MSK PROTOCOL COVER SHEET

A Phase I/II Study of DS-3201b, an EZH1/2 Inhibitor, in Combination with Irinotecan in Patients with Recurrent Small Cell Lung Cancer

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study Title:	A phase I/II study of DS-3201b, an EZH1/2 inhibitor, in combination with irinotecan in patients with recurrent small cell lung cancer
Study Design:	This study is a non-randomized phase I/II trial assessing the safety and tolerability of DS-3201b in combination with irinotecan in patients with recurrent small cell lung cancer.
Study Objectives:	**Part I: Dose-Escalation of DS-3201b in Combination with Irinotecan** Primary Objectives ▪ To assess the safety, tolerability, and maximum tolerated dose (MTD) of DS-3201b in combination with fixed-dose irinotecan in patients with recurrent small cell lung cancer (SCLC). ▪ To determine the recommended phase II dose (RP2D) of DS-3201b in combination with irinotecan in patients with recurrent SCLC. Secondary Objectives ▪ To assess the plasma pharmacokinetics (PK) after a single dose of DS-3201b in combination with irinotecan. **Part II: Phase II Study of DS-3201b in Combination with Irinotecan** Primary Objectives ▪ To determine the objective response rate (ORR) to treatment with DS-3201b at the RP2D in combination with irinotecan in patients with recurrent SCLC. Secondary Objectives ▪ To determine the progression-free survival and overall survival of patients with recurrent SCLC treated with DS-3201b in combination with irinotecan. ▪ To determine the duration of response or duration of stable disease in patients with recurrent SCLC treated with DS-3201b in combination with irinotecan. ▪ To explore SLFN11 expression by immunohistochemistry as a potential predictive biomarker of response to DS-3201b and correlate with trimethylation of H3K27 as measured by immunohistochemistry in

	pretreatment, on-treatment and post-treatment tissue samples as well as in circulating tumor cells (CTCs). ▪ To explore changes in the genomic landscape of pre-treatment, on-treatment and post-treatment tumor tissue using bulk RNA sequencing. ▪ To assess the plasma pharmacokinetics (PK) after a single dose of DS-3201b in combination with irinotecan.
Patient Population:	Patients with recurrent small cell lung cancer previously treated with a platinum-containing regimen.
Patient Sample Size:	Phase I: Minimum of 4 patients, maximum of 36 patients. Dose-Escalation, which enrolled a total of 12 patients at MSK, is completed. Phase II: Minimum of 16 patients (6 will be from Phase I), maximum of 31 patients. The maximum number of unique patients in Phase II will be 25 patients.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

Part I: Phase I Dose-Escalation of DS-3201b in Combination with Irinotecan

Primary Objectives

- To assess the safety, tolerability, and maximum tolerated dose (MTD) of DS-3201b in combination with fixed-dose irinotecan in patients with recurrent small cell lung cancer (SCLC).
- To determine the recommended phase II dose (RP2D) of DS-3201b in combination with irinotecan in patients with recurrent SCLC.

Secondary Objectives

- To assess the plasma pharmacokinetics (PK) after a single dose of DS-3201b in combination with irinotecan.

Part II: Phase II Study of DS-3201b in Combination with Irinotecan

Primary Objectives

- To determine the objective response rate (ORR) to treatment with DS-3201b at the RP2D in combination with irinotecan in patients with recurrent SCLC.

Secondary Objectives

- To determine the progression-free survival and overall survival of patients with recurrent SCLC treated with DS-3201b in combination with irinotecan.
- To determine the duration of response or duration of stable disease in patients with recurrent SCLC treated with DS-3201b in combination with irinotecan.
- To explore SLFN11 expression by immunohistochemistry as a potential predictive biomarker of response to DS-3201b and correlate with trimethylation of H3K27 as measured by immunohistochemistry in pretreatment, on-treatment and post-treatment tissue samples as well as in circulating tumor cells (CTCs)
- To explore changes in the genomic landscape of pre-treatment, on-treatment and post-treatment tumor tissue using bulk RNA sequencing.
- To assess the plasma pharmacokinetics (PK) after a single dose of DS-3201b in combination with irinotecan.

3.1 BACKGROUND AND RATIONALE

3.2 Background on SCLC

SCLC accounts for 13–15% of all lung cancers, with approximately 250,000 cases diagnosed annually worldwide.[1-5] Due to its extremely aggressive nature, the majority of patients will present with metastatic, or extensive-stage, disease. While patients with extensive-stage SCLC have robust responses to first-line platinum and etoposide, with response rates approaching 70-80%, most will experience a rapid and chemoresistant relapse.[6-12] Patients with limited-stage SCLC are treated similarly, with the addition of concurrent radiation. Recurrent disease after initial platinum-based therapy, whether initially limited or extensive-stage, is treated similarly. For many years, the topoisomerase inhibitor topotecan was the only FDA-approved therapy for the treatment of recurrent SCLC.[13] More recently in August 2018, immune checkpoint blockade using nivolumab was granted accelerated FDA approval for subsequent line therapy of recurrent SCLC.[14] However, both topotecan and nivolumab offer limited clinical benefit due to lower response rates in subsequent line settings in SCLC.[13,14] Because the mechanisms of acquired chemoresistance in SCLC are poorly understood, the standard of care for first-line treatment of recurrent SCLC has not changed in over 30 years and there is a clear need for novel and innovative therapies.[15]

3.3 Epigenetic Silencing of *SLFN11* in the Context of Acquired Chemoresistance in SCLC

In an effort to define mechanisms of acquired resistance to chemotherapy, paired chemonaive and chemoresistant patient-derived xenograft models of SCLC were developed in the Rudin laboratory at Memorial Sloan Kettering Cancer Center. Chemotherapy resistance was modeled *in vivo* by cycling weekly cisplatin and etoposide, followed by serial passaging and outgrowth of resistant tumors. Whole transcriptome (RNAseq), exome and high depth targeted sequencing approaches of paired parental and resistant tumors revealed epigenetic silencing of *schlafen family member 11* (*SLFN11)* in the context of acquired chemoresistance as a consistent finding across multiple models.[16] *SLFN11* had been previously identified as the

single most predictive gene for sensitivity to topoisomerase inhibitors across all tumor types in cell lines within the Cancer Cell Line Encyclopedia.[17] Based on these findings, we hypothesized that *SLFN11* inactivation may be a novel and highly penetrant determinant of resistance to systemic chemotherapy in patients.

