

A Phase1/2a Study of Rigosertib Plus Nivolumab in Stage IV Lung Adenocarcinoma Patients
With KRAS Mutation Who Progressed on First-Line Treatment

Rajwanth Veluswamy, MD

NCT04263090

Document Date: 3/16/2023



**A Phase1/2a Study of Rigosertib plus Nivolumab in Stage IV Lung Adenocarcinoma
Patients with KRAS Mutation who Progressed on First-Line Treatment**

Protocol #: CA209-74P (BMS)

Principal Investigator: Rajwanth Veluswamy MD MSCR
Tisch Cancer Institute
Icahn School of Medicine at Mount Sinai

One Gustave L Levy Place
Box 1079
New York, NY 10029
212-824-8580
rajwanth.veluswamy@mssm.edu

Co-Investigator(s): Jorge Gomez, MD
Cardinale Smith, MD
Thomas Marron, MD
Fred Hirsch, MD, PhD
Sheena Bhalla, MD

Biostatistician: John Mandeli PhD
One Gustave L. Levy Place
Box 1057
New York, NY 10029
John.mandeli@mssm.edu

Study Drug: Rigosertib (Onconova) + Nivolumab (Bristol-Myers Squibb)

IND Number: 145457

IND Holder Name: Veluswamy

Funding Source: Bristol-Myers Squibb

Initial version:

Version 1.0	April 6, 2019
Version 2.0	May 10, 2019
Version 3.0	May 14, 2019
Version 4.0	June 2, 2019
Version 5.0	July 7, 2019
Version 6.0	September 3, 2019
Version 7.0	September 24, 2019
Version 8.0	October 12, 2020
Version 9.0	December 7, 2022

BDW Approval Date: May 14, 2019
DFG Approval Date: May 16, 2019
RAE Approval Date: May 22, 2019





Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: Rajwanth Veluswamy MD MSCR.

PI Signature: _____

Date: _____





Summary of Changes

Version 7.0 : Administrative Changes in Title page.

Version 8.0:

- Updated time range for treatment , biopsy, imaging
- Clarification regarding non-mandatory biopsies pre and post treatment
- Clarification regarding iRECIST criteria
- Addition of dose modification schema
- Addition of dosing diary

Version 9.0:

- Replacement of patients who did not complete evaluation period due to reasons other than dose limiting toxicities or clinical deterioration determined by investigator to be secondary to disease.
- Requirement of pre- and on-treatment mandatory tissue biopsies
- Clarified ORR (primary endpoint of phase 2A) will be primarily assessed by RECIST criteria; iRECIST criteria will also be reported



Table of Contents

LIST OF ABBREVIATIONS	6
1.0 STUDY SYNOPSIS.....	8
2.0 BACKGROUND AND RATIONALE	12
2.1 Disease Background	12
2.2 Rationale for Combination	13
2.3 Study Agent(s) Background and Associated Known Toxicities.....	14
3.0 STUDY OBJECTIVES.....	22
3.1 Primary Objective	22
3.2 Secondary Objectives	22
3.3 Exploratory Scientific Objectives	22
4.0 STUDY ENDPOINTS.....	23
4.1 Primary Endpoints.....	23
4.2 Secondary Endpoints.....	23
4.3 Exploratory endpoints.....	23
5.0 PATIENT ELIGIBILITY.....	23
5.1 Inclusion criteria	24
5.2 Exclusion Criteria	26
6.0 TREATMENT PLAN.....	27
6.1 Treatment Dosage and Administration.....	27
6.2 Dose Modification (Escalation/Titration/Other)	28
6.3 Definition of DLT and MTD	28
6.4 Timing of Dose Administration	29
6.5 Dose Modification/Delays.....	30
6.6 Duration of therapy	31
6.7 Patient Withdrawal/Discontinuation Criteria	31
6.8 Patient Replacement.....	32
6.9 Clinical Criteria for Early Trial Termination	32
6.10 Accountability Procedures	32
6.11 Concomitant Medications/Vaccinations (allowed & prohibited)	33
7.0 STUDY PROCEDURES	34
7.1 Screening/Baseline Procedures	34



7.2 Procedures During Treatment	36
7.3 Follow-up Procedures	37
7.4 Study Calendar.....	37
7.5 Removal of Subjects from Study.....	38
8.0 MEASUREMENT OF EFFECT	38
8.1 Measurement of Antitumor Effect	38
8.2 Baseline evaluations	38
8.3 Tumor Response	38
8.4 Other response Criteria	39
9.0 ADVERSE EVENTS	39
9.1 Definition of Serious Adverse Events.....	39
9.2 Definition of Adverse Events	40
9.3 Definition of non-serious adverse event.....	41
9.4 Laboratory Test abnormalities	41
9.5 Potential Drug Induced Liver Injury	41
9.6 Pregnancy	42
9.7 Overdose	42
9.8 Other Safety Considerations	42
9.9 Adverse Event Monitoring.....	42
9.10 Steps to Determine If an Adverse Event Requires Expedited Reporting.....	44
9.11 Reporting Requirements for Adverse Events.....	45
9.12 Stopping Rules.....	46
10.0 CORRELATIVES/SPECIAL STUDIES	47
10.1 Assays	48
10.2 Sample Collection Guidelines.....	49
10.3 Clinical Metadata Banking	50
11.0 STATISTICAL CONSIDERATIONS	50
11.1 Analysis of Primary Endpoints.....	50
11.2 Analysis of Secondary Endpoints	50
11.3 Analysis of Exploratory Endpoints.....	51
11.4 Sample Size and Accrual	51
12.0 STUDY MANAGEMENT.....	52





12.1	Conflict of Interest	52
12.2	Institutional Review Board (IRB) Approval and Consent	52
12.3	Registration Procedures.....	52
12.4	Data Management and Monitoring/Auditing.....	53
12.5	Adherence to the Protocol.....	53
12.6	Amendments to the Protocol.....	54
12.7	Record Retention.....	54
12.8	Obligations of Investigators	54
13.0	APPENDIX	55
13.1	Nivolumab Adverse Event Management Algorithms	55
13.2	Rigosertib Adverse Event Management Algorithms	58





LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
ALC	Absolute Lymphocyte Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATD	Accelerated Titration Design
BID	Twice Daily
CI	Confidence Interval
CR	Complete Response
CRF	Case report form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CyTOF	Time-of-flight mass cytometry
DILI	Drug Induced Liver Injury
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
GFR	Glomerular filtration rate
H&P	History & Physical Exam
HAART	Highly active antiretroviral therapy
HIMC	Human Immune Monitoring Core
HR	Hazard Ratio
IB	Investigators Brochure
INR	International Normalized Ratio
IND	Investigational New Drug
IRB	Institutional Review Board
ISMMS	Icahn School of Medicine at Mount Sinai
iUPD	Unconfirmed Progressive Disease
MDS	Myelodysplastic Syndrome
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate
OS	Overall Survival
OTC	Over the counter
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD-1	Programmed Cell Death-1
PDL-1	Programmed Cell Death Ligand-1
PPK	Population Pharmacokinetics



Rigosertib+Nivolumab for KRAS+ NSCLC in Second Line

PI: Rajwanth Veluswamy MD, MSCR

Icahn School of Medicine at Mount Sinai

Version 9 Date: December 7, 2022



**Mount
Sinai**

The Tisch Cancer Institute

PR	Partial Response
QD	Once daily
Q2W	Every Two Weeks
SAE	Serious Adverse Effect
TCI	Tisch Cancer Institute
TEAE	Treatment Emergent Adverse Effect
TMB	Tumor mutational burden
WBC	White Blood Cells
WES	Whole exome Sequencing
WTS	Whole Transcriptome Sequencing





1.0 STUDY SYNOPSIS

Title	Rigosertib plus Nivolumab in Stage IV Lung Adenocarcinoma Patients with KRAS Mutation who Progressed on First-Line Treatment
Short Title	Rigosertib plus Nivolumab for KRAS+ NSCLC in Second or Third Line
Protocol Number	CA209-74P
Investigator and Study Center	Rajwanth Veluswamy MD MSCR Mount Sinai Hospital, One Gustave L. Levy Place, New York, NY 10029 Tel: 212-824-8500, Fax: 646-824-8580
Funding and Drug Source	Bristol-Myers Squibb 430 E. 29 th Street, 14 th Floor New York, NY 10016 Onconova Therapeutics, Inc. Newtown, PA
Background	The largest molecular subset (approximately 25%) of lung adenocarcinomas has a KRAS mutation as the predominant genetic driver. These tumors carry an overall worst prognosis than KRAS wild type tumors. The genomic heterogeneity and complex signalling networks associated with KRAS mutations make treatment of these tumors very challenging. Anti-PD1 checkpoint inhibitors have emerged as a promising therapeutic option of lung cancer. However, most lung cancer patients will either not respond or eventually develop resistance to checkpoint inhibitors. Recent data suggests KRAS expression may also cause immunomodulatory effects in the tumor microenvironment that can subvert the anti-tumor immune response. Therefore, inhibiting downstream KRAS signaling pathways may increase or reinvigorate response to immunotherapy. Rigosertib is a small molecule inhibitor of the RAS-binding domains of multiple downstream RAS effector pathways and has been shown to effectively disrupt RAS-RAF-MEK, PI3K, and Ral-GDS signaling. The combination of Rigosertib with Nivolumab may be an effective treatment for metastatic KRAS+ lung adenocarcinomas, based on both agents having 1) efficacy in lung cancer through different, but potentially synergistic mechanisms and 2) side effect profiles that do not overlap.
Objectives	<u>Primary Objective for Phase I:</u> Maximal Tolerated Dose (MTD), Recommended Phase 2 Dose (RP2D) <u>Primary Objective for Phase 2a:</u> Overall Response Rate (ORR). <u>Secondary Objectives:</u> Progression Free Survival (PFS), Overall Survival (OS)





Methodology	<u>Single-arm, dose-escalation + expansion phase</u> This is an open-label, dose-escalating Phase I study followed by a Phase 2a dose-expansion phase to study the combination of Rigosertib and Nivolumab in metastatic KRAS+ lung adenocarcinoma patients who have progressed on standard first line treatment. Study patients will have satisfied the inclusion/exclusion criteria enumerated in this protocol. The Phase I dose escalation plan will start with an accelerated titration design (ATD) using single patient cohorts until grade 2 toxicity is experienced. At that point, the ATD will be terminated and the dose escalation will enter a standard 3+3 design based on dose-limiting toxicities (DLT). Rigosertib escalation will occur with three dose levels (dose D1: 280mg twice daily; dose D2: 560mg qAM, 280mg qPM; dose D3: 560mg twice daily; taken by mouth for 21 consecutive days of the 28 day cycle), based on previous dose escalation studies in other malignancies, while Nivolumab dose will be fixed at the standard dose (240mg every 2 weeks, given intravenously). The MTD and RPTD (Phase 1 primary endpoint) are defined as the highest dose for which at most 1 patient out of 6 experiences a DLT. Starting with the dose D1, a single patient will be entered. If the patient does not experience any Grade 2 or higher toxicity, the next patient will be enrolled in the next dose cohort D2. The trial will proceed as a single patient ATD until either: 1) the third dose cohort D3 is reached or 2) Grade 2 or higher toxicity is experienced in D1 or D2. If D3 is reached without Grade 2 or higher toxicity, then the cohort will be expanded to 6 patients to determine the MTD. If Grade 2 or higher toxicity is experienced in D1 or D2, ATD will be terminated and two additional patients will be entered into that cohort. A 3+3 design will be implemented based on the occurrence of DLTs. If no patient in the expanded 3-patient cohort experiences DLT, the recruitment of 3 more patients at next dose level will commence. If 1 patient experiences a DLT, then the cohort will be expanded by 3 more patients (6 patients total) at the same dose. Then, if no further patients experience DLT, study moves to next dose level. If 2 or more patients experience a DLT in the expanded 3 or 6 patient cohort, the MTD will have been exceeded, and the prior/lower dose cohort will be expanded to assess MTD. For example, if 2 patients experience DLT at D2, then D1 cohort will be expanded to 6 patients to assess MTD. Once the MTD is determined, an additional planned 12 patients will be enrolled in the expansion phase to further study toxicity and to determine preliminary efficacy endpoints including ORR (phase 2a primary endpoint), PFS, and OS (secondary endpoints) of the combination.
Study Duration	3 years





Number of Subjects	The total number of subjects depends on the safety profile of the combination. If there are no Grade 2 toxicities in the accelerated dose cohorts, the number of patients in Phase I would be 8 patients. The maximum number of patients in Phase I would be $3(6) = 18$ patients. Together with the 12 patients in the expansion phase, the total number of patients would be 20-30.
Statistical Considerations	The ORR will be estimated from the 12 patients in the expansion cohort together with the 6 patients in the Phase I trial treated at the MTD. A total of 18 patients would allow for testing the null hypothesis that the ORR is $\leq 10\%$ (combination not interest) versus an alternative hypothesis that the ORR is $\geq 30\%$ (combination worthy of further study), with power of 0.84 and a type I error rate of 0.10. All translational research are exploratory in nature.
Diagnosis and Main Inclusion Criteria	Patients ≥ 18 years of age with histologically or cytologically confirmed stage IV NSCLC with KRAS mutation, who progressed on standard first line treatment for metastatic disease. Patients must have an ECOG performance score of 0-2, at least one measurable lesion according to RECIST criteria, and have a life expectancy of >3 months. Patients will be considered ineligible if they have a sensitizing EGFR mutation or ALK translocation, are receiving systemic glucocorticoids (except for treatment of adrenal or pituitary insufficiency) or other immunosuppressive treatments, have untreated brain metastases, have active autoimmune disease or interstitial lung disease, or received steroids for prior pneumonitis.
Study Product	Rigosertib will be supplied by Onconova Therapeutics, Inc. and will be administered twice daily by mouth for a continuous 21 day cycle. The dose will be increased following the study plan if toxicities are manageable. Nivolumab will be supplied by Bristol-Myers Squibb and will be administered at the fixed, standard dose of 240mg every 2 weeks via intravenous infusion.
Duration of administration	Treatment will be administered until occurrence of either unacceptable toxicity, disease progression based on Response Evaluation Criteria in Solid Tumors 1.1, intercurrent illness that prevents further treatment administration, withdrawal of consent, or general or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the Investigator. Patients with a response or stable disease can continue treatment for 6 months on study protocol; if patients continue to respond at the end of protocol, they can remain on treatment per investigator discretion.





