nitrogen freezers in Preston Research Building room 443.

6.1.6 Other Procedures

6.1.6.1 Discontinuation and withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 6.2.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the final study visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 6.2.

6.1.6.2 Blinding/Unblinding

No blinding is involved in this open-label study.

6.1.7 Visit Requirements

Visit requirements are outlined in Section 2.3 – Schedule of Activities. Specific procedure-related details are provided above in Section 6.1 - Trial Procedures.

6.1.7.1 Screening

6.1.7.1.1 Screening Period

All screening procedures will be performed during the screening period. Screening requirements are outlined in Section 2.3 – Table 1 Study Schedule of Activities.

6.1.7.2 Treatment Period

Treatment visits will occur every 2 weeks for the first 8 weeks, then every 2-4 weeks thereafter (at start of Q4W rigosertib cycle or start of Q6W pembrolizumab infusion). At all treatment visits, symptom evaluation, physical exam and laboratory studies will be performed as documented in Section 2.3 – Table 1 Schedule of Study Events.

6.1.7.3 Post-Treatment Visits

6.1.7.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study intervention or before the initiation of a new anti-cancer treatment, whichever comes first (See Section 5.6 Participant Discontinuation Criteria).

6.1.7.3.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin the Efficacy Follow-Up

Phase and should be assessed every 8 weeks (56 ± 7 days) by radiologic imaging to monitor disease status (See Section 5.6 Participant Discontinuation Criteria). After 6 months, the imaging time point will occur every 12 weeks (± 7 days). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, or end of the study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments will not have further efficacy assessments must enter the Survival Follow-up Phase.

6.1.7.3.3 Survival Follow-up Contacts

Participant survival follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, three years follow-up, or the end of the study, whichever occurs first.

The first survival follow-up assessment should be scheduled as described below:

For participants who discontinue treatment intervention and who will not enter the Efficacy Follow-up Phase (see immediately above section), the first survival follow-up contact will be scheduled 12 weeks after the discontinuation visit and/or safety follow-up visit (whichever is last)

For participants who completed assessments in the Efficacy Follow-up Phase, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

6.1.7.3.4 Post Study

Participants will be required to return to clinic approximately 30 (± 7) days after the last dose of study intervention for the poststudy visit. If the poststudy visit occurs less than 30 days after the last dose of study intervention, a subsequent follow-up telephone call should be made at 30 days post the last dose of study intervention to determine if any AEs have occurred since the poststudy clinic visit unless additional anticancer treatment has been started.

6.2 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 5.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

Adverse events will be graded according to the NCI's Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0, dated November 27, 2017, currently locatable via the following: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

If events are not listed in the CTCAE, severity may be designated as mild, moderate, severe, life-threatening, or fatal which respectively correspond to Grades 1, 2, 3, 4, and 5 on the NCI CTCAE, with the following definitions:

- **Mild:** Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated;
- **Moderate:** Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL) such as preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc;
- **Severe:** Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL such as bathing, dressing and undressing, feeding self, using the toilet, taking medications;
- **Life-threatening:** Urgent intervention indicated to prevent risk of death present at the time of the event;
- **Fatal:** An event that results in the death of the patient.

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before first dose of protocol-indicated treatment must be reported, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of initiation of rigosertib or pembrolizumab (whichever dose occurs first) through 30 days following patient's final dose of rigosertib or pembrolizumab (whichever dose occurs last) must be reported by the investigator.
- All AEs meeting serious criteria from the time of initiation of rigosertib or pembrolizumab (whichever dose occurs first) through 90 days following patient's final study-indicated treatment with rigosertib or pembrolizumab (whichever dose occurs last), or through 30 days following last dose of study treatment if the participant initiates new anticancer therapy, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of initiation of rigosertib or pembrolizumab (whichever dose occurs first) through 120 days following patient's final dose of rigosertib or pembrolizumab (whichever dose occurs last), or through 30 days following last dose of study treatment if the participant initiates new anticancer therapy, must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Coordinating Center (which will subsequently notify Onconova and Merck) if the event is considered by the investigator as possibly, probably or definitely related to study participation.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Coordinating Center (which will subsequently notify Onconova and Merck).

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Coordinating Center, Onconova and Merck within the time frames as indicated in **Table 8**.