3.4 EZH2 as a Novel Target in SCLC

Epigenetic processes play a central role in carcinogenesis, and response to treatment.[18-20] Hypermethylation of promoter regions in the DNA are associated with dense chromatin packing, leading to subsequent repressed gene expression.[21] Repression of tumor-suppressor genes and genes required for programmed cell death in this manner, as well as de-repression of oncogenes, can provide a fitness advantage for cancer.[19,20]

Post-translational modifications of histones through methylation play important roles in controlling the fidelity of cellular gene transcription patterns. Methylation of histone lysine and arginine residues, catalyzed by histone methyltransferases (HMTs), is a particularly important determinant of gene accessibility and transcription. Genetic alterations in a number of HMTs have been implicated in oncogenesis. For example, the polycomb repressor complex 2 (PRC2) is a multiprotein chromatin-modifying complex that inhibits gene expression by promoting local histone methylation. Enhancer of Zeste homolog 2 (EZH2) is the enzymatic histone-lysine *N*-methyltransferase subunit of PRC2, and it mediates histone H3 lysine 27 dimethylation and trimethylation (H3K27me2 and H3K27me3), which are suppressive marks associated with local chromatin condensation and gene silencing.[22] Aberrant EZH2 activity and alterations of key regulators of EZH2 in the SWItch/Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling complex have been implicated in oncogenesis in multiple tumor types.

Inhibition of EZH2 activity by either knock-down or small molecule inhibition induces tumor cell death and durable tumor regression in some preclinical models. EZH2 is mutated in a subset of human cancers at gain of function hot spots that increase its enzymatic activity and thereby promote H3K27me3.[23] Although EZH2 is not commonly mutated in SCLC, the Rudin laboratory showed that the level of EZH2 expression is higher in SCLC than in any other tumor type included in The Cancer Genome Atlas.[24,25] Expression of the *EZH2* gene is under the direct control of E2F family of transcription factors, including E2F1.[26,27] E2F transcriptional activity is negatively regulated by the protein product of the *RB1* tumor-suppressor gene (Rb); the nearly universal loss of *RB1* — and thus functional Rb — in SCLC cells results in a high level of E2F transcriptional activity, and consequent high EZH2 expression levels.[28] These observations define a model in which EZH2 expression is primarily promoted by one of the pathognomonic genetic alterations of SCLC.[15]

3.5 Preclinical Efficacy of EZH2 Inhibition in SCLC

In 2017, the Rudin laboratory used multiple patient-derived xenografts (PDXs) to define EZH2-mediated *SLFN11* gene silencing as a frequent mechanism of acquired chemoresistance in SCLC.[16] EZH2-mediated suppression of *SLFN11* was observed in 40% of SCLC models selected *in vivo* for acquired chemotherapeutic resistance.[16] Mechanistically, *SLFN11* has been proposed to bind to RPA1 and displace the RPA complex from damaged DNA or to increase replication stress by a similar mechanism. Importantly, EZH2 inhibition was found to

prevent *SLFN11* silencing and maintain the sensitivity of SCLC xenografts to chemotherapy, suggesting a potential combinatorial strategy to enhance the effectiveness of current standard therapies for this recalcitrant disease.[16]

The Rudin laboratory has further shown that chemical EZH2 inhibition can re-express *SLFN11* in SCLC cell lines with low-to-undetectable SLFN11 protein expression at baseline, effectively re-sensitizing these cell lines to DNA damaging agents. The extent of SLFN11 re-expression induced by an EZH2 inhibitor was strongly correlated with increase in sensitivity to the topoisomerase I inhibitor, topotecan. Finally, we have demonstrated that pharmacological inhibition of EZH2 in PDX models inhibited tumor growth and markedly improved chemotherapy efficacy when combined with irinotecan.

DS-3201b (Daiichi Sankyo) is an orally available, highly potent and selective inhibitor of EZH2 and the closely related EZH1 (an alternative histone lysine methyltransferase that can substitute for EZH2 in PRC2), with potential antineoplastic activity. Upon oral administration, DS-3201b selectively inhibits the activity of both wild-type and mutated forms of EZH1 and EZH2. Inhibition of EZH1/2 specifically prevents the methylation of lysine 27 on histone H3 (H3K27). *In vivo* and *in vitro* preclinical studies suggest that EZH2 inhibition rescues silencing of *SLFN11*, leading to treatment response in previously chemotherapy resistant models.

3.6 Clinical Experience with DS-3201b in Other Malignancies

The clinical development program of DS-3201b includes 9 company-sponsored clinical studies (3 completed and 6 ongoing) in Non-Hodgkin Lymphoma (NHL), AML, and ALL. The six ongoing studies are listed below in Table 1. Additionally, there were 3 non-company sponsored studies with healthy subjects ongoing. In the 3 non-company sponsored studies, 24 subjects have received valemetostat tosylate (DS-3201b). The three completed clinical are as follows: DS3201-A-J103: A Phase 1 study of valemetostat tosylate to assess the pharmacokinetics (PK) and safety after a single oral administration, the relative bioavailability, and the effect of food (in healthy subjects); DS3201-A-J104: A Phase 1 study to assess the effect of CYP3A inhibitors on valemetostat tosylate in healthy subjects; and DS3201-A-U105: A Phase 1 single dose study of [14C]valemetostat tosylate in healthy subjects. The 6 ongoing clinical studies are as follows: DS3201-A-J101: A Phase 1 multiple ascending dose study of valemetostat tosylate in subjects with NHL; DS3201-A-J107: A Phase 1 drug-drug interaction (DDI) study with rifampicin (strong CYP3A inducer) in healthy subjects; DS3201-A-J109: A food effect Phase 1 study in healthy subjects with low fat meal using to-be-marketed formulation; DS3201-A-J201: A Phase 2 Study in subjects with relapsed or refractory ATL; DS3201-A-U102: A Phase 1 study of valemetostat tosylate in subjects with AML or ALL; DS3201-A-U106: A Phase 1 study to assess the safety, tolerability, and PK of valemetostat tosylate in healthy subjects with normal and impaired hepatic function. The 3 non-company sponsored studies are as follows: NCT03879798/IIS-DS-3201-18-553: A non-randomized Phase 1/2 study assessing the safety and tolerability of valemetostat tosylate in combination with irinotecan in patients with recurrent small-cell lung cancer; NCT04388852: A Phase 1b, single-center, open-label study of valemetostat in combination with ipilimumab in patients with aggressive-variant prostate carcinoma, urothelial carcinoma, and renal cell carcinoma; NCCH1904/MK007/jRCT2031190268: A Phase 1 single-arm study to confirm pediatric safety and to explore broad efficacy of valemetostat tosylate in pediatric, adolescent, and young adult

patients with malignant solid tumors. For further details about these studies, please refer to current IB for study details.

Table 1.0 Ongoing Clinical Studies using DS3201 in Other Malignancies.