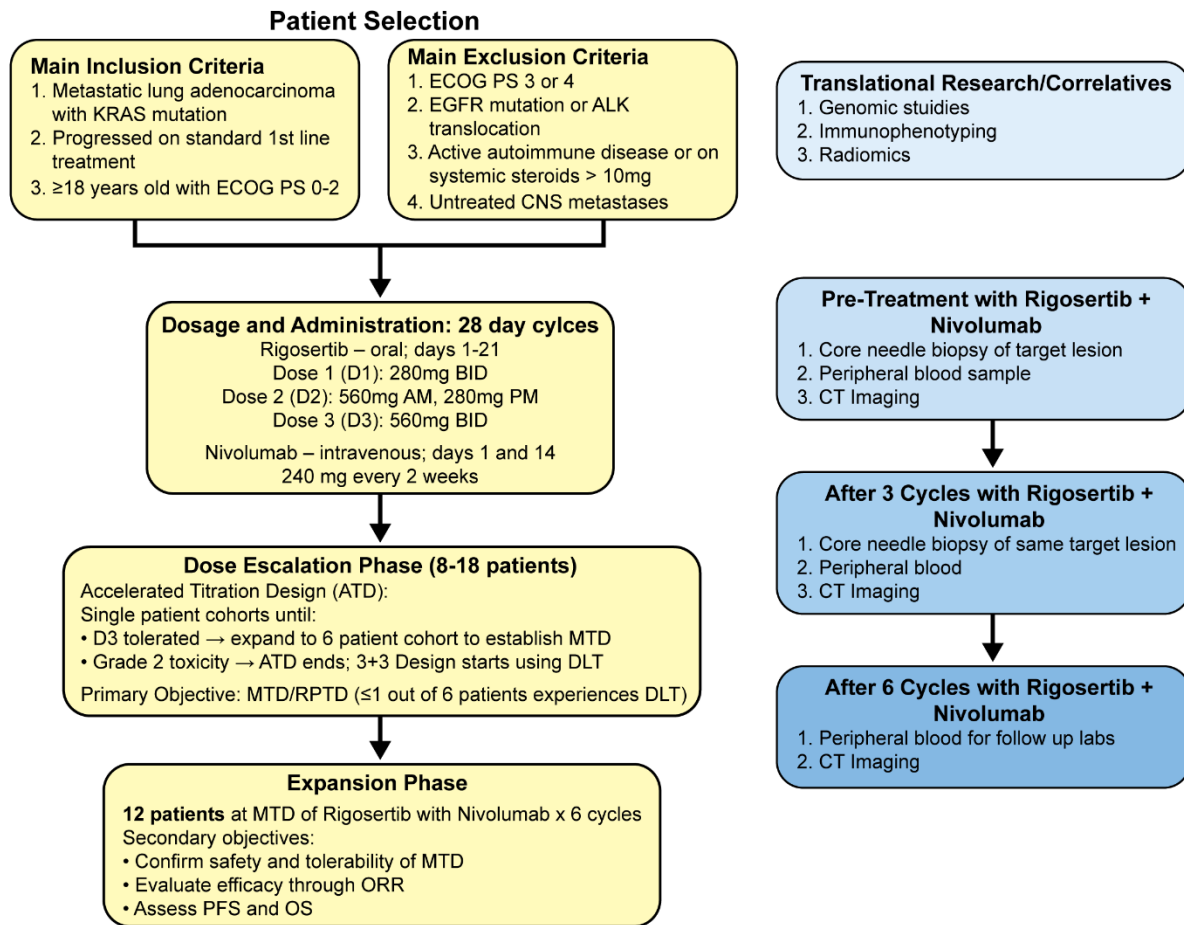
Criteria for Evaluation	Safety: Includes history, physical examination, vital signs, weight, ECOG performance status, laboratory data (CBC, Chemistry), urinalysis, adverse event assessment, and concurrent medications assessment. Efficacy: Efficacy will be evaluated according to iRECIST criteria. Image assessment will be performed at 12 weeks +/- 4 weeks or more frequently if clinically indicated.
-------------------------	---





STUDY SCHEMA

Rigosertib plus Nivolumab in Stage IV Lung Adenocarcinoma Patients with KRAS Mutation who Progressed on First-Line Treatment



PS: Performance status; CNS: EGFR: Epidermal Growth Factor Receptor; ALK: Anaplastic Lymphoma Kinase; IV: Central Nervous System; MTD = maximally tolerated dose; RPTD: Recommended Phase Two Dose; DLT = dose limiting toxicity, ORR = overall response rate, PFR = progression free survival, OS = overall survival





2.0 BACKGROUND AND RATIONALE

2.1 Disease Background

KRAS+ Lung Adenocarcinoma

Lung cancer has the second highest incidence among all cancers and is the leading cause of cancer-related mortality in the United States (US).(1) Over half of non-small cell lung cancers (NSCLCs) are classified as lung adenocarcinomas; of these, the largest molecular subset (approximately 25%) has a KRAS mutation as the predominant genetic driver. These mutations are mutually exclusive from other known driver mutations (i.e., EGFR, ALK, ROS1).(2) Aberrant KRAS expression leads to constitutive co-activation of multiple oncogenic signalling pathways, including RAF-MEK-ERK, PI3K-AKT-mTOR, RAL pathways, which promote cell proliferation.(3) Different KRAS mutations (i.e., G12C, G12V) and co-occurrence of other mutations (i.e., TP53, STK11) may result in preferential expression in different downstream pathways, leading to significant clinical variability amongst these tumors. The genomic heterogeneity and complex signalling networks associated with KRAS mutations make treatment of these tumors very challenging. A large meta-analysis evaluating the prognosis of NSCLCs according to molecular subtypes demonstrated KRAS mutated cancers were associated with 35% higher risk of death than other NSCLCs.(4) Furthermore, KRAS mutated NSCLCs are known to be associated with decreased response to standard platinum-based chemotherapy, so there has been considerable interest in finding novel treatments for these tumors.

Despite discovering the KRAS mutation over 30 years ago, little progress has been made in KRAS specific treatments. Attempts to directly target KRAS have thus far been unsuccessful due to lack of a suitable drug-binding pocket.(5) Competitive inhibition of GTP binding, required for activation of KRAS proteins, proved unfeasible due to the high affinity of GTP to KRAS. Strategies to inhibit RAS processing by inhibiting one of several enzymatic steps (i.e., farnesyl-transferase inhibitors) required for KRAS trafficking and membrane association have been disappointing.(3) Several failed studies likely are reflective of alternative mechanisms of resistance such as RAS amplification or other bypass mechanisms in RAS processing. More recent efforts in treating KRAS mutated NSCLCs have focused on targeting downstream kinases. A phase II clinical trial tested the combination of MEK inhibition using Selumetinib with Docetaxel (standard second line chemotherapy) demonstrated combination therapy was associated with 82% response and improved OS (9.4 months vs 5.2 months), hazard ratio [HR] 0.80, 80% confidence interval [CI]: 0.56-1.14) and PFS (5.3 months vs 2.1 months; HR: 0.58, 80% CI: 0.42-0.79) compared to docetaxel alone.(6) However, these promising results were not seen in the phase III trial (HR: 1.05, 95% CI: 0.85-1.30 and HR: 0.93, 95% CI: 0.77-1.12 for overall and median survival, respectively) – likely the result of greater heterogeneity in KRAS mutations captured with the larger study cohort.(7) Furthermore, MEK inhibition may have resulted in alternative expression of another pathway. It is widely believed that several RAS targets will need to be inhibited to effectively treat KRAS mutated NSCLCs.

Immune Checkpoint Inhibitors for Treatment of KRAS+ NSCLC





Recently, anti-PD1/PDL1 checkpoint inhibitors have emerged as a promising therapeutic option for NSCLCs. Immune recognition and elimination of malignant cells plays a pivotal role in cancer control.(8) Central to this process is the immune system's ability to be stimulated or turned off by checkpoint interactions. Immune activation leads to increased expression of Programmed Cell Death-1 (PD-1), an inhibitory receptor found on the surface of T-lymphocytes, and upregulation of Programmed Cell Death Ligand-1 or 2 (PD-L1 or PD-L2; the immune-inhibitory ligands of PD-1) on immune regulatory cells such as dendritic cells [DCs] and macrophages.(9, 10) Under physiologic conditions, the PD-1/PD-L1 interaction serves to prevent collateral tissue damage by restraining T-effector function during periods of prolonged immune activation. Immunogenic tumors like lung cancer escape immune surveillance via upregulation of PD-L1.(11-13) Recently, therapeutic monoclonal antibodies blocking PD-1 or PD-L1 have been developed to reinvigorate the anti-tumor immune response. In NSCLC, several randomized controlled trials (RCTs) have demonstrated improved efficacy and tolerability with PD-1 and PD-L1 inhibitors compared to standard chemotherapy, leading to FDA approval in multiple treatment settings.(14, 15)

Immunotherapy may be particularly effective in NSCLCs that harbor KRAS mutations.(16) Post-hoc analysis of the CheckMate 057 trial demonstrated patients with KRAS mutations were more likely to benefit from nivolumab than those with wild type KRAS.(17) KRAS mutated NSCLCs are commonly associated with smoking and often overlap with other mutations in tumor suppressor genes (i.e., TP53, STK11), both established risk factors for genomic instability and high tumor mutational burden (TMB). In an integrated analysis of genomic and clinical data from lung adenocarcinoma database, both KRAS and TP53 mutations were associated with increased mutation burden, thought likely secondary to alteration in genes involved in cell-cycle regulation, DNA replication and damage repair.(18) Furthermore, patients that harbored these mutations (especially those with co-occurring TP53/KRAS mutations), showed remarkable response to checkpoint inhibitors. High TMB may be a proxy for neoantigen exposure and several analyses have demonstrated cancers with high TMB respond better to immunotherapy across several tumor types.(19) However, despite this promising data, a significant fraction of all NSCLCs, including KRAS+ tumors, still do not respond to checkpoint inhibitors.(20) In fact, in NSCLC patients who are the most likely to respond to anti-PD1 checkpoint inhibitors according to the PD-L1 biomarker (PD-L1 expression $\geq 50\%$), less than half of patients demonstrate objective response. Furthermore, patients who do experience response will eventually acquire resistance to immune checkpoint inhibitors. Therefore, there is increasing interest in utilizing combination therapy to enhance or reinvigorate the anti-tumor response of immune checkpoint inhibitors.

2.2 Rationale for Combination

There is now increasing evidence that aberrant KRAS expression may drive specific immune-related pathways that modulate the anti-tumor immune response to promote tumorigenesis. 1) Oncogenic RAS signaling may independently upregulate PD-L1 expression through inhibition of tristetrapoline (TTP), which functions to destabilize PD-L1 mRNA.(21) In vivo, restoration of TTP function improved anti-tumor immunity. 2) Aberrant KRAS expression results in transcriptional induction of a plethora of immunoregulatory cytokines and chemokines (i.e., IL-10, TGF-B, GM-CSF, CXCL8), which may play an important role in subverting immunotherapy's antitumor response by inhibiting immune effector cells and increasing levels of immunosuppressive cells within





the tumor microenvironment (TME).(22) 3) KRAS mutations have also been shown to be strongly correlated with downregulation of HLA Class I on surgically resected NSCLCs.(23) Therefore, the inhibition of oncogenic KRAS signaling may be a promising strategy for combination with immunotherapy in metastatic KRAS+ NSCLCs.

Preclinical studies have demonstrated rigosertib's ability to disrupt multiple RAS-mediated pathways, including the RAF-MEK, Ral-GDS, PLK, and PI3K signaling, leading to direct inhibition of tumor growth through mitotic arrest.(24) In vivo efficacy studies using A549 xenograft models of lung cancers have shown that treatment with rigosertib resulted in dramatically decreased RAS signaling and tumor growth compared to placebo. Additionally, inhibition of aberrant KRAS signaling by rigosertib may also affect the immunogenicity of tumors. Flow cytometry analysis of surface PDL1 expression in human lung cell lines demonstrated upregulation of PDL1 upon exposure to rigosertib, even in PDL1 negative cell lines (i.e., A549), providing a potential target for anti-PD1/PDL1 checkpoint inhibitors. Finally, unpublished data from PDX mouse tumor models demonstrate that rigosertib has tumoricidal effects in lung cancer as both monotherapy and synergistically with anti-PD1 checkpoint inhibitor (HX-008).

Rigosertib is currently being tested in phase III clinical trials for treatment of myelodysplastic syndrome (MDS) and has been shown to be well tolerated.(25) The most common adverse effects (AEs) include fatigue and urinary symptoms – the latter was attenuated by adjusting the timing of dosing. The toxicity profile of rigosertib does not appear to overlap with that of immune checkpoint inhibitors.

The combination of rigosertib with an anti-PD1/PDL1 checkpoint inhibitor may be an effective treatment for metastatic KRAS+ lung adenocarcinomas, based on both agents having 1) efficacy in lung cancer through different, but potentially synergistic mechanisms and 2) side effect profiles that do not overlap.

2.3 Study Agent(s) Background and Associated Known Toxicities

Rigosertib

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. (Onconova hereafter). The compound is available in both intravenous (IV) and oral formulations and is evaluated as monotherapy or in combination with other anti-cancer agents.

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 rigosertib may inhibit multiple Ras-driven signaling pathways. 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. In addition, rigosertib was reported to destabilize cell microtubules and to inhibit Polo-like kinase 1 (PLK1) by interfering with its protein interaction domain, the Polo-Box Domain (PBD).

Also, rigosertib was 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. Screening safety pharmacology assays did not reveal any adverse effects of rigosertib. In cardiovascular safety studies, the human-eter-a-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 (QD) for 28 days at high doses of rigosertib.

Pharmacokinetics (PK): The PK evaluation of the oral rigosertib formulation in clinical studies showed an average of 35% oral bioavailability under fasting conditions. A strong negative food effect was observed, resulting in a significant decrease of oral absorption after a high-fat meal. Oral rigosertib must be administered in fasting conditions (defined as at least 2 hours after a meal), and patients must wait 1 hour before the next meal.

PK studies in rats and dogs after IV administration indicated that plasma concentrations were higher than the rigosertib concentrations necessary for anti-tumor activities predicted in cell culture models. Following IV administration, rigosertib was rapidly distributed and eliminated, with terminal half-lives ($t_{1/2,z}$) ranging from 2.7 to 5.8 hour in dogs and from 0.75 to 1.77 hour in rats. The maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) values increased with dose. Clearance (CL) values tended to decrease with higher doses. There was no significant accumulation with QD administration.

Excluding contents of the gastrointestinal (GI) tract and excreta, the highest concentrations of radioactivity were associated with the liver, uveal tract, and kidneys. Tissues with the lowest concentrations of radioactivity included the brain and spinal cord. In rat and dog absorption, distribution, metabolism, and elimination (ADME) studies, IV-administered rigosertib was minimally metabolized and eliminated primarily as unchanged drug in feces with minor excretion in urine.

Rigosertib exhibited extensive binding to plasma proteins in in vitro ultrafiltration and equilibrium dialysis binding experiments (> 98% in rat, dog, and human plasma, and 86% in mouse plasma).

Pharmacokinetic Interactions: Rigosertib was found to be a substrate, but not an inhibitor, of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Rigosertib was shown to be an inhibitor, but not a substrate, of organic anion transporter (OAT) 3, organic anion transporter polypeptide (OATP) 1B1, and OATP1B3 at clinically





relevant concentrations.

In induction and inhibition assays of cytochrome P450 (CYP) enzymes, rigosertib was found to inhibit CYP2C9 in vitro at clinically relevant concentrations. Rigosertib was also found to be a time-dependent inhibitor of CYP2C8, with an IC_{50} of 25.5 μ M (with pre-incubation in the presence of nicotinamide adenine dinucleotide phosphate), which is at clinically relevant concentration. Rigosertib has the potential for drug-drug interaction (DDI) with CYP2C9 but not with CYP2C8. Rigosertib did not significantly inhibit the following enzymes in human liver microsomes: CYP1A2, CYP2B6, CYP2C19, CYP2D6, and CYP3A4 or uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes in vitro.