Table 8 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

<u>Type of Event</u>	<u>Reporting Time Period:</u>			<u>Time Frame to Report Event and Follow-up Information to the Coordinating Center</u> (see Appendix 5)
	Consent to first dose of study treatment	First dose of study treatment through Protocol-specified Follow-up Period	After Protocol-specified Follow-up Period	
Serious Adverse Event (SAE)	Report if due to protocol-specified intervention.	Report all.	Report new SAE if considered possibly, probably or definitely related to participation in this study; follow previously reported ongoing SAE; report outcome.	Within 24 hours of the investigator becoming aware of the event.
Pregnancy/Lactation Exposure			Follow previously reported to completion/termination; report outcome	
Event of Clinical Interest (ECI) including new Cancer, Overdose and potential Drug-Induced Liver Injury (DILI) – see below in this Section 6.2.			Not required unless related to study participation.	

Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), new cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained or determined to be irreversible or not clinically significant, or the participant is lost to follow-up. In addition, the investigator will make every reasonable attempt to follow all nonserious AEs that occur in patients who initiate investigational treatment in this study. Further information on follow-up procedures is given in Appendix 5.

Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable country specific regulatory requirements, global laws and regulations.

Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Coordinating Center, Onconova and Merck.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Events of Clinical Interest (ECIs)

Selected nonserious and serious adverse events are also known as Events of Clinical Interest (ECIs) and must be reported to the Coordinating Center, Onconova and Merck in expedited fashion via the same process as an SAE (see Appendix 5).

Events of clinical interest for this study include:

1. No information on an overdose of rigosertib currently exists. In the event of overdose (defined as > 1120 mg or > 4 capsules taken within 4 hours), the participant should be closely observed for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an adverse event(s) is associated with ("results from") the overdose of an Onconova product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.
2. An overdose of pembrolizumab that is not associated with clinical symptoms or abnormal laboratory results. For purposes of this study, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥ 2.5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated. If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.
3. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper

limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.0 STATISTICAL ANALYSIS PLAN

7.1 Sample Size Assumptions

To determine the overall sample size and the interim sample size, a two-stage Simon's Optimal design was evaluated. To test the hypotheses (ORR=10% versus 30%, 2 responses from the first 10 patients would be required to progress to stage 2 and a total of 29 subjects will be needed to achieve the desired type I (< 5%) and type II error rate (power >80%).

If the true response rate to rigosertib plus pembrolizumab is: (%)	Probability of early termination after stage I
10%	0.7361
20%	0.375
30%	0.149

7.2 Baseline Characteristics and Other Analyses

Each relevant clinical characteristic will be recorded by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of patients treated, and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by descriptive statistics.

Drug accountability data for pembrolizumab and rigosertib will be collected during the study. Compliance with pembrolizumab administration will be measured by patients: 1) receiving unscheduled study agent infusions/injections; 2) missing an infusion/injection. Numbers and percentages of patients and infusion/injection visits with any deviation in these measures will be reported. Compliance with rigosertib will be measured by: 1) pill counts performed to document usage; 2) monitoring of patient-specific home administration log. Number and percentages of patients and rigosertib drug cycles with any deviations will be reported.

7.3 Efficacy Endpoints

7.3.1 Primary Endpoint

Objective response rate (ORR) as defined by immune-related response criteria will be the primary endpoint of the study. As mentioned, the primary hypothesis is that ORR of rigosertib

plus pembrolizumab will be 30%. We will enroll 10 patients in stage I to allow for early termination for futility. If <2 responses are observed, the trial will be terminated. However, if ≥ 2 objective responses occur, the trial will proceed to stage II.

In stage II, an additional 19 patients will be enrolled. If ≥ 6 responses occurring in all patients treated in stage I and stage II, the trial will be considered positive and we will reject the null hypothesis that the ORR is 10% or less.

7.3.2 Secondary Endpoints

7.3.2.1 Progression Free Survival

Progression-free survival (PFS) as defined as the time from the first dose of pembrolizumab to progression as defined by iRECIST criteria or death for any reason, whichever comes first. . PFS will be summarized in the method of Kaplan and Meier. Median PFS and PFS at one year will be reported with 95% confidence intervals. PFS analysis based on investigator's assessment using irRC will also be carried out.

Since disease progression is assessed periodically, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the primary analysis, for the patients who have PD, the true date of disease progression will be approximated by the date of first assessment at which PD is objectively documented using iRECIST1 criteria, regardless of discontinuation of study drug. Death is always considered as a confirmed PD event. Patients without documented PD/death will be censored at the last follow-up as (especially deaths) may be discovered at times other than scheduled assessments.