Study	Compound	Tumor type	Line of therapy	Phase	Location	Trial ID
DS3201-A-J101	DS-3201b	NHL (B cell and T cell lymphoma including ATL)	2nd line or greater	I	Japan	NCT02732275
DS3201-A-U102	DS-3201b	AML, ALL	2nd line or greater	I	USA	NCT03110354
DS3201-J-201	DS-3201b	ATL	2nd line or greater	II	Japan	NCT04102150

DS3201-A-J101

DS3201-A-J101 is an ongoing Phase 1 multiple ascending dose study of DS-3201b in Japanese patients with non-Hodgkin's lymphoma (NHL). The objectives of the study were to assess the safety and tolerability of DS-3201b, to identify a tentative recommended Phase 2 dose (RP2D), and to assess its pharmacokinetic (PK)/pharmacodynamics (PD) properties in subjects with non-Hodgkin's lymphoma (including adult T-cell leukemia-lymphoma [ATL] and peripheral T-cell lymphoma [PTCL]).

At the data cut-off date, 18 Jan 2021, a total of 81 subjects (48 male and 33 female) received DS-3201b of which 7 subjects received 150 mg, 65 subjects received 200 mg, 7 subjects received 250 mg, and 2 subjects received 300 mg of DS-3201b once daily. Twenty-one subjects have still been continuing with the study drug. A total of 60 subjects discontinued from the study drug: of these, 31 subjects discontinued due to progressive disease; 12 subjects discontinued due to clinical progression; 3 subjects discontinued due to adverse event (AE); 6 subjects withdrew consent; 3 subjects discontinued due to physician decision; and 5 subjects discontinued due to other reason.

Five subjects have discontinued from the treatment due to a TEAE (1 subject for Pneumocystis jirovecii pneumonia [PJP], 1 subject for lower leg edema, 1 subject for colitis, 1 subject for dysgeusia and 1 subject for disease progression) at the time of data cutoff date. There was 1 subject with a TEAE of disease progression with a fatal outcome, assessed as unrelated by the investigator.

The most commonly reported treatment emergent AEs were identified by Daiichi Sankyo in the Investigator Brochure (version 7.0) by system order class. Lab abnormalities were the most common AEs (57 [70.4%]), followed by nervous system disorders (48 [59.3%]) and skin and subcutaneous tissue disorders (44 [54.3%]). The most frequently reported TEAEs were hematologic changes, cytopenic in nature including platelet count decreased (48 [59.3%]), anemia (30 [37.0%]), neutrophil count decreased (28 [34.6%]), WBC count decreased (25 [30.9%]), and lymphocyte count decreased (24 [29.6%]). Other frequently reported TEAE >20% included dysgeusia (40 [49.4%]), alopecia (25 [30.9%]), diarrhea (22 [27.2%]), and nausea (17 [21.0%])

DS3201-A-U102

DS3201-A-U102 is an ongoing Phase 1, non-randomized, open-label study of DS-3201b in patients with relapsed/refractory acute myeloid (AML) or acute lymphocytic (ALL) leukemias. The objectives of Part 1 (dose escalation) of the study are to assess the safety and tolerability of DS-3201b in subjects with relapsed/refractory AML or ALL, to determine the recommended dose for expansion (RDE), and to evaluate PK and PD of DS-3201b in subjects with relapsed/refractory AML or ALL. The objective of Part 2 (dose expansion) of the study is to confirm the safety and tolerability of DS-3201b at the RDE in subjects with relapsed/refractory AML and ALL and for preliminary assessment of efficacy.

At the data cut-off date, 18 Jan 2021, the DS3201-A-U102 study enrolled 48 subjects and 26 subjects received treatment with DS-3201b in the dose escalation part of the study, 4 subjects received the drug at 100 mg QD, 4 subjects at 150 mg QD, 3 subjects at 250 mg QD, 8 subjects at 500 mg QD, and 7 subjects at 700 mg QD.

In Study DS3201-A-U102, there were a total of 69 serious TEAEs reported. Twenty-six subjects have discontinued the study. There have been 9 subjects experiencing TEAEs associated with fatal outcome. The events were disease progression (6 subjects), pulmonary sepsis (1 subject), sepsis (1 subject), hemorrhage intracranial (1 subject) and respiratory failure (1 subject). All events were assessed as not related to DS-3201b by the investigators.

DS3201-A-J201

DS3201-A-J201 is ongoing Phase 2, multicenter, open-label, single-arm study of valemetostat tosylate, 200 mg once daily, in subjects with relapsed or refractory ATL. As of 18 Jan 2021, a total of 25 subjects were enrolled and received treatment with DS-3201b. In this study, 7 subjects experienced at least one serious TEAE. There were 10 serious adverse events (SAEs) reported among these 7 subjects, which include 1 event each of acute kidney injury, hepatic function abnormal, cardiac failure, CMV infection, overdose, lower gastrointestinal hemorrhage, febrile neutropenia, platelet count decreased, and venous thromboembolism. The majority of these events were assessed as related by the investigator, none of these events were associated with a fatal outcome and all events recovered or are recovering. The most common all Grade TEAEs were platelet count decreased (17 subjects), anemia (12 subjects), dysgeusia (8 subjects), alopecia (7 subjects), lymphocyte count decreased (6 subjects), neutrophil count decreased (5 subjects), WBC count decreased (5 subjects), decreased appetite (5 subjects),

cytomegalovirus (CMV) infection (4 subjects), dry skin (4 subjects), pyrexia (4 subjects), and malaise (3 subjects). Of note, the event of neutropenia (1 subject) is a synonymous PT of neutrophil count decreased.

There have been no reports of events of thrombocytopenia, leukopenia, or lymphopenia, which are synonymous PTs of platelet count decreased, WBC count decreased, and lymphocyte count decreased, respectively. There have been 2 subjects who have experienced a TEAE associated with study drug discontinuation: one subject with platelet count decreased (Grade 4) and one subject with cardiac failure who had signs of impaired cardiac function prior to starting therapy with DS-3201b. There have been no reports of Pneumocystis jiroveci Pneumonia (PJP). Among the 5 subjects who experienced Cytomegalovirus (CMV), 2 subjects had onset of CMV infection after discontinuation of study drug due to other AEs or disease progression, 2 subjects recovered from the event without dose modification, and 1 subject experienced disease progression before the event recovered. Limited literature is available regarding the frequency of CMV infections in ATL populations In Study DS3201-A-J201, there have been no subjects with a TEAE of QT interval prolongation. Additionally, there have been no events of torsade de pointe, ventricular tachycardia, syncope, or other ventricular arrhythmia reported thus far. Review of ECG data for all DS3201-A-J201 subjects showed no subjects with QTcF >480 ms and no subjects with an increase from baseline >60 ms. There were no events related to increased histamine levels observed in Study DS3201-A-J201.