Toxicology: Toxicology studies of oral rigosertib were conducted in rats and dogs. Based on the repeat-dose toxicity studies, the rat was determined to be the more sensitive species. In a repeat-dose 28-day study in rats, in-life observations considered related to the test article included stained hair coat and hunched posture at doses $\geq$ 75 mg/kg twice daily (BID). No effects on body weight, food consumption, hematology parameters, or ophthalmology were found at any dose. The only effect on serum chemistry parameters was an increase in ALKP in rats receiving 100 mg/kg BID and 75 mg/kg BID. At doses $\geq$ 25 mg/kg BID, test article-associated histomorphologic changes consisted of spermatozoal degeneration in the epididymis in the male rats and lesions in the non-glandular stomach submucosa in the female rats. In female rats receiving doses of 100 and 75 mg/kg BID, lesions were also noted in the epicardium and pulmonary pleura. There were no test article-associated findings in male and female rats receiving 10 mg/kg BID. Based on these results, the severely toxic dose for 10% of animals (STD10) was estimated to be 75 mg/kg BID in rats.

Rigosertib is not genotoxic based on the composite results of Good Laboratory Practice (GLP)-compliant in vitro and in vivo studies.

Rigosertib administered to pregnant rats (at doses equivalent to human doses of 240 mg/m² and higher) resulted in fetotoxicity and teratogenicity, as evidenced by lower fetal weights and an increased incidence of malformed fetuses (primarily craniofacial malformations). No maternal toxicity was observed.

Rigosertib is also known to cause hyponatremia that has required hospitalization. While the cause is unknown, the hyponatremia is reported to resolve upon supportive management and holding rigosertib.

Clinical Efficacy and Safety: As of 18-May-2018, a total of 1199 patients with MDS and other hematologic malignancies (N = 738) or advanced cancer and solid tumors (N = 461) were treated with IV or oral rigosertib in 27 Phase 1 to 3 clinical studies conducted by Onconova. In addition, 6 healthy volunteers were enrolled in a mass balance study of IV rigosertib. Eight other Phase 1 studies of rigosertib in a total of 57 patients with MDS and other hematologic malignancies have been completed or are being conducted by other Sponsors (National Heart Lung and Blood Institute [NHLBI] and SymBio Pharmaceuticals) under different Investigational New Drug (IND) applications.

Studies of Rigosertib in MDS and Other Hematologic Malignancies Conducted by Onconova: In studies in MDS and other hematologic malignancies conducted by Onconova, 474 patients were treated with IV rigosertib as monotherapy, 168 patients were treated with oral rigosertib as monotherapy, and 96 patients were treated with oral





rigosertib in combination with AZA. The majority of patients enrolled in these studies had MDS: IV studies included mostly intermediate- to high-risk patients based on the International Prognostic Scoring System (IPSS), while patients in oral studies were mostly low-risk per IPSS. Patients with acute myeloid leukemia (AML) and chronic myelomonocytic leukemia (CMML) were also studied.

In the rigosertib-treated population (N = 738), patients were primarily male (66%), 65 years of age or older (83%), and White (78%); age and gender were consistent with an MDS patient population. In patients treated with rigosertib or comparator, the main reason for discontinuation from the studies was disease progression. The occurrence of AEs, irrespective of causality, led to withdrawal of 18% of patients in the IV studies, 20% of patients in the oral studies as monotherapy, and 11% of patients in the oral study as combination therapy.

Six patients died of treatment-emergent adverse events (TEAEs) considered possibly related to rigosertib infusion (renal failure (2), sepsis or septic shock (2), cardiac failure (1), other (1). Overall, the rigosertib safety profile has been acceptable in patients with advanced MDS and other hematologic malignancies.

In studies of oral rigosertib as monotherapy for the treatment of MDS and other hematologic malignancies:

- Drug-related TEAEs were $\geq$ Grade 3 in severity in 21% of patients. The most frequently reported $\geq$ Grade 3 drug-related TEAEs ($\geq 2\%$) by PT were neutropenia (7%); thrombocytopenia and cystitis (3% each); and leukopenia, dysuria, and hematuria (2% each).
- Among the 8% of patients with SAEs that were considered drug related, the events were mostly urinary related. The most frequent drug-related event was cystitis (3%).

In the oral rigosertib study in combination with AZA, administered IV or SC for the treatment of MDS and other hematologic malignancies:

- A total of 77% of patients experienced TEAEs that were considered drug related. Drug-related TEAEs were $\geq$ Grade 3 in severity in 36% of the patients. The most frequently reported $\geq$ Grade 3 drug-related TEAEs (≥ 2 of patients) were neutropenia (13%); thrombocytopenia (8%); hematuria (6%); anemia and dysuria (5% each); leukopenia (3%); and diarrhea and hyponatremia (2% each).
- Six patients (6%) experienced SAEs that were considered drug related. The most frequent drug-related SAE was hematuria (3%).

Studies of Rigosertib in Advanced Cancer and Solid Tumors Conducted by Onconova:

In studies in advanced cancer and solid tumors conducted by Onconova, 131 patients were treated with IV rigosertib as monotherapy, 190 patients were treated IV rigosertib in combination with other chemotherapeutic agents (gemcitabine [GEM], oxaliplatin, and irinotecan), 138 patients were treated with oral rigosertib as monotherapy, and 2 patients were treated with oral rigosertib as combination therapy.

The majority of patients enrolled in these studies had either pancreatic cancer (11% in IV studies as monotherapy, 76% in IV studies in combination therapy, and 4% in oral studies as monotherapy), ovarian cancer (31% in IV studies as monotherapy, 6% in IV studies in combination therapy, and 7% in oral studies), or cancer of the large intestine





(14% in IV studies as monotherapy, 4% of patients in IV studies in combination therapy, and 5% in oral studies as monotherapy. Overall, the patient population was 51% male and 63% of patients were between 18 and 64 years of age.

The main reason for discontinuation was disease progression based on RECIST or on symptomatic deterioration. AEs irrespective of causality led to withdrawal of 6% of patients in the IV studies as monotherapy, 24% in the IV studies in combination with other chemotherapeutic agents, 5% in oral studies as monotherapy, and 50% (1 patient) in the oral study as combination therapy. Ten of the 461 patients treated in Phase 1-3 studies conducted by Onconova died of TEAEs considered to be drug related. Overall, the rigosertib safety profile has been acceptable in patients with advanced cancer and solid tumors.

For patients treated with rigosertib in the oral studies as monotherapy (N = 138) for the treatment of advanced cancer and solid tumors:

- Drug-related TEAEs were $\geq$ Grade 3 in severity in 14% of patients. The most frequently reported $\geq$ Grade 3 drug-related TEAEs ($\geq 2\%$) were hematuria (4%); dysuria (3%); and nausea and fatigue (2% each).
- Three patients (2%) experienced 4 SAEs that were considered drug related: nausea, vomiting, ureteric obstruction, and deep vein thrombosis.

For patients treated with rigosertib in the oral study as combination therapy (N = 2) for the treatment of advanced cancer and solid tumors:

- Both patients had drug-related TEAEs. PTs occurring in both patients were mucosal inflammation, dysgeusia, fatigue, and erythema. Both patients experienced TEAEs $\geq$ Grade 3 in severity, one of which was considered drug related (dysphagia). There were no drug-related SAEs, no dose-limiting toxicities (DLTs), and no deaths due to TEAE.

Formulation: Rigosertib is supplied as soft gelatin capsules in 2 strengths:

- 70 mg capsule strength, which contains 1 mL of a 70 mg/mL solution of API in PEG 400. The 70 mg capsules are clear, transparent, and oblong.
- 280 mg capsule strength, which contains 1 mL of a 280 mg/mL suspension of rigosertib in PEG 400 and PEG 4000. The 280 mg capsules are of an opaque yellow-orange color.

Storage and Handling: Oral soft gelatin capsules of rigosertib should be stored under refrigeration (2C to 8C) and protected from light.

Safety Precautions: There are no data available specifically addressing first-aid procedures for IV or oral rigosertib at this time. Pharmacist, nurses, physicians, and other personnel who handle the drug products of rigosertib should follow acceptable procedures for the safe handling and disposal of anti-neoplastic drugs according to their institutional policies or published guidelines (National Institutes of Health Publication 83-2621, Occupational Safety and Health Administration Publication 8-1.1). In case of accidental contact with rigosertib liquid for infusion, the following measures should be taken by the patient or handler of the drug product (per the Material Safety Data Sheet):

General Guidance: Seek immediate medical attention and follow up with the Investigator as necessary.

In case of accidental overdose of the IV or oral formulation, if swallowed and the victim is





conscious, immediately give 2 glasses of water and induce vomiting. Seek immediate medical attention and follow up with the Investigator as necessary. No information on overdosage of oral rigosertib capsules currently exists, but forced emesis should be considered.

Nivolumab

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.(26) Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

OPDIVO (nivolumab) is approved for the treatment of several types of cancer in multiple regions including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014). Nivolumab is also being investigated in various other types of cancer as monotherapy or in combination with other therapies.

Pharmacokinetics: The PK of nivolumab was studied in subjects with cancer over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction from baseline values of approximately 25% resulting in a geometric mean (% coefficient of variation [CV%]) steady state clearance (CL_{ss}) of 8.2 mL/h (53.9%) in subjects with metastatic tumors. The decrease in CL_{ss} is not considered clinically relevant. The geometric mean (CV%) volume of distribution at steady state (V_{ss}) is 6.8 L (27.3%), and elimination half-life (t_{1/2}) is 25 days (77.5%). Steady-state concentrations of nivolumab were reached by approximately 12 weeks when administered at 3 mg/kg every 2 weeks (Q2W), and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered Q2W. Additionally, nivolumab has a low potential for drug-drug interactions. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1 expression, solid tumor type baseline tumor size, and hepatic impairment.

Although ECOG status, baseline glomerular filtration rate (GFR), albumin, and body weight (35 to 160 kg) had an effect on nivolumab CL, the effect was not clinically meaningful. PPK analysis suggested that nivolumab CL in subjects with cHL was approximately 32% lower relative to subjects with NSCLC; however, the lower CL in cHL subjects was not considered to be clinically relevant as nivolumab exposure was not a significant predictor of safety risks for these patients. PPK analysis also suggested that nivolumab CL in subjects with gastric cancer was approximately 33% higher relative to subjects with NSCLC; however, the higher CL in subjects with gastric cancer was not considered to be clinically meaningful as nivolumab treatment was beneficial in these





subjects. Subsequently, nivolumab CL in adjuvant melanoma subjects was 40% lower than baseline CL and approximately 20% lower than steady-state CL relative to subjects with advanced melanoma. These changes in CL are not considered to be clinically relevant given the observed safety and efficacy in these subjects. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab increased by 29%, whereas there was no effect on the clearance of ipilimumab.

PPK and exposure response analyses have been performed to support use of nivolumab 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W dosing regimens in subjects with cancer in addition to the 3 mg/kg Q2W regimen. A flat dose of nivolumab 240 mg Q2W was selected since it is equivalent to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in subjects treated with nivolumab in clinical trials, while the nivolumab 360 mg Q3W and 480 mg Q4W regimens allow flexibility of dosing with less frequent visits and in combination with other agents using alternative dosing schedules to Q2W. Using a PPK model, the overall distributions of nivolumab exposures (C_{max}, C_{avg}, and C_{min} after the first dose or at steady-state) are comparable between 3 mg/kg Q2W or 240 mg Q2W dosing regimens. Following nivolumab 360 mg Q3W and 480 mg Q4W, C_{avgss} are predicted to be similar to those following nivolumab 3 mg/kg Q2W or 240 mg Q2W, while C_{minss} are predicted to be approximately 6% and 16% lower, respectively, and are not considered to be clinically relevant. Following nivolumab 360 mg Q3W and 480 mg Q4W, C_{maxss} are predicted to be approximately ~3% and 43% higher, respectively, relative to that following nivolumab 3 mg/kg Q2W dosing. However, the range of nivolumab exposures following 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W dosing regimens across body weights (35 to 160 kg) are predicted to be maintained well below corresponding exposures observed with the safe and well-tolerated 10 mg/kg nivolumab Q2W dosing regimen.

Pharmacokinetic Interactions: Although monoclonal antibodies are not direct inhibitors/inducers of metabolizing enzymes, recent literature reports suggest that therapeutic proteins that are modulators of cytokines may indirectly affect expression of CYP enzymes.(27) The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes, at single and multiple doses of 0.3 to 10 mg/kg Q3W from CA209009 in subjects with RCC. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab (0.3, 2 and 10 mg/kg) during the course of treatment. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction. Nivolumab is an IgG4 monoclonal antibody, which is eliminated by mechanisms similar to that of other antibodies, namely by non-specific catabolism (mainly by enzymes in the reticuloendothelial system).(28) These enzymes are not known to be inhibited or induced by drugs, and therefore it is unlikely that other drugs will have an impact on the PK of nivolumab.

Toxicology: respiratory, and neurologic function conducted in cynomolgus monkeys as part of the repeat-dose toxicity studies for up to 3 months with nivolumab. In addition, the potential cardiovascular effect of nivolumab, when administered as a single IV dose, was examined in conscious cynomolgus monkeys. The single IV bolus administration of nivolumab at doses of 10 mg/kg or 50 mg/kg was well tolerated. There were no effects on clinical signs, body weights, body temperatures, mean arterial blood pressures, electrocardiograms, or cardiovascular parameters during the study.





Clinical Efficacy and Safety: Nivolumab has demonstrated durable responses exceeding 6 months as monotherapy and in combination with ipilimumab in several tumor types, including NSCLC, melanoma, RCC, cHL, SCLC, gastric cancer, SCCHN, urothelial cancer, HCC, and CRC. In confirmatory trials, nivolumab as monotherapy demonstrated a statistically significant improvement in OS as compared with the current standard of care in subjects with advanced or metastatic NSCLC, unresectable or metastatic melanoma, advanced RCC, or SCCHN. Nivolumab in combination with ipilimumab improved PFS and ORR over ipilimumab alone in subjects with unresectable or metastatic melanoma.

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 17,700 subjects treated to date. In general, for monotherapy, the safety profile is similar across tumor types. The only exception is pulmonary inflammation AEs, which may be numerically greater in subjects with NSCLC, possibly because in some cases, it can be difficult to distinguish between nivolumab-related and unrelated causes of pulmonary symptoms and radiographic changes. The most frequently reported treatment-related AE is fatigue, which is almost always of low grade. Most related AEs are thought to be due to the effects of inflammatory cells on specific tissues/organs including: pulmonary, GI, hepatic, skin, endocrine, hypersensitivity/ infusion reaction, and renal AEs.

In general, the approach to suspected nivolumab-related AEs is similar across any involved organ system. Subjects should have a thorough diagnostic work-up to evaluate potential drug- and non-drug-related diagnoses. For suspected nivolumab-related AEs, based on the severity of the event, management with immunosuppressants may be necessary. In general, dose delays and observation are adequate for low-grade AEs. For moderate- and high-grade AEs, immunosuppression with corticosteroids should be utilized (See Table 3). Once the AE has begun to improve, corticosteroids can be tapered over approximately 3 weeks to 6 weeks (depending on the severity of the AE). The management of AEs considered related to any combination treatment is similar to the management of AEs caused by either agent alone and utilizes the same safety management algorithms.