7.3.2.2 Overall Survival

Overall survival is defined as the interval between the first dose of pembrolizumab and death for any reason. The Kaplan-Meier method will be used to estimate the overall survival. Patients alive at last follow-up will be censored. Median survival and its 95% confidence interval will be estimated and reported.

7.3.2.3 Rate of Toxicity

Adverse events attributed to study drugs will be listed by CTCAE grade and reported in terms of the number of patients who experienced adverse events as a percentage of all treated patients.

This endpoint will be reported descriptively without formal statistical analysis.

8.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

8.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Rigosertib will be supplied by Onconova, and pembrolizumab will be provided by Merck as summarized in Table 9.

Table 9 Product Descriptions

Product Name & Potency	Dosage Form
Rigosertib 280 mg	Oral capsule
Pembrolizumab 100 mg/ 4mL	Solution for Injection

8.2 Packaging and Handling Information

8.2.1 Pembrolizumab

Each site will be provided pembrolizumab from Merck.

Pembrolizumab is typically available¹⁰¹ in a single-dose vial as a clear to slightly opalescent, colorless to slightly yellow solution (100 mg/4 mL = 25 mg/mL).

Pembrolizumab product does not contain a preservative. Pembrolizumab will be prepared consistent with the product label¹⁰¹; after preparation, store the diluted solution from the pembrolizumab 100 mg/4 mL vial either:

- At room temperature for no more than 6 hours from the time of dilution. This includes room temperature storage of the diluted solution, and the duration of infusion.
- Under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 96 hours from the time of dilution. If refrigerated, allow the diluted solution to come to room temperature prior to administration. Do not shake.

Discard after 6 hours at room temperature or after 96 hours under refrigeration.

Do not freeze.

The pharmacy manual and/or product label contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

8.2.2 Rigosertib

Rigosertib is supplied as soft gelatin capsules 280 mg/mL suspension of rigosertib in PEG 400 and PEG 4000. The 280 mg capsules are of an opaque yellow-orange color.

- Vials of ON 01910.Na concentrate 75mg/mL and oral soft gelatin capsules of rigosertib should be stored under refrigeration (2°C to 8°C) and protected from light.
-

8.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the participant, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text.

8.4 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

8.5 Returns and Reconciliation

A record of the number of rigosertib capsules dispensed to and taken by each subject must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delay will also be recorded. The Investigator will make every effort to bring non-compliant subjects into compliance.

The investigator is responsible for keeping accurate records of the clinical supplies received from Onconova and Merck or designee, the amount dispensed to and returned by the participants and the amount remaining at the conclusion of the trial.

After receiving written authorization in advance from the sponsor-investigator or designee upon completion or termination of the study or earlier, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

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10.0 APPENDICES

Appendix 1: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.1 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters				
Hematology	Platelet Count		RBC Indices: MCV MCH %Reticulocytes		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	RBC Count				
	Hemoglobin				
	Hematocrit				
	LDH				
Chemistry	BUN	Potassium	AST/SGOT		Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the ULN)
	Albumin	Bicarbonate	Chloride		Phosphorous
	Creatinine	Sodium	ALT/SGPT		Total Protein
	Glucose (non- fasting)	Calcium	Alkaline phosphatase		magnesium
Endocrine	Thyroid stimulating hormone (TSH)				
Cardiac	Troponin				
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick • Microscopic examination (if blood or protein is abnormal)				
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP)				
Other Screening Tests	• FSH (as needed in WONCBP only) • PT, PTT				
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; FSH=follicle-stimulating hormone; hCG=human chorionic gonadotropin; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin time; PTT= partial thromboplastin time; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential					

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

Appendix 3: Contraceptive Guidance and Pregnancy Testing

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP:

- Premenarchal
 - Premenopausal female with 1 of the following:
 - Documented hysterectomy
 - Documented bilateral salpingectomy
 - Documented bilateral oophorectomy
- Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
 - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
 - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Requirements

Male Participants:

Male participants with female partners of childbearing potential are eligible to participate if they agree to one of the following during the protocol defined time frame in Section 5.1.1:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 11 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant.
 - Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants:

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception that has a low user dependency consistently and correctly as described in Table 11 during the protocol-defined time frame in Section 5.1.1.