Ten subjects are continuing with the study drug. A total of 15 subjects discontinued from the study treatment: of those, 13 subjects discontinued due to progressive disease and per investigator report 2 subjects discontinued due to TEAEs of cardiac failure and platelet count decreased.

3.7 Study Rationale for Combining EZH2 Inhibition with Irinotecan

Our preclinical data pointed to particularly strong antitumor synergy between EZH2 and irinotecan in relevant *in vivo* models of recurrent chemoresistant SCLC. Irinotecan is among the standard therapies for SCLC, used together with cisplatin as part of the most commonly used standard first-line regimen in Japan and as a standard option for recurrent SCLC including in the NCCN treatment guidelines for SCLC in the United States.

We hypothesize that by adding the EZH1/2 inhibitor DS-3201b to irinotecan, we will induce and maintain SLFN11 expression and improve responses to irinotecan in patients with recurrent SCLC. While the primary objectives of this study are clinical, we will also use this study to further investigate *SLFN11* as a potential biomarker of response to chemotherapy in patients with SCLC.

The clinical and translational work proposed here will substantially advance our understanding of the *EZH2*-*SLFN11* axis in SCLC. By capitalizing on our discovery that chemosensitive relapse in SCLC proceeds through this axis, inhibition of EZH1/2 represents a novel targeted therapeutic approach in the treatment of patients with chemotherapy resistant recurrent SCLC.

Furthermore, we will explore the hypothesis that *SLFN11* will serve as a clinically informative biomarker of response to therapy.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

The first part of this study is a phase I trial to assess the safety and tolerability of DS-3201b in combination with fixed-dose irinotecan conducted only at Memorial Sloan Kettering Cancer Center. The second part of this study will be a multicenter, open-label, single-arm phase II study of DS-3201b at the established recommended phase II dose (RP2D) in combination with fixed-dose irinotecan. Participating sites for Phase II will include both Memorial Sloan Kettering Cancer Center (MSKCC) and Johns Hopkins Sidney Kimmel Comprehensive Cancer Center (JHU).

4.2 Intervention

Patients with SCLC who have received at least one prior line of platinum-based chemotherapy will be eligible for enrollment.

In phase I (dose-escalation) of the study, patients will receive oral daily DS-3201b following a standard 3+3 dose-escalation design in combination with fixed-dose irinotecan 125 mg/m^2 intravenously on days 1 and 8 every 3 weeks in a 21-day cycle.

In phase II of the study, patients will receive oral daily DS-3201b at the RP2D in combination with fixed-dose irinotecan 125 mg/m^2 intravenously on days 1 and 8 every 3 weeks in a 21-day cycle.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

<u>DS-3201b</u>

DS-3201b (Daiichi Sankyo) is an orally available and potent selective inhibitor of the histone lysine methyltransferases enhancer of zeste homolog 1 (EZH1) and 2 (EZH2) and has potential antineoplastic activity. Upon oral administration, DS-3201b selectively inhibits the activity of both wild-type and mutated forms of EZH1 and EZH2. Inhibition of EZH1/2 specifically prevents the methylation of lysine 27 on histone H3 (H3K27). This decrease in histone methylation alters gene expression patterns associated with cancer pathways, enhances transcription of certain target genes, and results in decreased proliferation of EZH1/2-dependent cancer cells. Our *in vivo* and *in vitro* preclinical studies suggest that EZH1/2 inhibition with DS-3201b rescues silencing of SLFN11 leading to treatment response in previously chemotherapy-resistant patient derived xenograft models. DS-3201b is well tolerated in animal models and when studied in combination with multiple chemotherapeutic agents including irinotecan, with no weight loss observed at effective doses DS-3201b is metabolized primarily by the liver.

The starting dose of 100 mg daily for DS-3201b in this study was selected based on the current available clinical data from ongoing studies of DS-3201b as detailed in Section 3.5.

Irinotecan

Irinotecan is a commercially available topoisomerase I inhibitor with activity against several solid tumors including lung, colon, and ovarian cancers. The cytotoxic effects are due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38 (its active metabolite). Irinotecan is FDA-approved as first-line treatment of metastatic colon cancer. Topotecan, a similar orally available topoisomerase I inhibitor, has been shown to increase survival in patients with recurrent SCLC compared with best supportive care and was FDA-approved in 2007 in the second-line setting for patients with small cell lung cancer who had a complete or partial response to first-line chemotherapy. Oral and intravenous formulations of topotecan have been extensively evaluated for the second-line treatment of recurrent SCLC and were found to be equally effective. Of note, topotecan has significant toxicities with most patients experiencing grade 3/4 neutropenia, anemia, or thrombocytopenia. Therefore, irinotecan is commonly used as a NCCN-designated alternative to topotecan in this context.

Drug accountability: All study drug supplies must be kept in a locked room with limited access. The study drug (DS-3201b) must not be used outside the context of this protocol. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, patients, or clinic, or allow supplies to be used other than directed by this protocol without prior authorization from Daiichi Sankyo. The pharmacist will maintain a complete drug accountability record with lot numbers, the dates drug was dispensed, and the dose of DS-3201b the patient received. The prescribed dose should also be recorded in the patient's medical records. At the conclusion of the study, all unused DS-3201b will be destroyed on-site as described in a standard operating procedure for the destruction of chemotherapeutic waste.

In prior clinical studies, average doses of irinotecan 200-350 mg/m^2 over 3 weeks have been used to treat patients with recurrent small cell lung cancer. For this clinical study, we have opted for a starting dose of irinotecan that is still recommended by the manufacturer's label, has been shown to be efficacious in prior studies in SCLC, and will help to ensure patient safety and ideally minimize toxicity when used in combination with an experimental agent.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

- Signed informed consent form (ICF)
- Ability to comply with the study protocol as per the investigator's judgment
- Age ≥ 18 years at the time of signing the ICF
- Life expectancy ≥ 12 weeks
- Karnofsky performance status ≥ 70% or ECOG 0, 1 or 2.
- Pathologically confirmed diagnosis of small cell lung cancer. Patients with a diagnosis of combined small cell lung cancer with other histologies may be considered for

inclusion if the predominant histology is SCLC and only after discussion with the study PI. Patients with transformed SCLC from NSCLC are allowed on study after discussing with the MSKCC or JHU Study PI.