There is no available information concerning overdose with nivolumab. Depending on the symptoms and/or signs leading to the suspicion of overdose, supportive medical management should be provided. There is no specific antidote.

Formulation: Nivolumab Injection and Placebo for Nivolumab Injection

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micronpore size, low-protein binding (polyethersulfone membrane) in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection. When the dose is based on patient weight (i.e., mg/kg), nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (e.g., 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Instructions for dilution and infusion of nivolumab injection may be provided in the clinical protocol, pharmacy binder,





pharmacy manual, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Storage and Handling: Nivolumab Injection Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours. Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container. The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (up to 25°C, 77°F) and room light. The maximum of 8 hours under room temperature and room light conditions includes the product administration period.

3.0 STUDY OBJECTIVES

3.1 Primary Objective

The primary objective of the Phase 1 dose escalation phase is to ascertain the MTD and RPTD for the combination of Rigosertib and Nivolumab on patients with KRAS mutated NSCLCs who have progressed on first line treatment. Rigosertib escalation will occur with three dose levels (dose D1: 280mg twice daily; dose D2: 560mg qAM, 280mg qPM; dose D3: 560mg twice daily), based on previous dose escalation studies in other malignancies, while Nivolumab dose will be fixed at the standard dose (240mg every 2 weeks).

The primary objective of the Phase 2a expansion phase is to estimate overall response rate (ORR) through radiographic assessment after 3 cycles of treatment on study drug.

3.2 Secondary Objectives

The clinical secondary objectives of this trial include:

- To further assess safety and tolerability in the expansion cohort.
- To assess PFS
- To assess OS

3.3 Exploratory Scientific Objectives

- To analyze molecular mechanisms of immunotherapy response and resistance in KRAS mutated NSCLCs receiving rigosertib/nivolumab combination using comprehensive whole exome and transcriptome sequencing of pre- and post-treatment tumor samples
- To determine if rigosertib/nivolumab combination can mobilize the effector immune response against KRAS+ NSCLCs and how it impacts the tumor immune microenvironment via multiplexed ion beam imaging (MIBI) analysis and Time-of-flight mass cytometry (CyTOF)
- To extract quantitative image features from restaging computer tomography (CT) to identify radiographic evidence of immune cell infiltration following treatment with rigosertib/nivolumab





4.0 STUDY ENDPOINTS

4.1 Primary Endpoints

The primary endpoint of the Phase 1 dose escalation phase is safety and tolerability, as defined by the percent of individuals who experience adverse events (according to NCI CTCAE v5.0) during the treatment period. The maximal tolerated dose will be used as the RP2D.

The primary endpoint of the Phase 2a expansion phase is to estimate the overall response rate (ORR), defined as the proportion of patients receiving the combination of Rigosertib and Nivolumab at the MTD/RP2D that experience radiographic response as per RECIST criteria (29). This includes the 6 patients in the Phase 1 dose escalation phase that received the combination at the MTD/RP2D.

4.2 Secondary Endpoints

The clinical secondary endpoints for the Phase 2a part of this trial include:

- 1) To further study occurrence of DLTs in the expansion cohort.
- 2) PFS: defined as the time, in days, between treatment initiation and when the patient is found to have recurrent and/or metastatic disease on imaging, or death for any reason.
- 3) OS: defined as the time, in days, between treatment initiation and when the patient dies from any cause regardless of etiology.

4.3 Exploratory endpoints

The goals of our translational studies are exploratory in nature and we cannot predict the data that will be revealed. Exploratory endpoints of this trial include molecular, immune and radiomic signatures associated with response to rigosertib/nivolumab.

5.0 PATIENT ELIGIBILITY

Diagnosis/Condition for Entry into the Trial

Subjects with Stage IV metastatic lung adenocarcinoma whose tumors harbor KRAS mutations and have progressed on standard first line treatment with anti-PD1 checkpoint inhibitor monotherapy, anti-PD1 checkpoint inhibitor in combination with platinum doublet chemotherapy, or other approved combination will be enrolled in this trial. Subjects must meet all of the inclusion and exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered.

5.1 Inclusion criteria

- 1) Be willing and able to provide written informed consent for the trial.
- 2) Be at least 18 years of age on the day of signing informed consent.
- 3) Have a histologically or cytologically confirmed diagnosis of Stage IV metastatic lung adenocarcinoma (AJCC version 8) with mutation analysis by next generation sequencing (NGS) confirming KRAS mutation either





at time of diagnosis or at progression on first line treatment.

- 4) Have progressed on or intolerant of standard of care first-line treatment with anti-PD1 checkpoint inhibitor monotherapy or anti-PD1 checkpoint inhibitor in combination with platinum doublet chemotherapy or other approved combination for Stage IV metastatic lung adenocarcinoma. The last cycle of first-line treatment must occur at least 28 days prior to administration of trial drugs (i.e., washout period)
- 5) Have measurable disease per RECIST criteria as assessed by the local site investigator/radiology. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesion.
- 6) Have a life expectancy of at least 3 months.
- 7) Have an ECOG Performance Status of 0-2.
- 8) Have adequate organ function as indicated by the following laboratory values in Table 1. Specimens must be collected within 14 days prior to the start of trial.
- 9) Patient must be willing and able to provide blood samples (12 green tops tubes, roughly 100mL) at the time points indicated in the Study Calendar.
- 10) Patient is willing and able to have core needle biopsies (Goal 4-8 biopsies, final number to be determined by the surgeon and radiologist performing the procedure as safe) of tumor prior to initiation of study drug, and at time points indicated in the StudyCalendar.
- 11) Women of child-bearing potential and men must agree to use adequate contraception prior to study entry, for the duration of study participation, and following completion of therapy for 5 months if female and 7 months if male. Female subjects of child-bearing potential must have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study drug. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. A female of child-bearing potential is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria: Has not undergone a hysterectomy or bilateral oophorectomy; or has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

Table 1: Inclusion Criteria: laboratory values

System	Laboratory Value
Hematologic⁺	
Absolute neutrophil count (ANC)	≥1,000 /mcL





Platelets	≥75,000 /mcL
Hemoglobin	≥9 g/dL
Renal*	
Serum creatinine <u>OR</u> Measured or calculated ^a creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) <u>OR</u> ≥60 mL/min for patient with creatinine levels > 1.5 X institutional ULN
Hepatic*	
Serum total bilirubin	≤ 1.5 X ULN <u>OR</u> Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 ULN
AST and ALT	≤ 2.5 X ULN <u>OR</u>
Albumin	≥2.5 mg/dL
Coagulation*	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless patient is receiving anticoagulant therapy as long as PTT is within therapeutic range of intended use of anticoagulants
^a Creatinine clearance should be calculated per institutional standard.	
* Patients must not receive blood products <1 week prior to enrollment to meet criteria. * If laboratory criteria are not met due to what the investigator determines to be a biologic cause (e.g. Gilbert's syndrome causing elevated bilirubin or excessive muscle mass affecting creatinine) or drug-related cause (e.g. elevating in transaminases due to HAART therapy, elevated INR due to anticoagulation) then the lab values will not be used to exclude patient from this trial. This determination will be made by PI.	

5.2 Exclusion Criteria

- 1) Patients may not be receiving any other investigational agents. If received as part of first line treatment, last administration of previous investigational agent must





- be greater than 4 weeks prior to administration of study drug combination.
- 2) Patients must not be pregnant or nursing due to the potential for congenital abnormalities or harm to nursing infants.
 - 3) Tumor harbors an EGFR-sensitizing (activating) mutation or an ALK translocation. All other co-mutations will be allowed.
 - 4) Has known untreated symptomatic CNS metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are without evidence of progression for at least 4 weeks by repeat radiological imaging, clinically stable, and without requirement of steroid treatment for at least 14 days prior to first dose of study drug. Patients with small asymptomatic CNS metastases who do not require immediate local ablative treatment will not be excluded.
 - 5) Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Patients on chronic steroids (more than 4 weeks at stable dose) equivalent to $\leq 10\text{mg}$ prednisone will *not* be excluded.
 - 6) Has active autoimmune disease that has required systemic treatment in the past 1 year (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is acceptable.
 - 7) Has a known additional malignancy that is progressing and/or required active treatment within the past 3 years. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or *in situ* cervical or anal cancer, prostate cancer on stable dose of hormonal therapy without rising PSA, and breast cancer whom have been treated with curative intent, who maybe on hormonal therapy.
 - 8) Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating Investigator.
 - 9) HIV positive with detectable viral load, or anyone not on stable anti-viral (HAART) regimen, or with <350 CD4⁺ T cells/microliter in the peripheral blood. No HIV testing is required.
 - 10) History of allogeneic hematopoietic cell transplantation or solid organ transplantation.
 - 11) Receipt of a live vaccine within 30 days of planned start of study medication
 - 12) History of interstitial lung disease (e.g., idiopathic pulmonary fibrosis, organizing pneumonia) or active, noninfectious pneumonitis that required immune-suppressive doses of glucocorticoids to assist with management. A history of radiation pneumonitis in the radiation field is permitted.
 - 13) Prisoners or subjects who are involuntarily incarcerated.
 - 14) Subjects who are compulsorily detained for treatment of either psychiatric or physical (e.g. infectious disease) illness.

6.0 TREATMENT PLAN

This is a Phase I/2, open-label, dose-escalating study with dose expansions designed to determine the dose limiting toxicities, the MTD/RPTD and preliminary efficacy of Rigosertib and Nivolumab combination in KRAS mutated NSCLC following progression on first line treatments. After the patient signs the informed consent form and after





confirming that the patient meets all eligibility requirements in section 5.0, the investigators will register the patient and assign a patient number. All trial treatments will be administered on an outpatient basis at the Ruttenberg Treatment Center (Mount Sinai). All study agents will be provided centrally by the Sponsors.

6.1 Treatment Dosage and Administration

The treatments to be used in this trial are outlined below in Table 2

Rigosertib escalation will occur with three dose levels (dose D1: 280mg twice daily; dose D2: 560mg qAM, 280mg qPM; dose D3: 560mg twice daily), based on previous dose escalation studies of Rigosertib in other malignancies, taken daily for 21 consecutive days followed by 7 days off (total cycle duration: 28 days). Nivolumab dose will be fixed at the standard dose (240mg on days 1 and 15 of 28 day cycle) as per the approved product label. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

Rationale for Starting Dose: The starting dose for rigosertib escalation was determined based on prior Phase 1 dose-escalation studies, where rigosertib bioavailability and tolerability (and food effect) were established. In the Phase 1 study 09-01, 36 patients with MDS refractory to at least 1 prior standard treatment received oral doses of 70, 140, 280, 560, and 700 mg administered twice daily. The MTD/RPTD was identified as 560mg twice daily. Then, twelve patients in the confirming cohort underwent full PK evaluation at this oral MTD/RPTD. In the phase 1 Symbio Pharmaceuticals Study 2012002, 9 high-risk MDS patients refractory to chemotherapy in Japan received either 280 mg (n=3) or 560 mg (n=6) twice daily and tolerated this dose. Subsequent dose escalation studies of oral rigosertib combinations (e.g., rigosertib + azacitadine in high risk MDS) have shown that the combination of oral rigosertib at doses 560mg qAM/280mg qPM and 560mg BID given with standard dose AZA can be safely administered and appears to be well tolerated in repetitive cycles.(29)

Table 2: Treatment dosage and administration

REGIMEN DESCRIPTION				
Agent	Dosage level(s)	Route of Administration	Schedule	Cycle
Rigosertib	Dose D1: 280mg twice daily Dose D2: 560mg qAM, 280mg qPM Dose D3: 560mg twice daily	By Mouth	Days 1-21	28 days
Nivolumab	240mg	IV infusion	Days 1 and 15	28 days

6.2 Dose Modification (Escalation/Titration/Other)

The Phase I dose escalation plan will start with an ATD followed by a standard 3+3 design





to determine the MTD/RPTD. The MTD and RPTD (primary endpoint) are defined as the highest dose for which at most 1 patient out of 6 experiences a DLT. Patients will be enrolled sequentially in 3 rigosertib dose-escalating cohorts. A Cohort Review meeting will be conducted after the last patient in any cohort completes the 28-day cycle.

Accelerated Titration Design Phase

- Starting with the dose D1, a single patient will be entered. If the patient does not experience any Grade 2 or higher toxicity in the 28-day evaluation window from the start (day 1) of D1, the next patient will be enrolled in the next dose cohort D2.
- The trial will proceed as a single patient ATD until either:
 - 1) The third dose cohort D3 is reached. If D3 is tolerated, then the cohort will be expanded to 6 patients so the MTD can be established.
 - 2) Grade 2 or higher toxicity is experienced in the 28-day evaluation window of D1 or D2. If Grade 2 or higher toxicity is experienced in D1 or D2, the ATD will be terminated and two additional patients will be entered into that cohort. A 3+3 design will be implemented based on the occurrence of DLTs.
- There will be no inpatient dose escalation. Patients will stay in dose cohort throughout the trial period.

3+3 Design Phase

- If no patient in the expanded 3-patient cohort experiences a DLT in the 28-day evaluation window of the dose, the recruitment of 3 more patients at the next dose level will commence.
- If 1 patient experiences a DLT in the 28-day evaluation window of the dose, then the cohort will be expanded by 3 more patients (6 patients total) at the same dose. Then, if no further patients experience DLT, study moves to next dose level.
- If 2 or more patients experience a DLT in the expanded 3 or 6 patient cohorts within the 28 day evaluation window of the dose, the MTD will have been exceeded, and no further dose escalation will occur. The prior/lower dose cohort will be expanded to 6 patients to assess MTD. For example, if 2 patients experience DLT at D2, then D1 cohort will be expanded to 6 patients to assess MTD.

Expansion Phase

- Once the MTD is determined, an additional planned 12 patients will be enrolled in the expansion phase to further study toxicity and to determine preliminary efficacy endpoints including ORR, PFS, and OS (secondary endpoints) of the combination.

6.3 Definition of DLT

DLT will be defined from toxicities observed from the beginning of treatment through the 28 day-evaluation period. Subjects who experience a DLT will be discontinued from treatment.

The occurrence of any of the following toxicities during the DLT window, if assessed by the Investigator to be related, probably related, or possibly related to rigosertib/nivolumab will be considered a DLT:

- Grade 4 non-hematologic toxicity (not laboratory)
- Grade 4 hematologic toxicity
- Grade 3 thrombocytopenia with clinically significant bleeding
- Grade 3 neutropenia lasting ≥ 7 days
- Grade ≥ 3 increase in AST, ALT, or total bilirubin





- Grade ≥ 3 renal failure or nephritis
- Any non-hematologic AE $\geq$ Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤ 5 days; Grade 3 nausea, vomiting, or diarrhea lasting ≤ 72 hours despite supportive care. Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.
- Grade 4 non-hematologic laboratory
- Grade 3 non-hematological laboratory will be considered DLT if:
 - the abnormality leads to hospitalization, or
 - the abnormality persists for > 72 hours despite appropriate interventions
- Febrile neutropenia Grade 3 or Grade 4
- Any elevated AST or ALT $> 3 \times$ ULN and concurrent total bilirubin $> 2 \times$ ULN without initial findings of cholestasis (elevated ALP, e.g., findings consistent with Hy's law or FDA definition of potential drug-induced liver injury [p-DILI]). Note that this specific category of DLT uses ULN rather than CTCAE grade for definition.
- Any $\geq$ Grade 2 immune-mediated uveitis
- Grade 5 toxicity

While rules for adjudicating DLTs are specified here, DLTs, AEs, and irAEs may be defined after consultation with sponsor and principal investigator based on emerging data from the use of rigosertib or checkpoint blockade therapy. irAEs are defined as AEs of inflammatory immune nature in the absence of a clear alternative etiology such as infection.