Table 11 Highly Effective Contraceptive Methods That Have Low User Dependency

Highly Effective Methods That Have Low User Dependency <i>Failure rate of <1% per year when used consistently and correctly.</i>
● Progestogen- only contraceptive implant ^{a, b} ● Intrauterine hormone-releasing system (IUS) ^b ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Note: males with partners who are females of reproductive potential, and females of reproductive potential to use effective contraception during treatment for at least 4 months following the final dose of any study therapy (either pembrolizumab or rigosertib)

Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements.

Following initiation of treatment additional pregnancy testing will be performed every 3 months during the treatment period and at treatment discontinuation.

Pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

Appendix 4: Description of the RECIST Process for Assessment of Disease Progression

Assessment at Screening and Prior to iRECIST Progression

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

Assessment and Decision at RECIST 1.1 Progression

In participants who show evidence of radiological PD by RECIST 1.1 the Investigator will decide whether to continue a participant on study treatment until repeat imaging 4 to 8 weeks later is obtained (using iRECIST for participant management (see Table 7 and Figure 2). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

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

Any participant deemed clinically unstable should be discontinued from study treatment at site-assessed first radiologic evidence of PD and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment.

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

- Increase in the sum of diameters of target lesion(s) identified at baseline to $\geq 20\%$ and ≥ 5 mm from nadir
 - Please note: the iRECIST publication uses the terminology “sum of measurements”, but “sum of diameters” will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

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

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

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

Assessment at the Confirmatory Imaging

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

Confirmation of Progression

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

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

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

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

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

Management Following the Confirmatory Imaging

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

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.

Detection of Progression at Visits After Pseudo-progression Resolves

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

- Target lesions
 - Sum of diameters reaches the PD threshold ($\geq 20\%$ and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
 - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
 - If non-target lesions had shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
 - New lesions appear for the first time
 - Additional new lesions appear

- Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
- Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

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

Additional details about iRECIST are provided in the iRECIST publication ³⁹.

Appendix 5: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of Adverse Event (AE)

An adverse event is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

Definition of Serious Adverse Event (SAE)

A serious adverse event is an undesirable sign, symptom or medical condition which:

- Is fatal or life-threatening;
- Requires or prolongs inpatient hospitalization;
- Results in persistent or significant disability/incapacity;
- Constitutes a congenital anomaly or birth defect; or
- Jeopardizes the participant and requires medical or surgical intervention to prevent one of the outcomes listed above.

Events not considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures.
- Elective or pre-planned treatment for a pre-existing condition that did not worsen.
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission.
- Respite care.

Expectedness

Expected: Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as a potential risk.

Unexpected: An adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as a potential risk.

Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

Additional Events Reported in the Same Manner as SAE

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Coordinating Center, Onconova and Merck in the same time frame as SAEs to meet certain local requirements. Therefore, these events are also considered serious for collection and reporting purposes in this study:

- New cancer (that is not a condition of the study), or
- Event associated with an overdose of rigosertib or pembrolizumab (see Events of Clinical Interest in Section 6.2), or
- An elevated AST or ALT lab value that is $\geq 3x$ the upper limit of normal and an elevated total bilirubin lab value that is $\geq 2x$ the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is $< 2x$ the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing (see Events of Clinical Interest in Section 6.2).

Recording AE and SAE

AE and SAE recording

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

There may be instances when copies of medical records for certain cases are requested by the Coordinating Center, Onconova and/or Merck. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Coordinating Center, Onconova and Merck.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

An event is defined as “serious” when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI Common Terminology for Adverse Events (CTCAE), Version 5.0, dated November 27, 2017, currently locatable via the following:

<https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf>. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
- Grade 4: Life threatening consequences; urgent intervention indicated.
- Grade 5: Death related to AE.

Assessment of causality

1. Did rigosertib and/or pembrolizumab cause the AE?
2. The determination of the likelihood that rigosertib and/or pembrolizumab caused the AE will be provided by an investigator who is a qualified physician. The investigator’s signed/dated initials/signature on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This signed/initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.
3. The following components are to be used to assess the relationship between rigosertib/pembrolizumab and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely rigosertib/pembrolizumab caused the AE:

- **Exposure:** Is there evidence that the participant was actually exposed to rigosertib/pembrolizumab such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
- **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of rigosertib/pembrolizumab? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
- **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
- **Dechallenge:** Was rigosertib/pembrolizumab discontinued or dose/exposure/frequency reduced?
 - If yes, did the AE resolve or improve?
 - If yes, this is a positive dechallenge.
 - If no, this is a negative dechallenge.