- Radiographically documented progression of disease after prior treatment with a platinum doublet regimen. Patients who received a platinum doublet regimen in combination with immunotherapy are still eligible for the study.
- Measurable disease according to RECIST v1.1
- Adequate tissue sample available for both IHC testing of IHC testing of SLFN11 and H3K27me3 and molecular profiling (archived tissue block or 20 unstained slides). Tissue sample can be either from an initial pre-platinum-based chemotherapy sample OR from a repeat biopsy sample after progression on platinum-based chemotherapy.
- Concurrent consent to the appropriate biospecimen research protocols at MSKCC (#06-107 Storage and Research Use of Human Biospecimens) and at JHU.
- Adequate hematologic and end-organ function, as defined by the following laboratory test results obtained within 14 days prior to initiation of study treatment:
    - Adequate bone marrow function as defined by:
        - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (1500/μL) without granulocyte colony-stimulating factor support within 2 weeks prior to starting study therapy
        - Hemoglobin ≥ 9 g/dL (transfusions to meet this criterion are allowed)
        - Platelets ≥ 150 x 10^9/L without transfusion
    - Adequate renal function as defined by:
        - Creatinine clearance ≥ 30 mL/min as calculated using the modified Cockcroft-Gault equation or Modification of Diet in Renal Disease (MDRD) formula OR serum creatinine ≤ 1.5 × ULN
    - Adequate hepatic function as defined by:
        - AST, ALT, and alkaline phosphatase (ALP) ≤ 3 x ULN with the following exceptions
            - Patients with documented liver metastases: AST, ALT and ALP ≤ 5 x ULN
        - Total bilirubin ≤ 2.0 mg/dL
        - For patients not receiving therapeutic anticoagulation:
            - INR ≤ 1.5 × ULN
            - aPTT ≤ 1.5 × ULN
        - For patients receiving therapeutic anticoagulation:
            - stable anticoagulant regimen

  Patients with baseline clinical symptoms or laboratory abnormalities that do not meet the definition of dose-limiting toxicity (DLT) as outlined in Section 11.7 are eligible for treatment on this study.
- Nonsterilized female patients of reproductive age group and male patients should use highly effective methods of contraception through defined periods during and after study treatment as specified below:
    - Female patients must meet 1 of the following:
        - Postmenopausal for at least 1 year before the screening visit, or

- Surgically sterile, or
- If she is of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception, at the same time, from the time of signing the informed consent through 6 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

- Female patients must agree to not donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug(s).
  - A woman is considered to be of childbearing potential if she is post-menarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).
  - Examples of highly effective contraceptive methods (with a failure rate of < 1% per year) include bilateral tubal ligation, male sterilization, and established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
- Male patients, even if surgically sterilized (i.e., status post vasectomy), must agree to 1 of the following:
  - Practice highly effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or
  - Practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods for the female partner] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Male patients must agree to not donate sperm during the course of this study or 6 months after receiving their last dose of study drug(s).
- Patient is willing and able to comply with scheduled visits, drug administration plan, laboratory tests, other study procedures, and study restrictions.

6.3 Subject Exclusion Criteria

- Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of study procedures.
- Untreated CNS metastases
- Patients with treated CNS metastases are allowed on the study as long as their clinical symptoms are adequately controlled, and the daily dose of steroid use is equivalent to or less than 10 mg of prednisone.
- Is receiving concomitant treatment with a strong inhibitor or inducer of CYP3A4/5 within 7 days of first receipt of DS-3201b.
    - Consumption of herbs/fruits that may have an influence on PK of DS-3201b (strong CYP3A inhibitors or inducers) such as St. John’s wort, star fruit, Seville orange or Seville orange-containing foods and beverages, grapefruit or grapefruit-containing food or beverages should be avoided from 14 days prior to the start of the study and throughout the entire study.
- Prior exposure to DS-3201b or other inhibitors of enhancer of zeste homologue-2 (EZH2)
- Prior exposure to topotecan and irinotecan
- Refractory nausea and vomiting, malabsorption, biliary shunt, significant bowel resection, or any other condition that significantly affects gut motility or absorption and would preclude adequate absorption of DS-3201b in the opinion of the treating physician and/or PI.
- Currently receiving anticancer therapies or who have received anticancer therapies within 2 weeks prior to the initiation of study treatment. Anticancer therapies include chemotherapy, biologics, targeted therapies, immunologics, or other investigational therapy.
- Currently receiving radiation therapy, or who have received radiation within 2 weeks prior to the initiation of study treatment.
- Patients who have not recovered to Grade ≤1 or baseline from adverse events due to prior anticancer therapy.
- Patients who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia).
    - NOTE: Procedures such as a percutaneous biopsy, pleural catheter insertion, placement of a central venous catheter or other minor procedures are permitted.
- Uncontrolled or significant cardiovascular disease, including the following:
- Evidence of prolongation of QT/QTc interval (e.g., repeated episodes of QT corrected for heart rate using Fridericia’s method [QTcF] >450 ms for men and >470 ms for females) ECG from 12-lead electrocardiogram for measurement of corrected QT interval according to the Fridericia formula: electrocardiogram must be registered at rest. For any EKG assessment, if the initial EKG shows a prolonged QTc, then two additional EKGs will be obtained, resulting in three specimens taken after a space of 1 minute, and the mean of the 3 EKGs will be used to determine eligibility and for grading of TRAEs.

- Diagnosed or suspected long QT syndrome, or known family history of long QT syndrome
- History of clinically relevant ventricular arrhythmias, such as ventricular tachycardia, ventricular fibrillation, or Torsade de Pointes
- Uncontrolled arrhythmia (subjects with asymptomatic, controllable atrial fibrillation may be enrolled), or asymptomatic persistent ventricular tachycardia
- Subject has clinically relevant bradycardia of <50 bpm unless the subject has a pacemaker
- History of second- or third-degree heart block. Candidates with a history of heart block may be eligible if they currently have pacemakers, and have no history of fainting or clinically relevant arrhythmia with pacemakers, within 6 months prior to Screening
- Myocardial infarction within 6 months prior to Screening
- Angioplasty or stent graft implantation within 6 months prior to Screening
- Uncontrolled angina pectoris within 6 months prior to Screening
- New York Heart Association (NYHA) Class 3 or 4 congestive heart failure
- Coronary/peripheral artery bypass graft within 6 months prior to Screening
- Uncontrolled hypertension (resting systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg)
- Complete left or right bundle branch block
- Patients who are currently taking medications that are known to prolong the QT interval and are clearly associated with a known risk of Torsades de Pointes (TdP) even when taken as recommended. Please see Section 11.6 for a full list of excluded medications. Patients who are able to discontinue any prohibited medication prior to the start of study drug at Day -7 will still be considered eligible for the study.