Subjects who experience a DLT after 28 day-evaluation period (i.e., late toxicity) will be discontinued from treatment. Late toxicities will be reported and upon consultation with sponsor and principal investigator, may result in dose adjustment of RP2D.

Patients that experience DLT requiring discontinuation from the study will enter the monitoring phase of the study with regular scheduled imaging and symptom assessment as per standard of care practice (SOP), and their symptoms and disease course will be recorded.

6.4 Timing of Dose Administration

Study components will be administered as laid out in Study Calendar (Section 8.4).

Rigosertib should be dosed twice a day for 21 consecutive days, followed by 7 days off treatment (each cycle duration: 28 days). If single dose is missed, subject will be instructed not to take the missed dose and to continue to take the next dose at the scheduled time. Decreased oral absorption of rigosertib was observed after a high-fat meal. Therefore, patients must fast for 2 hours before taking oral rigosertib and must wait 1 hour after taking the drug before eating. Nivolumab should be dosed once every 2 weeks (twice per 28-day cycle). Every attempt should be made to perform all assessments and administer all treatments as per the calendar below but may be adjusted by the treating physician based on what is determined to be in the best interest of the patient. Each treatment day and follow up may occur ± 3 days from the originally scheduled day if required.

All treatments will be administered on an outpatient basis. Oral rigosertib pills will be supplied to the patient at the beginning of each cycle. The Pharmacy Manual contains specific instructions for the preparation of the nivolumab infusion fluid and administration of infusion solution.





6.5 Dose Modification/Delays

Any patient who receives treatment on this protocol will be evaluable for toxicity. Toxicity will be assessed according to the NCI CTCAE v5.0.

AEs (both non-serious and serious) associated with rigosertib and nivolumab exposure may represent individual toxicities associated with each drug or synergistic toxicities due to the combination. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Study drugs must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Appendix 13.1 and 13.2 for further guidelines further AE management, including dose adjustments.

Table 3: Holding Parameters for Adverse Effects

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Patient
Diarrhea/Colitis	2	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue	Permanently discontinue
Endocrinopathy	Symptomatic with abnormal lab/pituitary scan	Toxicity resolves with or without hormone replacement	Resume study drugs therapy when patients are clinically and metabolically stable
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Patient
			or less of prednisone or equivalent per day within 12 weeks.





	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue	Permanently discontinue
Hematuria/ Dysuria	4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity	2 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	3-4	Permanently discontinue	Permanently discontinue
Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event. Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within of the last dose.			

6.6 Duration of therapy

All patients may continue therapy for at least six cycles unless rapid disease progression or drug intolerance from unacceptable AEs. Patients with dose delays will be allowed to continue treatment unless due to unacceptable toxicities (i.e., DLTs). Patients with an objective clinical response or stable disease can continue treatment for up to 2 years. Further continuation will be determined by the clinical judgment of the Investigator.

6.7 Patient Withdrawal/Discontinuation Criteria

Patients may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the Investigator should any untoward effect occur. In addition, a patient may be withdrawn by the Investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A patient must be discontinued from the trial for any of the following reasons:

Progressive disease

- The patient or legal representative (such as a parent or legal guardian) withdraws consent
- Unacceptable AEs as described in Section 9
- Patients who experience DLTs
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the patient





- The patient has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The patient is lost to follow-up
- Administrative reasons

If a patient is dropped from the study prematurely, the Investigator will clearly document the reason in the medical record and complete the appropriate case report form (CRF) page describing the reason for discontinuation. After the end of study treatment, each patient will be followed for 30 days for AE monitoring. Patients will have post-treatment follow-up (with routine SOC surveillance) for 5 years or until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each patient will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs earlier.

6.8 Patient Replacement

Patients enrolled and withdrawn from study any time prior to first dose of rigosertib/nivolumab will not be considered evaluable for assessment and will be replaced with another patient.

All patients who discontinued rigosertib and nivolumab prior to first assessment imaging scans, for reasons other than 1) dose limiting toxicities or 2) clinical deterioration determined to be from disease progression by the investigator, will not be considered evaluable for efficacy assessments and will be replaced with another patient.

6.9 Clinical Criteria for Early Trial Termination

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

- Quality or quantity of data recording is inaccurate or incomplete
- Poor adherence to protocol and regulatory requirements
- Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to patients
- Plans to modify or discontinue the development of the study drug

In the event of a decision by either Bristol-Myers Squibb or Onconova to no longer supply study drug, ample notification will be provided so that appropriate adjustments to patient treatment can be made.

6.10 Accountability Procedures

Drug accountability records will be maintained for all clinical supplies. All empty and partially used study containers and clinical trial supplies will be destroyed locally according to the institution's standard operating procedures for drug destruction. The pharmacy will maintain detailed documentation of the number and identification of drug containers that are destroyed, and copies of documents will be provided to the Sponsor.

6.11 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 may be required. The Investigator should discuss any questions regarding this with the Study PI and Sponsor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the patient's primary physician.

Acceptable Concomitant Medications and Therapies

All treatments that the Investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All standard pre-medications given with chemotherapy (for NSCLC cohorts) are permitted including steroids. All concomitant medication will be recorded on the CRF including all prescription, over-the-counter (OTC), herbal supplements, and intravenous 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 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded.

Localized, limited radiotherapy of short duration (eg, 5 days) for palliative purposes may be permitted but only after discussion with and approval by the sponsor's medical monitor.

Prohibited Concomitant Medications

Patients 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
- RT therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than those used to modulate symptoms from an AE of suspected immunologic etiology, or used as pre-medication for the chemotherapy used in NSCLC cohorts. The use of physiologic doses of corticosteroids may be approved after consultation with the PI, and patients on long-term steroids equivalent to 10mg or less of prednisone daily may be enrolled.

Patients who, in the assessment by the Investigator, require the use of any of the aforementioned prohibited treatments for clinical management should be removed from the trial. Patients may receive other medications that the Investigator deems to be medically necessary.

7.0 STUDY PROCEDURES

7.1 Screening/Baseline Procedures





Assessments performed exclusively to determine eligibility for this study will be done only after obtaining informed consent. Assessments performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

All screening procedures must be performed within 28 days prior to registration unless otherwise stated. The screening procedures include:

1) Informed Consent

Before a patient undergoes screening, a medically qualified member of the Study Team who has been specifically trained in the implementation of this Protocol during the Site Initiation Visit or thereafter, such as the Site Principal Investigator, any of the co-Investigators, or a Clinical Research Nurse must obtain documented consent from each potential patient prior to participating in a clinical trial.

Consent must be documented by the patient's dated signature or by the patient'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 patient before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the patient must receive the IRB/ERC's approval/favorable opinion in advance of use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

2) 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 5 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the patient has enrolled in this study will be recorded separately and not listed as medical history.

3) Review subject eligibility criteria

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

4) Review previous and concomitant medications

The Investigator or qualified designee will review all prior cancer treatments including systemic treatments, RT and surgeries, as well as all current medications, meaning medications received within the 28 days prior to enrollment.

5) Physical exam including vital signs, height and weight Vital signs and a full physical exam will be





documented.

6) ECOG Performance Scale

The Investigator or qualified designee will assess ECOG status.

7) Adverse event assessment

Baseline adverse events will be assessed. See section 9.9-9.11 for Adverse Event monitoring and reporting.

8) Laboratory Procedures/Assessments

Pregnancy Test: A serum or urine pregnancy testing is required within 24 hours of starting study drug in women who have menstruated within the preceding 48 months.

Laboratory testing at screening: CBC w/differential, CMP, magnesium, TSH (with reflex Free T4), PT/PTT.

Laboratory testing prior to each 28 day cycle: Within 72 hours prior to treatment, labs must be drawn which include CBC w/differential, CMP, magnesium, TSH (with reflex Free T4), urinalysis and cortisol.

Details regarding timing of specific laboratory procedures/assessments to be performed in this trial are provided in the Study Calendar footnotes (Section 7.4) and as specified in Table 4 below).

9) Imaging

Patients will have baseline CT chest/abdomen/pelvis or PET/CT imaging to confirm progression and identify measurable lesions according to RECIST criteria. MRI brain should also be done to exclude untreated symptomatic CNS metastases and/or carcinomatous meningitis (imaging obtained prior to screening may be used as long as it was obtained within 60 days of screening).

Table 4 Laboratory Tests (Hematology/chemistry/urinalysis/other)

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Urine pregnancy test †	Serum β -human chorionic gonadotropin(β -hCG)†
Hemoglobin	Alkaline phosphatase	Urinalysis	PT (INR)
Platelet count	Alanine aminotransferase (ALT)		aPTT
WBC (total and differential)	Aspartate aminotransferase (AST)		Reflex free thyroxine (T4)
Hematology	Chemistry	Urinalysis	Other
Red Blood Cell Count	Carbon Dioxide (CO ₂ or bicarbonate)‡		Thyroid stimulating hormone (TSH)





Absolute Neutrophil Count	Calcium		Correlative studies (blood)
Absolute Lymphocyte Count	Chloride		Random cortisol
	Glucose		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin (<i>If total bilirubin is above upper limit normal</i>)		
	Total protein		
	Blood Urea Nitrogen		
	Creatinine clearance		

† For women of childbearing potential, specifically anyone who has menstruated within the 48 months before enrollment. If urine pregnancy not confirmed negative, serum pregnancy test required. ‡ If considered standard of care in your region.

Laboratory tests for screening should be performed within 28 days prior to the first dose of treatment; CBC, CMP, magnesium, TFTs, urinalysis and random cortisol should be checked at the start of each cycle. At ISMMS the CMP laboratory panel includes all components listed above in “chemistry” other than Direct Bilirubin and Magnesium.

Results must be reviewed by the Investigator or qualified designee and found to be acceptable prior to each dose of trial treatment (with the exception of TFTs and cortisol which will often take longer and are to be checked regularly for trends suggestive of endocrinopathies).

7.2 Procedures During Treatment

1) Biopsy

Patients will undergo core needle biopsy during the screening period and after 6 weeks of treatment. The target collection is 4-8 samples, final number to be determined as safe by the interventional radiologist or pulmonologist performing the procedure. This tissue will be evaluated by pathology to confirm presence of malignant cells, and remaining tissue will be transported to the Human Immune Monitoring Core (HIMC).

Archival tissue (ie FFPE or fresh frozen tissue) before first line treatment will also be collected to understand dynamic changes with different treatments.

2) Peripheral blood

Laboratory testing during screening and prior to each treatment cycle will be done as outlined in section 7.1. Patients will also have peripheral blood (12 green top tubes, roughly 100mL), which will be processed by the HIMC, to be used for CyTOF analysis;

PBMCs and Serum will be cryopreserved for future investigations. Blood will be drawn 1) before the 1st cycle of rigosertib/nivolumab (this may be done during screening or on





D1), then after 3 and 6 months of treatment. A specialized tube meant for preservation of ctDNA will also be drawn during screening and prior to each treatment cycle.

7.3 Follow-up Procedures

1) Standard follow up

Patients will have their first standard follow-up imaging (CT or PET/CT) performed after 12 weeks (+/- 4 weeks) of treatment, then every 12 weeks (+/- 4 weeks) thereafter until PD regardless of discontinuation of study treatment or initiation of subsequent anti-cancer therapy.

7.4 Study Calendar

D1 represents the first day of rigosertib and nivolumab. Patient continues rigosertib day 1-21. Nivolumab is given day 1 and day 15.

Table 5: Study Calendar

	Screening	Cycle 1 and higher		Follow Up		
	≤28 days prior to enrollment	Day 1 (+/- 3 days)	Day 15 (+/- 3 days)	6 weeks (+/- 1 week)	12 weeks (+/- 4 weeks)	24 weeks (+/- 4 weeks)
Informed Consent	X					
Medical history	X					
Physical exam	X	X	X		X	X
ECOG determination	X	X	X		X	X
Toxicity Evaluations	X	X	X		X	X
Imaging ¹	X				X	X
Standard Labs ²	X	X			X	
Screening Labs ³	X					
Biopsy ⁴	X			X		
Research Blood ⁵	X				X	X
ctDNA Tube ⁶	X	X				
Sequencing of Tumor ⁷	X				X	
Study Drug Administration ⁸		Rigosertib: Day 1-21 Nivolumab: Day 1 and Day 15				

¹ Standard surveillance imaging to be performed starting after 12 weeks (+/- 4 weeks) of therapy, and then at regular intervals, as per SOC described within the protocol, or more frequently if clinically indicated

² Standard labs include CBC w/differential, CMP, Magnesium, TSH (with reflex free T4), cortisol and urinalysis

³ Screening labs include the standard labs, as well as pregnancy test (urine or serum), PT/PTT (or PT/aPTT).

⁴ Biopsies to include (target) 4-8 core needle biopsies of tumor, or as determined as safe by surgeon and/or radiologist.

⁵ As described above, 100mL (roughly 12 large green top heparinized tubes) of research blood to be collected at regular intervals pre-treatment, and after 12 and 24 weeks of





treatment

⁶A specialized tube of blood dedicated to preservation of plasma ctDNA will be drawn at screening and prior to each treatment cycle.

⁷A portion of surgically excised tissue will be submitted for genomic analysis

⁸Start of Rigosertib and Nivolumab infusion may occur +/- 3 days if clinically warranted

Dosing Diary

Patients will be provided a dosing diary where the date and time of study drug administration, as well as side effects and missed doses will be recorded. Complete instructions will be provided with the study manual. The diary card will be reviewed at each visit (Appendix 13.3).

7.5 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted);
- Patient withdraws consent (termination of treatment and follow-up);
- Patient is unable to comply with protocol requirements;
- Patient experiences toxicity that makes continuation in the protocol unsafe;
- Treating physician judges that continuation on the study would not be in the patient's best interest;
- Patient becomes pregnant (pregnancy to be reported along same timelines as a serious adverse event);
- Lost to follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.

8.0 MEASUREMENT OF EFFECT

8.1 Measurement of Antitumor Effect

Objective disease response must be measured according to the RECIST criteria (iRECIST criteria will also be reported). A radiological evaluation of malignancy, as judged appropriate by the Investigator, and in line with the protocol, must be performed before starting the study treatment. The same methods that detect lesions at baseline will be used to follow these lesions post treatment. Tumor size on imaging will be measured in millimeters using the longest diameter of tumor masses and lymph nodes for response assessment.

8.2 Baseline evaluations

All patients should have baseline radiological measurements of the extent of disease by CT chest/abdomen/pelvis or PET/CT. All areas of disease present must be mentioned (even if specific lesions are not going to be followed for response) and the measurements of all measurable lesions must be recorded on the scan reports. Any non-measurable lesions must be stated as being present.