(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of rigosertib/pembrolizumab; (3) the study is a single-dose drug study; or (4) rigosertib/pembrolizumab is/are only used 1 time.)

- **Rechallenge:** Was the participant re-exposed to rigosertib/pembrolizumab in this study?
 - If yes, did the AE recur or worsen?
 - If yes, this is a positive rechallenge.
 - If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) rigosertib/pembrolizumab is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY RIGOSERTIB/PEMBROLIZUMAB, OR IF RE-EXPOSURE TO RIGOSERTIB/PEMBROLIZUMAB POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS

PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF
REQUIRED, THE IRB/IEC.

4. **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding rigosertib/pembrolizumab or drug class pharmacology or toxicology?
5. The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
6. Use the following scale of criteria as guidance (not all criteria must be present to be indicative of rigosertib/pembrolizumab relationship).
 - Yes, there is a reasonable possibility of rigosertib/pembrolizumab relationship:
 - There is evidence of exposure to rigosertib/pembrolizumab. The temporal sequence of the AE onset relative to the administration of rigosertib/pembrolizumab is reasonable. The AE is more likely explained by rigosertib/pembrolizumab than by another cause.
 - No, there is not a reasonable possibility of rigosertib/pembrolizumab relationship:
 - Participant did not receive rigosertib/pembrolizumab OR temporal sequence of the AE onset relative to administration of rigosertib/pembrolizumab is not reasonable OR the AE is more likely explained by another cause than rigosertib/pembrolizumab. (Also entered for a participant with overdose without an associated AE.)
7. For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
8. There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Coordinating Center. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Coordinating Center.
9. The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
10. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

11. For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Coordinating Center (which will subsequently report to Onconova and Merck) within 2 business days but no longer than 3 calendar days of receipt of the information.
- Upon discontinuation of study treatment (whether completion or termination), evaluation for AE and/or SAE will occur at follow-up visit 30 days

Reporting of AEs, SAEs, and Other Reportable Safety Events to the Coordinating Center, Onconova and Merck

General Considerations

All adverse events will be captured on a centralized electronic case report form. Specified members at each participating site will submit all regulatory documents to the sponsor.

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs, and avoid colloquialisms and abbreviations. If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g. record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death." Deaths that occur during the protocol specified adverse event reporting

period that are attributed by the investigator solely to progression of disease should be recorded only in the study eCRF and not reported as an SAE.

A pre-existing medical condition is one that is present prior to initiation of protocol specified treatment. Such conditions should be reported as medical and surgical history. A pre-existing medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for pre-existing conditions; or
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study; or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

Serious Adverse Events

All serious adverse events, regardless of causality to study drug, will be reported to the Principal Investigator and/or the Study Coordinator at each institution, and also to the Coordinating Center.

All serious adverse events must be reported to the Coordinating Center within 24 hours of the investigator becoming aware of the event. Events should be reported using the Vanderbilt SAE form, located in the packet of supplemental forms. This form must be fully completed and emailed or scanned to:

ATTN: VICC CTSR Personnel

EMAIL: Coordinating.Center@vumc.org

Follow-up information must also be reported within 24 hours of receipt of the information by the investigator.

The Coordinating Center will disseminate information regarding serious adverse events to the participating sites as described in FDA guidance only in the case that the event(s) is/are

unexpected, and is/are believed to be related (i.e., possibly, probably or definitely) to the study device/medication. The Coordinating Center will be responsible for reporting of events to supporters, as appropriate (outlined below).

Institutional Review Board

All adverse events and serious adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification of the study protocol, these modifications will be provided to the IRB as soon as is possible.

Food and Drug Administration (FDA)

In this trial, unexpected serious adverse events believed to be definitely, probably, or possibly related to study treatment (as determined by the sponsor-investigator) will be reported to the FDA via MedWatch 3500A, currently available at:
< <https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf> >.
Submissions by the sponsor can be submitted via fax or electronically (e.g. email) and must be addressed to the Regulatory Project Manager in the FDA review division that has responsibility for review of the IND. The Coordinating Center will be responsible for correspondence regarding adverse events with the FDA for all participating sites.