- Have a known hypersensitivity to any of the components of or known hypersensitivity to either the study drug itself or any of the inactive ingredients in the study drug product.
- Known liver cirrhosis.
- Uncontrolled active infection requiring IV antibiotic, antiviral, or anti-fungal medications within 14 days prior to initiation of study treatment.
    - Infections controlled on concurrent anti-microbial agents and anti-microbial prophylaxis per institutional guidelines are acceptable.
- Congenital or acquired immunodeficiency, including patients with known history or infection with human immunodeficiency virus (HIV).
    - NOTE: HIV-positive patients who are taking anti-retroviral therapy are still ineligible due to potential PK interactions with DS-3201b.
- Active tuberculosis
- Active hepatitis B virus (HBV) infection (chronic or acute), defined as having a positive hepatitis B surface antigen (HBsAg) test. Hepatitis B testing (HBV surface antigen and core antibody) is required only if not done previously

- Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test are eligible for the study. Hepatitis B testing is required only if not done previously
- Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test followed by a positive HCV RNA test. Hepatitis C testing (HCV antibody) is required only if not done previously
  - The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
- Female patients who have a positive serum pregnancy test during screening or a positive urine pregnancy test on Day 1 before first dose of study drug.
- Female patients who are lactating and/or plan to breastfeed during the study treatment.

7.1 RECRUITMENT PLAN

Patients with SCLC who have progressed following a prior platinum-based therapy and who meet entry criteria define above will be eligible for the study. Available patients will be enrolled without regard to race or ethnicity, but every effort will be made to include women and minorities in the study. Participation is voluntary.

Potential research subjects will be identified by a member of the patient's treatment team or the protocol investigator. If the investigator is a member of the treatment team, he or she will screen their patients' medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. The consenting physician will inform patients of their diagnosis, current treatment options, including standard treatment, and the risks, benefits and experimental nature of this treatment program. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC or JHU in order to further assess eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligible and to contact the patient regarding study enrollment. If the patient turns out to be ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment

team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened, and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3) handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

8.1 PRETREATMENT EVALUATION

To be completed upon acceptance signature on ICF and within 28 days of initiating treatment (unless a different timeframe is required per the specific item):

- History and physical examination (including patient characteristics)
- Concomitant medications
- Clinical examination (including tumor assessment)
- ECOG Performance Status
- Serum pregnancy test for women of childbearing potential (obtained at baseline)
- Serum or urine pregnancy test for women of childbearing potential (needs to be obtained on the start date of each treatment cycle)
- Blood biochemistry and complete blood count (CBC), needs to be within 14 days of initiating treatment
- Comprehensive metabolic panel
- Urinalysis
- ECG. 12-lead electrocardiogram for measurement of corrected QT interval according to the Fridericia formula: electrocardiogram must be registered at rest. For any EKG assessment, if the initial EKG shows a prolonged QTc, then two additional EKGs will be obtained, resulting in three specimens taken after a space of 1 minute, and the mean of the 3 EKGs will be used to determine eligibility and for grading of TRAEs.
- Hepatitis B testing (HBV surface antigen and core antibody) if not previously performed (at any time)
- Hepatitis C testing (HCV antibody) if not previously performed (at any time)
- HIV antibody testing if not previously performed (at any time)
- CT scan of chest, abdomen and pelvis with and without IV contrast
    - For patients with allergy to iodinated IV contrast, pre-medication with steroids is acceptable. Alternatively, MRIs with and without contrast can be obtained.
- Brain MRI with and without IV contrast
- IHC testing of SLFN11 and H3K27me3 of any tumor tissue obtained prior to treatment with DS-3201b.
- Confirmation of sufficient pre-treatment tissue for correlative analyses using bulk RNA sequencing. Archival tissue may be used. If there is insufficient tissue for bulk RNA testing (testing requires 20 unstained slides or a paraffin block), then a repeat biopsy will be required prior to the initiation of study treatment.

9.1 TREATMENT/INTERVENTION PLAN

Phase I Dose-Escalation: There will be a 7-day safety run-in starting prior to C1D1 with only DS-3201b administered orally daily. Starting on C1D1, irinotecan will be administered

intravenously at a fixed dose of 125 mg/m^2 on days 1 and 8 every 21 days. DS-3201b will continue to be administered orally daily. Cohorts of patients will be enrolled following a 3+3 dose escalation design based on the table below starting on C1D1 (Table 2). In the first cohort, study treatment initiation will be staggered. A delay of at least 7 days will occur between each patient dosed in the first 3-patient cohort. In subsequent 3-patient cohorts, the study treatment can be started in the second and third patients one day after first administration in the first patient. Patients will be treated until disease progression or until unacceptable toxicity develops. There is no maximum number of cycles of study drugs that may be administered to each patient on the study. Dose-Escalation, which enrolled a total of 12 patients at MSK, is completed. Phase 1 of this study determined that the highest and safest dose of DS-3201b in patients was 100 mg daily.

Table 2.0 Phase I Dose-Escalation Schema of DS-3201b.

Dose Level	DS-3201b Dose	Irinotecan Dose
Level -1	50 mg once daily	125 mg/m^2 on day 1 and 8 every 21 days
Level 1 (Starting Dose)	100 mg once daily	125 mg/m^2 on day 1 and 8 every 21 days
Level 2	150 mg once daily	125 mg/m^2 on day 1 and 8 every 21 days
Level 3	200 mg once daily	125 mg/m^2 on day 1 and 8 every 21 days
Level 4	250 mg once daily	125 mg/m^2 on day 1 and 8 every 21 days
Level 5	300 mg once daily	125 mg/m^2 on day 1 and 8 every 21 days

Table 2.1 Dose Escalation Decision Rules.

Number of Patients with DLT at a Given Dose Level	Dose Escalation Decision Rule
0 of 3	Enter the next cohort (3 patients) at the next higher dose level. If this occurs at Level 5 (the highest dose level), then 3 more patients will be treated at Level 5 to confirm that Level 5 will be the MTD.
1 of 3	Enter next cohort (3 patients) at the same dose level. Out of these 3 patients: ▪ If 0 of 3 experience DLT, proceed to the next higher dose level. ▪ If 1 or more experience DLT, dose escalation will be stopped. 3 additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose level.
≥ 2 of 3	Dose escalation stopped. 3 additional patients will be entered at the next lower dose level if only 3 patients were treated previously at that dose level.

≤ 1 of 6	Recommended Phase II dose (RP2D) determined. 6 patients must be entered at the RP2D prior to proceeding to the Phase II study.

1. If 0 out of 3 patients treated at a given dose level experience a dose-limiting toxicity (DLT) as defined in Section 11.0, then the next group of 3 patients will be treated at that dose level +1.
2. If 1 of 3 patients treated at a given dose level experiences a DLT, then 3 more patients will be treated at this dose level to expand the cohort to 6 patients. If 1 out of these 6 patients experience DLT, then the dose level for the next 3 patients will be escalated to the next higher dose level. This process will continue until the maximum tolerated dose (MTD) is determined.
3. If ≥2 of 3-6 patients treated at a given dose level experience a DLT, then this dose level will be defined as the toxic dose level and dose escalation will stop.
4. The MTD is defined as the highest dose level at which ≤1 out of 6 patients experience a DLT. The MTD is typically the highest dose level right below the toxic dose level. The MTD will be the same dose as the recommended phase II dose (RP2D).
5. If 0 of 3 patients or ≤1 of 6 patients experience a DLT at Dose Level 5 and no toxic level is reached, then Dose Level 5 will be defined as the MTD.