Tumor assessment will be repeated after 12 weeks (+/- 4 weeks) of treatment and every 12 weeks (+/- 4 weeks) thereafter or more frequently if clinically indicated. All lesions measured at baseline, must be measured at subsequent disease assessments and recorded on the scan reports. All non-measurable lesions noted at baseline must be reported as present or absent.

8.3 Tumor Response

All patients included in the study must be assessed for response to treatment, even if there is a protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Response definitions that will be used are as follows:

RECIST 1.1:

Complete response (CR): disappearance of all target lesions.

Partial Response (PR): at least a 30% decrease in the sum of the longest diameter of target lesions.

Progressive Disease (PD): at least a 20% increase in the sum of the longest diameter of target lesions or the appearance of one or more new lesions.

Stable Disease (SD): When there is neither sufficient increase nor decrease in size of tumor to qualify as PR or PD, the result is determined to be.

iRECIST:

Unconfirmed Progressive Disease (iUPD): iRECIST defines progression of disease (including presence of new lesions) as iUPD and requires subsequent confirmation with either 1) a further increase in size in the lesion in which progression was first identified in, 2) progression in lesions that had not previously met RECIST-defined progression criteria, or 3) presence of new lesions in subsequent scan (within 4-8 weeks). If on the subsequent scan, progression is not confirmed, and lesions stay the same size, then response is still considered iUPD and must be confirmed on the next scan. If, however, iUPD is followed by tumor shrinkage (compared with baseline) on the subsequent scan (i.e., iCR, iPR, iSD), the bar is reset and any progression thereafter would be considered unconfirmed again.

Patients who demonstrate iUPD per iRECIST can continue on study treatment until confirmatory imaging obtained within 4-8 weeks. This decision should be based on the overall clinical condition of patient. Clinical stability is defined as the following: (1) Absence of symptoms or signs indicating clinically significant progression of disease, (2) No decline in ECOG performance status, (3) No requirements for intensified management, including radiation or other palliative care.

ORR will be defined as the proportion of patients who achieved a CR or PR as their best ORR based on RECIST, using imaging data routinely collected as part of standard care at 12 weeks (+/-4 weeks) after treatment initiation. Using the same criteria, PFS will be determined as the time since treatment initiation to progression using imaging data collected every 12 weeks (+/- 4 weeks) months while on treatment.





8.4 Other response Criteria

- 1) Safety/tolerability: analyses will be performed for all patients having received at least one dose of study drug. The study will use the NCI CTCAE v5.0 for reporting of non-hematologic adverse events (<http://ctep.cancer.gov>) and modified criteria for hematologic adverse events.
- 2) PFS: calculated based on the time from treatment initiation until the time of radiographic evidence of progression.
- 3) OS: defined as the time from treatment initiation until the time of death from any cause.

9.0 ADVERSE EVENTS

9.1 Definition of Serious Adverse Events

A *Serious Adverse Event (SAE)* is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.
- although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.
- any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

The following hospitalizations are not considered SAEs:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health





- status (e.g., routine colonoscopy)
- medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

9.2 Definition of Adverse Events

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following:

- Related: There is a reasonable causal relationship between study drug administration and the AE.
- Not related: There is not a reasonable causal relationship between study drug administration and the AE.
- Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

9.3 Definition of non-serious adverse event

A non-serious AE is an AE not classified as serious.

Non-serious AE Collection and Reporting

- The collection of non-serious AE information should begin at initiation of study drug. All non-serious AEs (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.
- Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

9.4 Laboratory Test abnormalities

All laboratory test results captured as part of the study should be recorded. The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug





discontinued or interrupted

- any laboratory abnormality that required the subject to receive specific corrective therapy.

9.5 Potential Drug Induced Liver Injury

Potential drug induced liver injury is defined as:

- ALT or AST elevation > 3 times upper limit of normal (ULN)
AND
- Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
AND
- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

9.6 Pregnancy

If, following initiation of the trial, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the agents will be permanently discontinued in an appropriate manner.

The investigator must immediately notify Worldwide.Safety@bms.com of this event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures. Protocol-required procedures for study discontinuation and follow-up must be performed on the participant. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the CIOMS, MedWatch, BMS Pregnancy Surveillance Form, or approved site SAE form. A BMS Pregnancy Surveillance Form may be provided upon request.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the Sponsors. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

9.7 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

9.8 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.





9.9 Adverse Event Monitoring

The Investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Study Calendar (as toxicity evaluations), every 14 days while patient is receiving rigosertib and nivolumab. At each of these toxicity evaluation periods, patients will have a history and physical performed every 14 days, and blood analyses (CBC w/differential, CMP, magnesium, TSH [with reflex free T4], cortisol, urinalysis) every 28 days to screen for any potential AEs. Patients will be evaluated during regular standard-of-care surveillance every 3 months while on study drugs. AEs will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE v5.0 (ctep.cancer.gov). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment. All AEs regardless of CTCAE grade must also be evaluated for seriousness as noted in Table 6.

Table 6: Common Terminology Criteria for Adverse Effects (CTCAE)

CTCAE Grading	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 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
Seriousness	A serious AE is any AE occurring during trial that:	
	† Results in death ; or	
	† Is life threatening ; or places the subject, in the view of the Investigator, at immediate risk of death from the event as it occurred (Note: This does not include an AE that, had it occurred in a more severe form, might have caused death.); or	
	† Results in a persistent or significant disability/incapacity (substantial disruption of one's ability to conduct normal life functions); or	
	† Results in or prolongs an existing inpatient hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious AE.); or	
	† Is a congenital anomaly/birth defect (in offspring of subject taking the product regardless of time to diagnosis); or	
	Is a new cancer ; (that is not a condition of the study) or	
	Is an overdose (whether accidental or intentional). Any AE associated with an overdose is considered a serious AE. An overdose that is not associated with an AE is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious AE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	





Duration	Record the start and stop dates of the AE. If less than 1 day, indicate the appropriate length of time and units
Action taken	Did the patient have to come off study due to the AE?
Relationship to investigational agent	Which investigational agent is most likely responsible for AE? The determination of the likelihood that one of the investigational products caused the AE will be provided by an Investigator who is a qualified physician. The Investigator's signed/dated initials 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 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 drug and the AE based upon the available information. The following components are to be used to assess the relationship between the presumed causative agent and the AE; the greater the correlation with the

	components and their respective elements (in number and/or intensity), the more likely the product caused the AE:
Exposure	Is there evidence that the subject was actually exposed to the product 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 the product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials 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
Rechallenge	Was the subject re-exposed to the product 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.
Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the product or drug class pharmacology or toxicology?

9.10 Steps to Determine If an Adverse Event Requires Expedited Reporting

Step 1: Identify the type of adverse event using the NCI CTCAE v5.0.

Step 2: Grade the adverse event using the NCI CTCAE v5.0.

Step 3: Determine whether the adverse event is related to the protocol therapy

Attribution categories are 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.

Unrelated – The AE is clearly NOT related to the study treatment.





Note: This includes all events that occur within 30 days of the last dose of treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

Step 4: Determine the prior experience of the adverse event.

Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

- the current known adverse events listed in the Agent Information Section of this protocol;
- the drug package insert;
- the current Investigator's Brochure

9.11 Reporting Requirements for Adverse Events

1) Expedited Reporting

- The Principal Investigator must be notified within 24 hours of learning of any SAE, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.
- The IRB/PPHS must be notified within 5 business days of "any unanticipated problems involving risk to subjects or others" (UPR/UPIRSO).
- The following events meet the definition of UPR
 - Any new information that indicates a new or increased risk, or safety issue (e.g., interim analysis, safety monitoring report, publication, updated sponsor safety report), that indicates an unexpected change to the risk/benefit ratio for the research.
 - An investigator brochure, package insert, or device labeling is revised to indicate an increase or magnitude of a previously known risk, or describes a new risk.
 - Withdrawal, restriction, or modification of a marketed approval of a drug, device, or biologic used in research protocol
 - Protocol deviation or violation that harmed subjects or others or that indicated subjects or others might be at increased risk of harm.
 - Complaint of subject that indicates subjects or others might be at increased risk of harm or at risk of a new harm
 - Any breach in confidentiality that may involve risk to the subject or others.
 - Any harm experienced by a subject or other individual that in the opinion of the investigator is unexpected and at least probably related to the research procedures.
- Reporting to BMS
 - Following the subject's written consent in the study, all SAEs, whether or not related to the BMS product associated with this study, must be collected, including those thought to be associated with protocol-specified procedures. CIOMS, MedWatch, or site approved form and reported to BMS within 24 hours to comply with regulatory requirements. Either the CIOMS, MedWatch, or approved site SAE form should be completed for any event where doubt exists regarding its status of seriousness.





- All SAEs must be reported by confirmed facsimile (fax) transmission or reported via electronic mail to the below email address and BMS Protocol number must be included in the SAE form or on the cover sheet with the SAE form transmission

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1-609-818-3804

- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.
- All SAEs should be followed to resolution or stabilization.
- SAEs should be reported on MedWatch Form 3500A, which can be accessed at: <http://www.accessdata.fda.gov/scripts/medwatch/>. The website will instruct you where to send the SAE forms.

2) Routine Reporting

- All other adverse events—such as those that are expected, or are unlikely or definitely not related to the study participation—are to be reported annually as part of regular data submission.

9.12 Stopping Rules

We will continuously monitor the dose limiting toxicities in the expansion cohort. Accrual to the expansion cohort will be halted if there is sufficient evidence that the toxicity rate in the first cycle exceeds the target rate of 30% by more than 15%. If the cumulative number of patients experiencing a DLT in the first 28 day cycle, is greater than the associated boundary b_k listed in the table below, among the k patients in the expansion cohort, then accrual will be halted for safety considerations.

# of Patients k	1	2-3	4-6	7-9	10-12
Boundary b_k	-	2	3	4	5

Specifically if more than 2 of the first 3 patients, more than 3 of the first 6 patients, more than 4 of the first 9 patients or more than 5 of the first 12 patients experience DLT, then the expansion cohort will be halted for safety considerations.

The operating characteristics of this stopping rule are as follows:

	30%	True Toxicity Rate 40%	50%
Probability of Early Stopping	0.43	0.68	0.87

Using these boundaries, if the true toxicity is 30%, 40%, or 50%, the probability of stopping the trial early is 0.43, 0.68, and 0.87 respectively. This stopping rule was computed using the `toxbdry` function in R and calculations are based on methods





described in Jennison and Turnbull (2000) and Ivanova, Qaquish and Schell (2005).(30, 31)

An enrollment rule to prevent an excessive number of toxicities as described in Song and Ivanova(33) will be used to inform us of the number of additional patients we can recruit when the current patient has not yet completed cycle 1. Formally, the trial can enroll m new patients such that $r+x+m \leq b_{n+m}$, $r+x+m-1 < b_{n+m-1}$, and $n+m \leq K$ where r is defined as the number of patients that have not completed follow-up and are still being followed for toxicity; x is the number of patients that have experienced toxicity and n is the total number of patients enrolled to date. This enrollment is conservative in that it assumes the worst case scenario, that every patient in the follow-up will experience a dose-limiting toxicity.

Accrual plan for expansion cohort: Initially 3 patients will be enrolled. If none of these patients experience DLT, 5 more patients will be enrolled. The final 4 patients in the expansion cohort will be accrued based on the incidence of DLTs of the previous 8 patients.

10.0 CORRELATIVES/SPECIAL STUDIES

Genomic Analysis:

Genomic analysis will be performed to better understand tumor heterogeneity and subclonal populations within the context of the immune and neoantigen repertoire, KRAS co-mutations and resistance to prior therapies. Prior diagnostic testing and treatment history will be collated into individual patient timelines using the Sema4 Oracle software. Available biopsied tissue specimens will be assessed for tumor cellularity and if possible, 2-3 tumor blocks or tumor foci will be used for whole exome (WES) and whole transcriptome (WTS) sequencing. If archived frozen tumor tissue is available, we will also sequence 2-3 foci of the frozen tissue. This analysis will be performed to better understand tumor heterogeneity and subclonal populations within the context of the immune and neoantigen repertoire, KRAS co-mutations and resistance to prior therapies.

Additionally, cell-free DNA and RNA will be isolated from the three blood samples for liquid biopsy testing and use the buffy coat for germline baselines to confirm somatic variants. All nucleic acid isolation and genomic testing will be performed by the CAP-CLIA certified Sema4 Genomics laboratory in Branford, CT. Data analysis will include but may not be limited to exome level somatic variant annotation, gene fusions, copy number analysis, tumor mutation burden analysis, T-cell clonality, neoantigen prediction and differential gene expression. Particular attention will be paid to KRAS differential gene expression classes defined by STK11 and TP53 co-mutation status, KEAP1 loss, XPO1, and existing immunotherapy biomarkers (e.g., TMB, PD-L1 expression).(8-10)

Immune Studies:

We will map the immune repertoire and quantify changes in the TME within tumors via MIBI analysis of formalin-fixed, paraffin-embedded (FFPE) tissue from core needle biopsies. The goal of these studies is to quantify the dynamic infiltration of effector lymphocytes and immunoregulatory cells at both biopsy sites prior to and after treatment, to understand the change in the immune contexture induced locally within the TME by the rigosertib plus nivolumab combination.





Even with the impressive features of MIBI (spatial, quantitative, >50 markers, single cell resolution, permissive to small FFPE specimens), there are some limitations; for one, markers are selected by prior knowledge, and two, the analysis is made on a portion of tissue (i.e., biopsy sites). We thus propose to complement our imaging studies with high dimensional single cell characterization of dissociated tumor and blood specimens with CyTOF. We will use CyTOF lymphoid and myeloid panels that we have developed to examine multiple subclasses of immune cells and cytokines, which allows us to quantify and characterize peripheral blood and tumor infiltrating lymphocytes taken during the course of treatment to measure the degree that rigosertib plus nivolumab is able to stimulate an effector T cell response.

The immune studies described above will be performed in the Mount Sinai Human Immune Monitoring Core (HIMC), Miriam Merad, Director, Sacha Gnjatic, PhD Associate Director. In 2017, the HIMC was acknowledged as an NCI Cancer Immune Monitoring and Analysis Center (CIMAC) with the receipt of a U24 grant, for the purpose of standardizing immune assays across all NCI-sponsored IO trials. Towards this, the HIMC has demonstrated excellence in sample handling, assay reproducibility, and data management, as well as competence in a large number of assays including those described here.

Radiomics:

CT is the standard approach to determine treatment response in lung cancer patients. These images provide features that can be extracted, quantified, and converted into minable data using computer vision and machine learning techniques.(12) Higher-order statistical features based on densities and spatial relationship of voxels can provide highly granular descriptions of tumors. Using CTs performed prior to and after study drug administration, we will analyze quantitative image features based on tumor intensity, shape, size, volume and texture to improve tumor phenotyping by describing the underlying TME and immune cell infiltrates.