Reporting to Supporters

SAE reports and any other relevant safety information are to be forwarded by the Coordinating Center to Onconova and Merck. Vanderbilt University Medical Center acting as the Coordinating Center will notify Onconova and Merck of any serious adverse event (SAE) that occurs during the reporting period as defined above in Section 6.2. Within 2 business days but no longer than 3 calendar days after the Coordinating Center initially receives the safety information from the site, the Coordinating Center will report the SAE (on the MedWatch, funder, or Vanderbilt SAE form approved by the Coordinating Center and funder) to point(s) of contact specified by Onconova and Merck (details below). Follow-up SAE reports received by the Coordinating Center should be sent within 2 business days but no longer than 3 calendar days to the funder using the same procedure used for transmitting the initial report.

Merck: SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-661-6229

Onconova: Send completed forms to PRA Safety & Risk management: Preferred method – email: FTWSafety@iconplc.com. North America – Fax: 1-888-772-6919

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission.

Additionally, investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-661-6229) at the time of submission to FDA.

Appendix 6: Data Safety and Monitoring

Data Management and Reporting

Data will be collected using a centralized electronic case report form called Online Clinical Oncology Research Environment (Oncore). Oncore is a highly secure, web based, cancer specific, and customizable system that provides fully integrative clinical data management and study administration capabilities developed in an ongoing collaborative effort with NCI designated Comprehensive Cancer Centers. It fully integrates study administration functionality including protocol tracking, patient registration, NCI reporting, review committee tracking, and SAE tracking, with clinical data management functionality including electronic case report forms (eCRF) design, clinical data capture, protocol and regulatory compliance monitoring. The system is capable of storing basic protocol information (e.g., IRB approval dates, dates for annual renewals) and clinical trial research data. Oncore allows the investigator to define specific protocol requirements and generate data collection forms. Creation of the data collection form is done with a single button click after the parameters of an individual protocol have been specified. Oncore permits specification of study protocols, management of patient enrollment, clinical data entry and viewing, and the generation of patient or study-specific reports based on time stamping. Oncore is embedded with a comprehensive domain repository of standard reference codes and forms to promote standardization. The sources for the repository include CDUS, CTC, CDEs from NCI, ICD, MedDRA and various best practices from contributing NCI-designated Comprehensive Cancer Centers. Oncore provides several reporting features specifically addressing NCI Summary 3 and Summary 4 and other reporting requirements. Data may also be exported in a format suitable for import into other database, spreadsheets or analysis systems (such as SPSS). This system will be used to manage VICCC clinical trials data. Oncore is maintained and supported in the VICC Clinical and Research Informatics Resource.

Meetings

The Vanderbilt melanoma research team includes medical oncologists, research nurses, data managers, and regulatory specialists. The team meets on a regular basis to discuss AEs/SAEs, accrual, compliance, safety issues, adherence to protocol, etc. pertaining to cancer studies conducted by the team. In addition, teleconferences between the Coordinating Center and the research team at Vanderbilt may be scheduled as necessary, in order to discuss relevant issues related to the trial (e.g. AEs/SAEs, accrual, compliance, safety issues, adherence to protocol, reviews).

Auditing and Monitoring

The Vanderbilt-Ingram Cancer Center (VICC) oversees patient safety and data monitoring for its investigator-initiated and NIH-NCI funded clinical trials through its Data and Safety Monitoring Committee (DSMC). The purpose of the DSMC is to ensure the efficient implementation and management of the VICC Data and Safety Monitoring Plan (DSMP). The Committee maintains authority to intervene in the conduct of studies as necessary to ensure clinical research performed at VICC achieves the highest quality standards.

The VICC DSMC meets on a quarterly basis and ad hoc to discuss data and safety monitoring of clinical trials and to oversee the VICC DSMP. Internal audits for compliance with adverse event reporting, regulatory and study requirements, and data accuracy and completion are conducted

according to the VICC DSMP according to study phase and risk. The committee reviews all serious adverse events (SAE) on Vanderbilt sponsored investigator-initiated studies on a quarterly basis and provides DSMC SAE review reports to the Vanderbilt IRB.

The trial additionally will be monitored by the VICC Multi-Institutional Coordinating Center. The actual frequency of monitoring will depend on the enrollment rate and performance of the site. Monitoring will be conducted through onsite and/or remote monitoring, teleconferences with the Investigator and site staff, and appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions, and to ensure the quality and integrity of the data.