Patients will be asked to complete a pill diary to document the date and dosage amount of each dose of DS-3201b. The DS-3201b dose will be administered without food (no food for at least 2 hours before and 1 hour after the dose). A missed dose of DS-3201b may be administered later that same day (until midnight), otherwise the dose will be recorded as a missed dose. No replacement dose is administered if the patient vomits after taking DS-3201b.

Phase II: Irinotecan will be administered intravenously at a fixed dose of 125 mg/m^2 on days 1 and 8 every 21 days. DS-3201b will be administered orally once daily at the RP2D defined by the phase I portion of this study. The 7-day safety run-in prior to C1D1 will still be utilized for every patient enrolled in Phase II of this study. Similar to the Phase I portion of the study, patients will be treated until disease progression or until unacceptable toxicity develops. There is no maximum number of cycles of study drugs that may be administered to each patient on the study.

Follow-up Period: Patients will be followed for survival every 3 months at routine clinic visits or via phone call if they are no longer being seen at MSKCC or JHU for a minimum of 2 years after the last dose of study drug treatment.

10.1 EVALUATION DURING TREATMENT/INTERVENTION

Each cycle will consistent of 21 days. All assessments, imaging and procedures will be performed within a window of +/- 4 days (with the exception of the pharmacokinetic assessments). The following assessments will apply to all patients enrolled in both the Phase I and Phase II portions of the study.

Table 3.0 Study Assessments.

	Baseline Labs[1]	Safety Run-In for DS-3201b	Cycle 1			Cycle 2		Cycle 3+		EOT
		7 days prior to C1D1 (C1D-7)	Day 1	Day 8	Day 15	Day 1	Day 8	Day 1	Day 8	
Informed consent	X									
History, physical exam, (including vital signs and performance status)	X	X	X	X	X	X	X	X	X	X
Medication review (both prior and concomitant)	X	X	X	X	X	X	X	X	X	X
Adverse events monitoring (both serious and all others)	X	X	X	X	X	X	X	X	X	X
Serum or urine pregnancy test (for women of childbearing potential). Serum test only at screening.	X (serum)	X	X			X		X		
CBC with differential	X	X	X	X	X	X	X	X	X	X
Comprehensive metabolic panel[2]	X	X	X	X	X	X	X	X	X	X
Urinalysis with microscopic analysis[3]	X		X			X		X		X
EKG	X		X	X		X	X	X	X	X
Hepatitis B, Hepatitis C and HIV antibody testing	X (if not done prior)									
Coagulation profile including fibrinogen	X									
Lipid profile	X									
CT chest abdomen and pelvis with contrast[4]	X							X[4]		
Brain MRI with and without contrast[4]	X							X[4]		
Research bloods for PDX engrafting in Rudin Lab (MSK		X				X				X

main campus patients only)[5]										
Research bloods for circulating tumor cell (CTC) analyses with EPIC Sciences[6]	X	X	X	X	X	X	X	X		X
Research bloods for cfDNA banking at MSKCC[7]	X	X	X	X	X	X	X	X		X
Tissue sample for study correlatives (archival or fresh tissue)[8]	X									
Tissue sample for study correlatives (fresh biopsy only)[8]								X		X[9]
DS-3201b Administration (daily)		X	X	X	X	X	X	X	X	
Irinotecan administration (Days 1 and 8 only)			X	X		X	X	X	X	
PK assessment[10]		X	X	X	X	X				

[1] All baseline testing needs to be obtained with 28 days of starting therapy. Exceptions include CBC, CMP, coagulation profile including fibrinogen, which must be obtained within 14 days.
[2] Includes electrolytes, BUN/creatinine, sodium, potassium, chloride, carbon dioxide, BUN/creatinine, calcium, glucose, AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, total protein, magnesium, phosphorus, LDH.
[3] Urinalysis will include assessments of turbidity and color, pH, specific gravity, protein, ketones, bilirubin, occult blood, nitrite, glucose, and leukocyte esterase. Urine microscopic analysis will include erythrocytes, leukocytes, bacteria, casts, and crystals.
[4] CT scans and brain MRIs will be obtained at the completion of every 2 cycles (approximately every six weeks).
[5] CTCs for PDX engrafting will only be collected from samples from patient's treatment at MSKCC main campus. Due to feasibility barriers with transporting samples, no patient samples from MSKCC Regional Care Centers or from JHU will be collected for this purpose. Each sample will include two 10 cc EDTA tubes to be transported on ice.
[6] CTCs for analysis by EPIC Sciences will be collected from all MSKCC sites and all JHU sites. Each sample will include one 10 cc Streck tube to be transported at room temperature.
[7] CTCs for banking at MSKCC will be collected from all MSKCC sites and all JHU sites. Each sample will include one 10 cc Streck tube to be transported at room temperature.
[8] Any fresh tissue biopsy will be performed ONLY if deemed medically safe by the institutional PI. There will be a window of +/- 4 days for the biopsy. The pre-treatment tissue sample can be archival if there is adequate tissue.
[9] Post-progression tissue biopsy is OPTIONAL.

[10] PK draws: There is a ± 15-minute window for PK blood draws. PK assessments will be obtained in both Phase I and Phase II. Please see Table 4 for the complete PK schedule. Each PK blood draw will include 5 cc of blood collection.

Table 4.0 Pharmacokinetics (PK) Schedule for DS-3201b (Phase I and Phase II)

Cycle and Day	Time point						
7 days prior to C1D1	0.5-hour post-dose	1-hour post-dose	2-hour post-dose	4-hour post-dose	6-hour post-dose	8-hour post-dose	
Cycle 1 Day 1	Pre-dose	0.5-hour post-dose	1-hour post-dose	2-hour post-dose	4-hour post-dose	6-hour post-dose	8-hour post-dose
Cycle 1 Day 8	Pre-dose						
Cycle 1 Day 15	Pre-dose	0.5-hour post-dose	1-hour post-dose	2-hour post-dose	4-hour post-dose	6-hour post-dose	8-hour post-dose
Cycle 2 Day 1	Pre-dose						

Correlative Studies:

Studies Using Tumor Tissue:

We will obtain mandatory on-treatment core biopsies at Cycle 3 Day 1 +/- 4 days. The Cycle 3 Day 1 biopsy may be canceled if deemed medically unsafe (e.g., prior biopsy resulting in pneumothorax or other complication, bleeding diathesis, etc.) by the PI. The end of trial (EOT) biopsy will be optional.