After image acquisition, we will develop a comprehensive *gold standard*, triple- adjudicated lung tumor segmentation data set from our study population, where each tumor segmentation is independently verified by a qualified radiologist. This task can be best and most efficiently generated through semi-automated, expert-driven techniques (i.e., the Bhattacharyya Gradient Flow), followed by adjudication.(13) Once tumors are delineated from surrounding lung environment using segmentation, radiomic features will be generated using previously validated statistics based on: 1) First-order intensity information: Through histogram-based methods, the distribution of values of individual voxels within the CT image are described using basic metrics such as mean, median, range, uniformity, randomness (entropy)/skewness of the image intensities; 2) Shape-based analysis: Includes compactness/convexity, maximum diameter, aspect ratio, sphericity, surface area, and volume (computed as the ratio of nodule volume to its convex hull). Together these features can evaluate intratumoral heterogeneity by quantifying shape variation of the tumor border and demonstrating differences in growth patterns and interactions with surrounding normal tissue; and 3) Intra-nodule heterogeneity information or textural features: Includes autocorrelation, contrast and entropy ratio (which scores heterogeneity of pixel attenuation coefficients across the tumor in terms of the Shannon or information-theoretic entropy).(12, 14, 15) After identification of quantitative image features, we will then use a variety of machine





learning techniques to train a classifier to identify a set of features that identifies immune infiltrates following treatment with the study drugs.

This work will be accomplished in close collaboration with Dr. Anthony Costa, Director of Sinai BioDesign and Sinai Artificial Intelligence (AI) Consortium at Mount Sinai, who has significant experience with radiomic methods and computational image analysis.

10.1 Assays

Whole exome sequencing (WES)/whole transcriptome sequencing (WTS): We will use WES/WTS to identify tumor mutations and copy number variations (CNV),

mutational load, neoantigen identification, tumor clonality, TCR clonality, and HLA heterozygosity. Neoantigen identification will allow for us to develop tetramers in our tetramer core which can be applied to patient samples (blood, biopsy and tumor) to identify and phenotype tumor-reactive T cells.

ctDNA: We will also analyze ctDNA to assess correlation with response and/or progression. Patients will have WES/WTS performed on their tumors which will allow for detection of tumor-specific DNA in plasma that will be collected in specialized tubes to preserve ctDNA, and cryopreserved over the course of treatment.

Multiplex Ion Beam Imager (MIBI): A tissue multiplexed imaging platform which is capable of analyzing more than 50 parameters on one single histological section of FFPE tissue specimens. MIBI can achieve parts-per-billion sensitivity with a dynamic range of 10^5 , and spatial resolution of 50 nm or better, allowing unprecedented measurement of spatial and cellular interactions at the tumor site(32). Using the MIBI technology, hundred tumor lesions including early NSCLC lesions, reveal unique tumor cell interactions with immune and stromal cells environment.

Time-of-flight Mass Cytometry (CyTOF): CyTOF allows the simultaneous analysis of over 50 parameters on peripheral blood or tumor cell suspensions without need for compensations. This novel mass cytometry barcoding strategy allows multiple samples to be pooled together, processed, and analyzed as a single sample, thereby reducing batch effects and dramatically enhancing the robustness and reproducibility. This will be used to phenotype the tumor immune infiltrate.

10.2 Sample Collection Guidelines

As laid out in the calendar and schedule above, patients will provide:

- 1) Peripheral blood samples (12 green top tubes, roughly 100cc)
 - a. During screening (or before first dose of rigosertib and nivolumab)
 - b. At 3 and 6 month response assessment
- 2) Core needle biopsies will be performed (Goal 4-8 core biopsies to be obtained)
 - a. Before the initiation of treatment
 - b. At 3 months post treatment

Core needle or excisional biopsies and surgical specimens will both initially be evaluated by qualified medical personnel in the department of Pathology, and after confirmation of presence of malignant cells, it will be transported directly to the HIMC. All samples as well as the blood that is harvested will be processed by the HIMC.





Human Immune Monitoring Core at ISMMS
Managing Director: Seunghee Kim-Schulze Ph.D.
1470 Madison Avenue, 5th floor, Room 310
New York, NY 10029
212-824-9354

Sample allocation: Assays have been prioritized based on the tissue available; the core needle biopsies will likely be a limiting factor given the limited amount of tissue that can safely be procured through biopsy. The goal is for 4-8 core needle biopsies to be obtained, we anticipate 2 of these will be used by pathology for diagnostic purposes, and the remainder will be made available to use for analyses.

Blood processing: Whole blood will be separated into serum, which will be cryopreserved, and peripheral blood mononuclear cells (PBMCs). PBMCs will be 1) cryopreserved for future analysis, 2) used for fresh analysis by CyTOF, and 3) used for ctDNA analysis.

Core Needle Biopsy processing: A component of the whole tissue will be cryopreserved and/or paraffin embedded, while additional fresh tissue will be dissociated into single cell suspension for MIBI and CyTOF analysis (these analyses can only be performed on fresh tissue). Whole tissue and peripheral blood will also undergo bulk WES/WTs. Remaining blood will be provided to the HIMC which will process and cryopreserve and/or paraffin embed all remaining samples.

10.3 Clinical Metadata Banking

The following information obtained from the subject's medical record will be deidentified and may be provided to research collaborators when specimens are made available, including:

- Diagnosis
- Any pertinent medical history, including concomitant medications, and comorbidities that pre-date enrollment in the trial, or that occur during enrollment in the trial
- Laboratory values from time of tissue and/or blood procurement
- All imaging studies performed from time of initial diagnosis until death, and any needed imaging studies that pre-date enrollment that may serve as a comparator to pre/post treatment imaging studies
- Collection time of samples in relation to study treatment
- Demographic data

Unless consent is withdrawn, patients will continue to be followed and data regarding their cancer and survival will continue to be stored. Data management will be the responsibility of the Investigators and study-associated staff.

11.0 STATISTICAL CONSIDERATIONS.

11.1 Analysis of Primary Endpoints

The primary goal for the Phase 1 dose escalation phase of this study will be to establish the MTD/RPTD, which is defined as the highest dose for which at most 1 patient out of 6 experiences a DLT. All subjects who receive any amount of either study drug will be





included in summaries and listings of safety data. Safety summaries will be presented by dose cohort separately. AEs and DLTs will be characterized by type, frequency, and severity.

11.2 Analysis of Secondary Endpoints

Once the MTD is determined, an additional planned 12 patients will be enrolled in the expansion phase to determine overall response rate at the MTD/RP2D.

ORR will be determined as the proportion of patients who achieved a CR or PR as their best overall response based on RECIST, using imaging data collected as described in the protocol. A two-sided Clopper-Pearson 80% CI for ORR will be constructed. The 6 patients in Phase 1 treated at the MTD/RP2D will be included in this analysis.

Safety and tolerability will be further assessed in the expansion cohort. The stopping rule in section 9.12 will be employed.

PFS is defined as the time from treatment initiation to date of progression according to RECIST or death. OS is defined as the time from treatment initiation to date of death. PFS and OS will be analyzed using the Kaplan-Meier method.

11.3 Analysis of Exploratory Endpoints

Translational studies are primarily descriptive and exploratory in nature. Given the novelty of some of the assays that will be incorporated, we cannot predict the data that will be revealed. Paired tissue analyses within patients (pre-treatment biopsy vs. core needle biopsy after 3 cycles of Rigosertib+Nivolumab) will be conducted on the frequency of the tumor immune microenvironment subsets (NK cells, Treg, CD141+DC, clonal PD1+ cells, etc.). Subjects will participate in an exploratory study evaluating the predictive role of circulating tumor DNA (ctDNA) at separate time points during treatment (pre-treatment, day 1 of every cycle). Specifically assessing dynamic changes in levels while on immunotherapy. This is highly exploratory, and descriptive statistics will summarize dynamic changes over time.

Comparisons of measurements before treatment and after 3 or 6 cycles of treatment will be conducted by the Wilcoxon signed rank test and separately for responders and non-responders.

11.4 Sample Size and Accrual

The phase III trial of Selumetinib+Docetaxel compared with Docetaxel alone in stage IIIB-IV patients with KRAS-mutant non-small cell lung cancer resulted in an ORR of 20% with selumetinib+docetaxel and an ORR of 14% with docetaxel.(7) Progression-free survival was not significantly different between the groups. This phase III trial enrolled Stage IIIB as well as Stage IV patients.

The ORR will be estimated from the 12 patients in the expansion cohort together with the 6 patients in the Phase 1 trial treated at the MTD. A total of 18 patients would allow for testing the null hypothesis that the ORR is less than or equal to 10% (combination not of interest) (a lower response rate is set for the null hypothesis since the present study will only enroll Stage IV patients) versus an alternative hypothesis that the ORR is greater than or equal to 30% (combination worthy of further study) with power of 0.84 and one-sided type 1 error rate of 0.10. The PASS14 software was used to calculate





required sample size.

The total sample size depends on the safety profile of the combination. If there are no grade 2 toxicities in the accelerated dose cohorts, the number of patients in Phase 1 would be 8 patients. The maximum number of patients in phase 1 would be $3(6) = 18$ patients. Together with the 12 patients in the expansion phase, there will be total 20-30 patients.

This trial is designed to enroll patients at Mount Sinai Hospital, with treatment performed at The Rutenberg Treatment Center (1470 Madison Avenue). Patients may be enrolled into the trial at any of the Mount Sinai Health System campuses in New York City by a designated co-investigator, and follow-up visits may occur at any of the Mount Sinai Health System campuses in New York City with a designated co-investigator, however, all treatment visits and/or blood draws must occur at the Rutenberg Treatment Center. We have a growing lung cancer program and based on tumor registry data, we expect rapid accrual into this clinical trial. We anticipate the trial to be finished enrolling within 2 year of opening, with treatment to be complete at 1-2 years, after which time the patients will be monitored by the treating medical oncologist.

12.0 STUDY MANAGEMENT

12.1 Conflict of Interest

Any research personnel who has a conflict of interest with this study (patent ownership, intellectual property, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must declare their conflict of interest to the appropriate institutional review bodies. Local institutional conflict of interest policies will be followed for all research personnel associated with the research project.

12.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.





12.3 Registration Procedures

All patients must be enrolled onto trial through the Cancer Clinical Trials Office Central Registration process. Prior to registration, a member of the study staff must scan and email the following documents as individual PDF files to the Central Registration Mailbox (central.registration@mssm.edu) with a cc to the Central Registrars.

- Signed Informed Consent(s)
- Signed CCTO Registration Form
- Signed Eligibility Checklist
- Additional supporting documentation (i.e. lab/scan reports) may be included at the study teams' discretion.
- The designated Central Registrar will review all received documents for consistency and completeness.
- If there is any concern or discrepancy noted, the study staff member who originated the central registration request will be contacted immediately for clarification.
- If the patient is deemed eligible for study enrollment based on a thorough review by the Central Registrar, the patient will be entered into the CTMS system and a Registration Confirmation Letter is generated and sent to the following individuals:
 - Study team
 - Treating Physician
 - Research Infusion Nurse designee
 - Research Pharmacy

12.4 Data Management and Monitoring/Auditing

The principal investigator and study coordinator will be responsible for data accuracy and completeness. Subjects will be monitored for side effects of study medication, medication compliance, and birth control practices/pregnancy. Data will be collected electronically using Mount Sinai's secure Web-based Electronic Research Application Portal (ERAP). Accumulated safety and data information which includes adverse events, immune-related toxicities, subject compliance with the protocol, study member adherence to protocol, subject drop-outs, subject screening/ enrollment, and interim analysis of efficacy outcomes will be reviewed by the monitor(s) and the Tisch Cancer Institute Data Safety Monitoring Committee (TCI DSMC) as per standard procedure at Tisch Cancer Institute of Mount Sinai. The PI and Study team will meet weekly to monitor and discuss study safety and data. Information will be reviewed and summarized at regular intervals by the PI. A written record of this review will be maintained and submitted to the DSMC prior to the DSMC review. The PI can submit the written review to the DSMC and request an emergency meeting of the DSMC as needed.

12.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

1) Emergency Modifications





Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

2) Other Reportable New Information and Protocol Deviations/Violations

In accordance with local IRB requirements, the following information will be reported within five (5) business days:

- Non-compliance with federal regulations governing human research or with the requirements or determinations of the IRB, or an allegation of such non-compliance
- Failure to follow the protocol due to the action or inaction of the investigator or research staff.
- Breach of confidentiality
- Premature suspension or termination of the research by the sponsor or investigator.

12.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB for approval prior to implementation.

12.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator retain all study documentation pertaining to the conduct of a clinical trial. Because this is a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization region.

12.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.





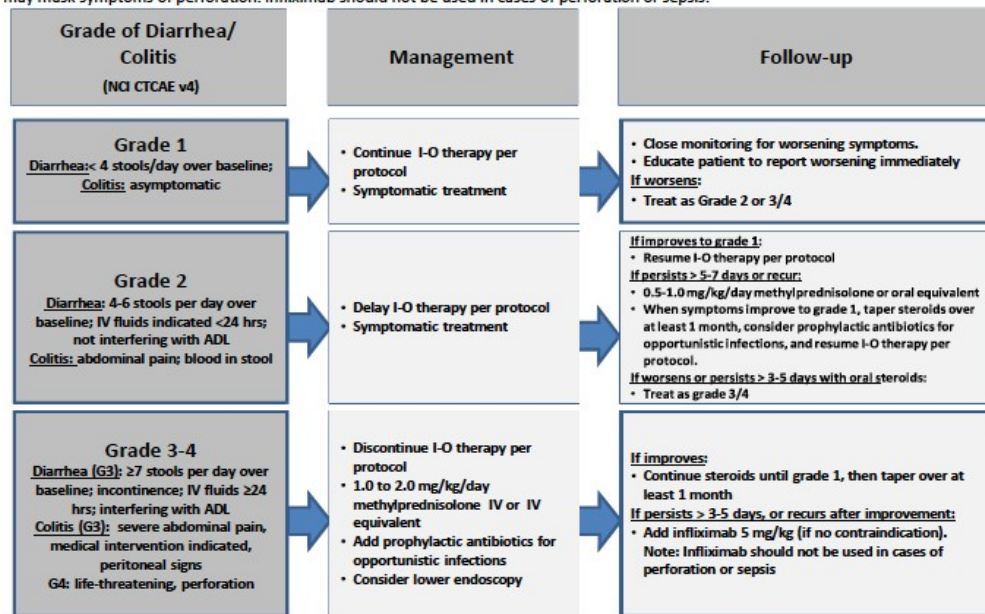
The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

13.0 APPENDIX

13.1 Nivolumab Adverse Event Management Algorithms

GI Adverse Event Management Algorithm

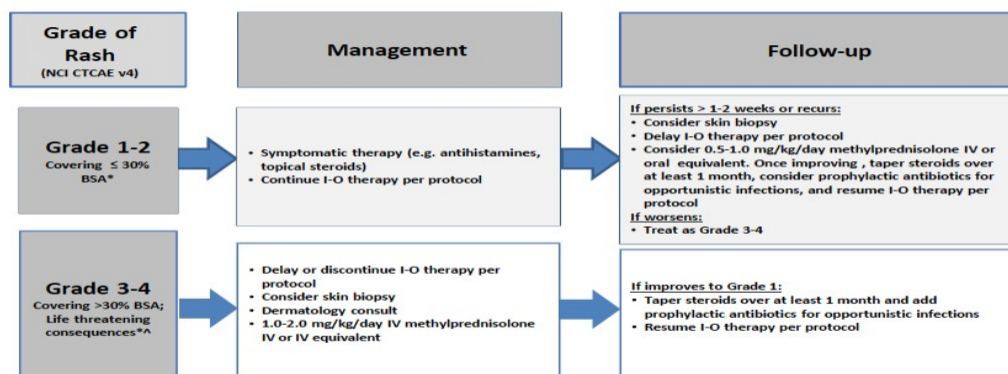
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v4 for term-specific grading criteria.