During scheduled monitoring visits, investigators and the investigational site staff must be available to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests, provide required regulatory documents, and respond to any other trial-related inquiries of the monitor.

In addition to the above, the FDA may review the conduct or results of the study at the investigational site.

Data Handling and Record Keeping

An electronic case report form (eCRF) is required and must be completed for each included participant. The completed dataset should not be made available in any form to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without written permission from Vanderbilt.

To enable evaluations and/or audits from health authorities and Vanderbilt, the site investigator agrees to keep records including: The identity of all participants (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. To comply with international regulations, the records should be retained by the investigator in compliance with regulations.

Queries resulting from review of the eCRFs will be generated for the site and corrections will be made by the study site personnel. This will be done on an ongoing basis.

Appendix 7: Regulatory Considerations and Study Coordination

Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per current institutional standards.

The trial will not be initiated until there is approval by the local IRB of the protocol, informed consent document and any other material used to inform the patient about the nature of the trial. The IRB should be duly constituted according to local regulatory requirements. The investigator will inform the IRB of the progress of the trial at least yearly.

Any changes to the protocol will be made in the form of a written amendment and must be approved by the sponsor-investigator and the local IRB prior to local implementation. All amendments will also be submitted as necessary to the FDA by the sponsor-investigator (or designee).

Protocol changes to eliminate an immediate hazard to a trial patient may be implemented by the investigator immediately. The investigator must then immediately inform the local IRB; and the sponsor-investigator (or designee), who will communicate as appropriate with the FDA.

The sponsor-investigator (or designee) is responsible for the coordination and development of all protocol amendments and will disseminate this information to the participating centers.

Informed Consent

The investigator (or designee) will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each participant will be informed that participation in the study is voluntary, that s/he may withdraw from the study at any time, and that withdrawal of consent will not affect subsequent medical treatment or relationship with the treating physician(s) or institution.

The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The participant should read and consider the statement before signing and dating it and will be given a copy of the document. No patient will enter the study or have study-specific procedures done before his/her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

Confidentiality

It is the responsibility of the investigator to ensure that the confidentiality of all patients participating in the trial and all of their medical information is maintained. Case report forms (CRFs) and other documents submitted to regulatory authorities must not contain the name of a trial patient. All patients in the trial will be identified by a unique identifier which will be used on all CRFs and any other material submitted to regulatory authorities. All case report forms and any identifying information must be kept in a secure location with access limited to the study staff directly assisting with the trial.

Study Termination

The sponsor-investigator reserves the right to terminate the study at any site and at any time. Reasons for study termination may include, but are not limited to, the following:

- Investigator non-compliance with the protocol, GCP or regulatory requirements.
- Insufficient enrollment.
- Safety concerns.
- Decision by suppliers to modify or discontinue the availability, development or manufacture of protocol-indicated treatment.
- A request to discontinue the study by the IRB or FDA.

Trial Compliance

This is an investigator-initiated study. The Principal Investigator, Douglas Johnson, M.D., M.S.C.I. (who may also be referred to as the Sponsor-Investigator), is conducting the study and acting as the sponsor. Therefore, the legal and ethical obligations of the Principal Investigator include both those of a sponsor and those of a principal investigator.

Changes to Protocol and Informed Consent Document

Any change to the protocol or informed consent document must be reviewed and approved by the Coordinating Center before being submitted to the Institutional Review Board/Independent Ethics Committee at participating institutions. Amendments should not be implemented until all necessary approvals have been obtained, except when necessary to eliminate an immediate hazard to study subjects.

Protocol Deviations

The Coordinating Center is responsible for implementing and maintaining quality assurance and quality control to ensure that studies are conducted according to the protocol, GCP, and all applicable regulatory requirements. A protocol deviation is any noncompliance with the protocol. Noncompliance can be on the part of the study participant, the investigator, or the study site staff. Deviations to the protocol are not permitted except when necessary to eliminate an immediate hazard to study subjects.

Data Verification

Data will be collected via eCRFs and entered into the database per Coordinating Center guidelines. The Coordinating Center will check data accuracy by performing source data verification. Source data verification is a direct comparison of the entries made on the CRFs against the appropriate source documentation. This will be conducted remotely, with the possibility of on-site verification periodically. Discrepancies in the data will be brought to the attention of the investigator and/or the investigator's staff. Any necessary corrections will be made directly to the eCRFs or via queries by the investigator and/or the investigator's staff.

Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The required documents include but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.), IRB membership rosters, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

The requirements for data management, submissions, and monitoring are outlined below. The participating sites will submit all the research related information inclusive of:

- Source documents (patient registration list, CRF info, toxicity assessments, tumor measurements / responses, etc.) are required to be provided within 30 days of visit or 10 days in advance of a monitoring visit or audit.
- Essential Documents (IRB approval documents, financial disclosure forms, 1572, delegation of authority log, protocol training, etc.) are required to be provided within one week of receiving the updated documents.

Personnel from the VICC Clinical Trials Office will monitor the trial and may periodically visit the investigative site to assure proper conduct of the trial and proper collection of the data. The investigators at other sites will allow the monitor to review all source documents used in the preparation of the case reports.

Study Closure

The Coordinating Center reserves the right to discontinue a site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

Records Retention

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by each Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at such time that the records may be destroyed.

Appendix 8: Enrollment Procedures

The Vanderbilt-Ingram Cancer Center (VICC) Coordinating Center will coordinate enrollment in the study.

Prior to registration, a copy of the IRB approval at the site will be kept on file at the Vanderbilt-Ingram Cancer Center (VICC) Coordinating Center. Eligible participants will be entered on study centrally at the VICC Coordinating Center. All sites should email the Coordinating Center at Coordinating.Center@vumc.org to verify slot availability prior to enrollment.

All patients MUST be registered with the VICC Coordinating Center prior to the start of study procedures such as tissue acquisition. Registration can only be conducted during the business hours of 8AM – 5PM Central Time, Monday through Friday.

- 1) All sites must email the VICC CTSR Coordinating Center at Coordinating.Center@vumc.org to notify of upcoming registration and ensure slot availability. The following information should be included in this email:
 1. Study number.
 2. Patient initials.
 3. Disease type.
 4. Anticipated consent date.
 5. Anticipated start date.
- 2) If a subject ID number is required prior to patient enrollment (i.e. at screening due to sample collection requirement), the site must submit the following documents with their email notification to the Coordinating Center:
 - Copy of the patient's signed and dated Informed Consent including documentation of the consent process.
 - HIPAA authorization form (if separate from the main consent form).
 - VICC Patient Enrollment Form.

The Coordinating Center will then provide a subject ID number via email.

- 3) Email the following documents to the Eligibility team and the Coordinating Center for eligibility review and patient enrollment (viccctrregistrar@vumc.org and Coordinating.Center@vumc.org):
 - Copy of the patient's signed and dated Informed Consent, including documentation of the consent process.
 - HIPAA authorization form (if separate from the main consent form).
 - VICC Patient Enrollment Form.

- Eligibility supporting documents such as pathology reports, laboratory tests, etc. *or* EMR access. Note: all source documents should be de-identified and screening/subject ID number added prior to sending.
- Tissue Block Registration Form.
- Signed and completed Eligibility Checklist. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criterion listed in the eligibility checklist.**

Note: The Eligibility team requires 3 business days to review all documents and confirm eligibility. Registrations will only be accepted with prior notice and discussion with the Lead Institution. Please email the clinical trials office (CTO) if enrollment is needed sooner at viccctsregistrar@vumc.org.

Upon satisfactory review of eligibility documents submitted, the Eligibility team and the Coordinating Center will approve enrollment and issue a subject ID number if one was not issued at screening. Once registration/enrollment confirmation from the Coordinating Center is received, proceed with protocol procedures.

Please contact the assigned Study Contact with any questions regarding this process. You can also reach out to your assigned CRA once the study is activated.

The VICC Coordinating Center will assign Subject ID numbers to all patients whose eligibility has been confirmed. Only patients deemed eligible will be registered to the study. Sequence/study ID numbers will not be re-used if a patient screen fails. Following registration, eligible participants should begin the study consistent with the protocol no later than 28 days after registration/enrollment by the VICC Coordinating Center. If a participant does not begin the study following registration within the allowed time period, the participant's registration on the study will be canceled. The Study Contact will be notified of cancellations as soon as possible. Patients being re-screened will need to consent to repeated procedures. As such, the Eligibility team and the Coordinating Center will require a new, signed Informed Consent document.

Issues that would cause treatment delays should be discussed with the sponsor-investigator.

As is generally accepted, standard of care procedures performed prior to consent, but within the protocol defined screening window for each assessment, can be used for study purposes. All research-only procedures must be performed after patient consent.