**If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.





Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	Continue I-O therapy per protocol	- Continue LFT monitoring per protocol - If worsens: - Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	- Delay I-O therapy per protocol - Increase frequency of monitoring to every 3 days	If returns to baseline: - Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen: 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili > 3 x ULN	- Discontinue I-O therapy* - Increase frequency of monitoring to every 1-2 days 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent* - Add prophylactic antibiotics for opportunistic infections - Consult gastroenterologist	If returns to grade 2: - Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: - Add mycophenolate mofetil 1 g BID - If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.

Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	- Consider delay of I-O therapy - Monitor for symptoms every 2-3 days - Consider Pulmonary and ID consults	- Re-image at least every 3 weeks - If worsens: - Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	- Delay I-O therapy per protocol - Pulmonary and ID consults - Monitor symptoms daily, consider hospitalization 1.0 mg/kg/day methylprednisolone IV or oral equivalent - Consider bronchoscopy, lung biopsy	- Re-image every 1-3 days - If improves: - When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics - If not improving after 2 weeks or worsening: - Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	- Discontinue I-O therapy per protocol - Hospitalize - Pulmonary and ID consults 2-4 mg/kg/day methylprednisolone IV or IV equivalent - Add prophylactic antibiotics for opportunistic infections - Consider bronchoscopy, lung biopsy	If improves to baseline: - Taper steroids over at least 6 weeks If not improving after 48 hours or worsening: - Add additional immunosuppression

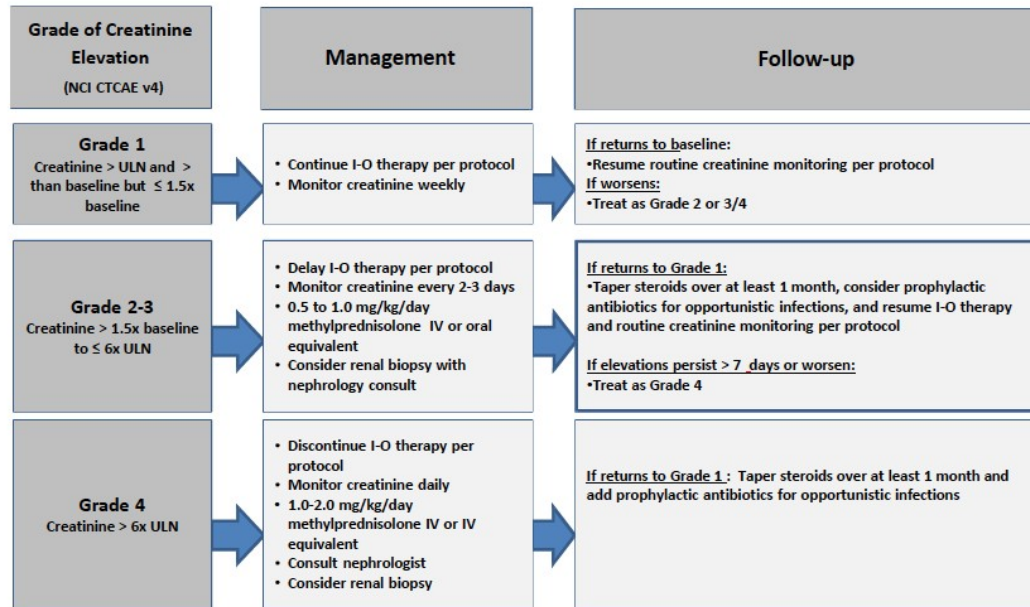
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.





Renal Adverse Event Management Algorithm

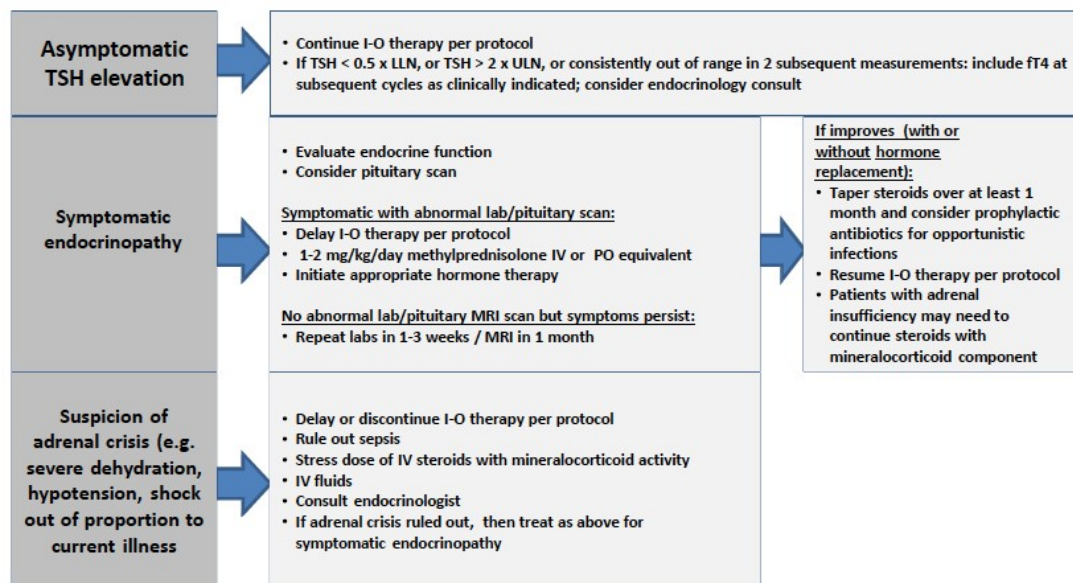
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Endocrinopathy Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

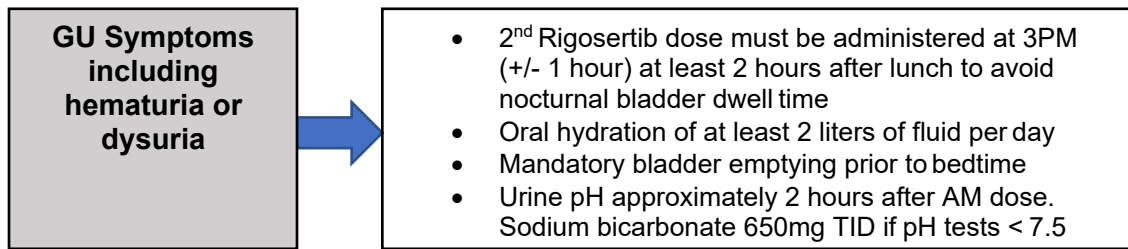


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.





13.2 Rigosertib Adverse Event Management Algorithms



13.2.1. Dose modification for treatment-related toxicity

If any treatment-related toxicity of Grade 2 or higher in severity develop during the treatment period:

1. Treatment will be withheld until resolution to $\leq$ Grade 1 or baseline status; Upon resumption of dosing, the original rigosertib dose should be continued.
2. If the toxicity recurs after resumption of original dose, treatment will again be withheld until resolution to $\leq$ Grade 1 or baseline status; upon resumption of dosing, the original rigosertib dose will be reduced to the previous dose level (eg. If at D3, will be reduced to D2; if at D2, will be reduced to D1). Should the toxicity reoccur at dose D1, treatment will be discontinued. The dose of the Nivolumab will not be modified.
3. If investigators feel that patient would tolerate rigosertib better with dose reduction upon resumption, one dose level down will be allowed

13.3 Dosing Diary

Patient Name:

MRN:

Study ID:

Cycle:

Current Rigosertib Dose: 560mg (2 pills) twice a day

Instructions: Take 2 Rigosertib capsules in the morning and 2 Rigosertib capsules in the afternoon (around 3PM). Do not eat 2 hours before or 1 hour after taking Rigosertib.

Date	Rigosertib AM Time	Rigosertib PM Time	Comments
1.			
2.			
3.			
4.			
5.			
6.			



Rigosertib+Nivolumab for KRAS+ NSCLC in Second Line

PI: Rajwanth Veluswamy MD, MSCR

Icahn School of Medicine at Mount Sinai

Version 9 Date: December 7, 2022

**Mount
Sinai***The Tisch Cancer Institute*

7.			
8.			
9.			
10.			
11.			
12.			
13.			
14.			
15.			
16.			
17.			
18.			
19.			
20.			
21.			

Patient Signature: _____ Date: _____

Investigator Signature: _____ Date: _____





REFERENCES:

1. 2018 ACSCFFAACCS.
2. Hirsch FR, Scagliotti GV, Mulshine JL, Kwon R, Curran WJ, Jr., Wu YL, et al. Lung cancer: current therapies and new targeted treatments. *Lancet* (London, England). 2017;389(10066):299-311.
3. Vasan N, Boyer JL, Herbst RS. A RAS renaissance: emerging targeted therapies for KRAS-mutated non-small cell lung cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2014;20(15):3921-30.
4. Zhang Y, Fang W, Yan Y, Wang M, Kang S, Sheng J, et al. The efficacy of first-line chemotherapy is associated with KRAS mutation status in patients with advanced non-small cell lung cancer: a meta-analysis. *Med Oncol*. 2015;32(3):61.
5. Ostrem JM, Peters U, Sos ML, Wells JA, Shokat KM. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature*. 2013;503(7477):548-51.
6. Soria JC, Fulop A, Maciel C, Fischer JR, Girotto G, Lago S, et al. SELECT-2: a phase II, double-blind, randomized, placebo-controlled study to assess the efficacy of selumetinib plus docetaxel as a second-line treatment of patients with advanced or metastatic non-small-cell lung cancer. *Annals of oncology : official journal of the European Society for Medical Oncology*. 2017;28(12):3028-36.
7. Jänne PA, van den Heuvel MM, Barlesi F, et al. Selumetinib plus docetaxel compared with docetaxel alone and progression-free survival in patients with kras-mutant advanced non-small cell lung cancer: The select-1 randomized clinical trial. *Jama*. 2017;317(18):1844-53.
8. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. *Annu Rev Immunol*. 2004;22:329-60.
9. Taube JM, Anders RA, Young GD, Xu H, Sharma R, McMiller TL, et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. *Sci Transl Med*. 2012;4(127):127ra37.
10. Kinter AL, Godbout EJ, McNally JP, Sereti I, Roby GA, O'Shea MA, et al. The common gamma-chain cytokines IL-2, IL-7, IL-15, and IL-21 induce the expression of programmed death-1 and its ligands. *J Immunol*. 2008;181(10):6738-46.
11. Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature*. 2014;515(7528):568-71.
12. Green MR, Monti S, Rodig SJ, Juszczynski P, Currie T, O'Donnell E, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. *Blood*. 2010;116(17):3268-77.
13. Vibhakar R, Juan G, Traganos F, Darzynkiewicz Z, Finger LR. Activation-induced expression of human programmed death-1 gene in T-lymphocytes. *Exp Cell Res*. 1997;232(1):25-8.
14. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *The New England journal of medicine*. 2015;373(17):1627-39.
15. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csomos T, Fulop A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *The New England journal of medicine*. 2016;375(19):1823-33.
16. Lee CK, Man J, Lord S, Cooper W, Links M, GebSKI V, et al. Clinical and Molecular Characteristics Associated With Survival Among Patients Treated With Checkpoint Inhibitors for Advanced Non-Small Cell Lung Carcinoma: A Systematic Review and Meta-analysis. *JAMA oncology*. 2018;4(2):210-6.
17. Horn L, Spigel DR, Vokes EE, Holgado E, Ready N, Steins M, et al. Nivolumab Versus Docetaxel in Previously Treated Patients With Advanced Non-Small-Cell Lung Cancer: Two-Year Outcomes From Two Randomized, Open-Label, Phase III Trials (CheckMate 017 and CheckMate 057). *J Clin Oncol*. 2017;35(35):3924-33.
18. Biton J, Mansuet-Lupo A, Pecuchet N, Alifano M, Ouakrim H, Arrondeau J, et al. TP53, STK11, and EGFR Mutations Predict Tumor Immune Profile and the Response to Anti-PD-1 in Lung Adenocarcinoma. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2018;24(22):5710-23.





19. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 2015;348(6230):124-8.
20. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *The New England journal of medicine*. 2015;372(21):2018-28.
21. Coelho MA, de Carné Trécesson S, Rana S, Zecchin D, Moore C, Molina-Arcas M, et al. Oncogenic RAS Signaling Promotes Tumor Immuno-resistance by Stabilizing PD-L1 mRNA. *Immunity*. 2017;47(6):1083-99.e6.
22. Cullis J, Das S, Bar-Sagi D. Kras and Tumor Immunity: Friend or Foe? *Cold Spring Harb Perspect Med*. 2017.
23. He XP, Song FJ, Liu XY, Wang Z, Li XX, Liu FY, et al. The relationship between KRAS gene mutations and HLA class I antigen downregulation in the metastasis of non-small cell lung cancer. *The Journal of international medical research*. 2013;41(5):1473-83.
24. Athuluri-Divakar SK, Vasquez-Del Carpio R, Dutta K, Baker SJ, Cosenza SC, Basu I, et al. A Small Molecule RAS-Mimetic Disrupts RAS Association with Effector Proteins to Block Signaling. *Cell*. 2016;165(3):643-55.
25. Navada SC, Silverman LR. The safety and efficacy of rigosertib in the treatment of myelodysplastic syndromes. *Expert Rev Anticancer Ther*. 2016;16(8):805-10.
26. Sharpe AH, Wherry EJ, Ahmed R, Freeman GJ. The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection. *Nature immunology*. 2007;8(3):239-45.
27. Lee JI, Zhang L, Men AY, Kenna LA, Huang SM. CYP-mediated therapeutic protein-drug interactions: clinical findings, proposed mechanisms and regulatory implications. *Clinical pharmacokinetics*. 2010;49(5):295-310.
28. Keizer RJ, Huitema AD, Schellens JH, Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. *Clinical pharmacokinetics*. 2010;49(8):493-507.
29. Navada S, Garcia-Manero G, Wilhelm F, Hearn K, Odchimar-Reissig R, Demakos E, et al., editors. A Phase I/II Study of the Combination of Oral Rigosertib and Azacitidine in Patients with Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML). *ASH Annual Meeting*; 2014.
30. Jennison C, Turnbull BW. Sequential equivalence testing and repeated confidence intervals, with applications to normal and binary responses. *Biometrics*. 1993;49(1):31-43.
31. Ivanova A, Qaqish BF, Schell MJ. Continuous toxicity monitoring in phase II trials in oncology. *Biometrics*. 2005;61(2):540-5.
32. Angelo M, Bendall SC, Finck R, Hale MB, Hitzman C, Borowsky AD, et al. Multiplexed ion beam imaging of human breast tumors. *Nat Med*. 2014;20(4):436-42.
33. Song G, Ivanova A. Enrollment and stopping rules for managing toxicity requiring long follow-up in phase II oncology trials. *Journal of Biopharmaceutical Statistics*. 2015;25(6):1206-14. doi 10.1080/10543406.2015.1086779.