Biopsy Samples from MSKCC: For each biopsy, a minimum of 7 cores will be obtained, including 4 required cores and 3 optional cores. Core #1 will be sent to Surgical Pathology for confirmation of diagnosis, IHC for SLFN11 and H3K27me3, and for IMPACT testing (formalin). Core #2 will be sent to the Rudin Lab for PDX modeling (saline). Core #3 will be sent to the Rudin Lab for bulk RNA sequencing (flash frozen). Core #4 will be sent to Surgical Pathology for multiplex IHC to characterize T cells (formalin). Cores #5 and #6 will be sent to the Rudin Lab and used for single cell RNA sequencing (saline). Core #7 will be sent to Surgical Pathology for storage as a formalin-fixed paraffin-embedded (FFPE) block for further studies in the future (formalin).

Biopsy Samples from JHU: For each biopsy, a minimum of 4 required cores will be obtained, sent to JHU surgical pathology, and then shipped to MSKCC. JHU will process the samples and preserve the rest of the tissue in paraffin blocks, then ship to MSKCC according to standard institutional procedures. Core #1 will be sent to Surgical Pathology for confirmation of diagnosis, IHC for SLFN11 and H3K27me3, and for IMPACT testing (formalin). Core #2 will be sent to the Rudin Lab at MSKCC for bulk RNA sequencing (flash frozen). Core #3 will be sent to Surgical Pathology for multiplex IHC to characterize T cells (formalin). Core #4 will be sent to Surgical Pathology for storage as a formalin-fixed paraffin-embedded (FFPE) block for further studies in the future (formalin).

We hypothesize that EZH1/2 inhibition will increase SLFN11 expression and decrease the H3K27me3 repressive mark, leading to chemotherapy re-sensitization. SLFN11 and H3K27me3 will be measured by IHC on pretreatment and on treatment tissue as well as in peripheral blood circulating tumor cells at the designated study timepoints indicated above. Our prior studies suggest that the PDX lines most

sensitive to combination therapy with an EZH2 inhibitor have co-mutations in components of the SWI/SNF complex. To further explore this possible association, and in a broader exploratory effort to identify somatic alterations predictive of response or resistance to therapy, we will perform next generation sequencing (NGS) of pre-treatment, on-treatment and post-treatment (post-treatment only if available) tumors using the MSK-IMPACT platform. DNA will be isolated from tumor tissue as well as matched normal peripheral blood and will be subjected to hybridization capture deep-coverage NGS to detect somatic mutations in a panel of over 400 cancer-related genes, including small insertions and deletions, copy number alterations and chromosomal rearrangements. All mutations will be called against the patient's matched normal sample and mean overall coverage of sequencing depth ranged from 500 – 1000X.

Studies Using Peripheral Blood:

Samples for CTC analysis will be shipped within 48 hours of collection and analyzed at EPIC Sciences as there is currently no requisition for CTC samples to be analyzed inhouse at MSKCC or JHU. Analysis at Epic Science may include, but is not limited to, CTC enumeration, cancer cell sub-typing, specific biomarker expression levels, subcellular biomarker localization, genomics, heterogeneity of cancer expression, and clonality. During analysis of samples performed, it is possible that some patients whose tumors are analyzed through investigational "next-generation" profiling in a research (non-CLIA) environment will be found to have somatic or germline mutations in genes that are known to be associated with an increased risk of cancer or other diseases. It will be stated in the consent that the participants will not receive any specific results from research tests. The consent will tell participants that if they wish to have genetic testing done for personal reasons than they should make an appointment with the MSK Clinical Genetics Service or the appropriate service at JHU. Samples for CDX models will be sent to the Rudin Lab only at MSK. CDX models will not be collected for samples collected at JHU.

If in the course of this research a research finding is obtained that, in the opinion of the investigator, may be critical to the preventive care of the participant or their family, the investigator can communicate that finding to the IRB Genomic Advisory Panel (GAP). The finding will be reviewed by the GAP to determine whether the incidental finding should be discussed with the participant. For both MSK and JHU, in the event that the GAP determines that the finding should be discussed with the participant, and the participant has consented to be re-contacted, then the treating/consenting physician shall be contacted by the panel and asked to refer the participant to the Clinical Genetics Service for further discussion of the research finding.

The following information must be provided to GAP for review:

- Participant Name/MRN #
- Type of Biospecimen (tissue, blood, saliva)
- Incidental Finding
- Collection Protocol #

Contact: rtmgapirb@mskcc.org

11.1 TOXICITIES/SIDE EFFECTS

NCI Common Terminology Criteria (CTCAE): This study will utilize the most recent version of the Common Terminology Criteria version for Adverse Event (CTCAE) reporting (currently 5.0). A copy of the CTCAE can be downloaded from http://ctep.info.nih.gov. All treatment areas have access to a copy of the CTCAE.

All toxicities will be graded according to the CTCAE version 5.0. The grade of toxicity should be that seen despite maximal medical management. Attempts will be made as best as possible to determine whether the toxicity is related to irinotecan, DS-3201b, or the combination. Given overlap of some of the toxicities between DS-3201b and irinotecan, any toxicity that results in a dose adjustment in DS-3201b will be attributed only to DS-3201b. Any toxicity that results in a dose adjustment in irinotecan only will be attributed only to irinotecan. Any toxicity that results in dose adjustments in both DS-3201b and irinotecan will be attributed to both DS-3201b and irinotecan. Attribution of each toxicity to either DS-3201b and/or irinotecan will be determined by the treating physician if it is felt that the toxicity is at least possibly related to either one or both of the study drugs.

11.2 1 Definition of Treatment Emergent Adverse Events (TEAEs)

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or life-threatening suspected adverse reaction.

An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or serious suspected adverse reaction.

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction.

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

11.3 2 Possible Treatment Emergent Adverse Events (TEAEs) for DS-3201b

COMMON:

- Platelet Count Decreased
- Altered taste (Dysgeusia)
- Anemia
- Neutrophil Count Decreased
- Alopecia
- White Blood Cell Count Decreased
- Lymphocyte Count Decreased
- Diarrhea
- Nausea

OCCASIONAL (Uncommon):

- Alanine Aminotransferase Increased
- Aspartate Aminotransferase Increased
- Decreased Appetite
- Common cold (Nasopharyngitis)
- Cough
- Fatigue
- Arthralgia
- Dyspnea
- Fever (Pyrexia)
- Pruritus
- Rash
- Dry Skin
- Gamma-Glutamyltransferase Increased

RARE:

- None

Contraindications regarding the use of DS-3201b in human subjects have not been established. DS-3201b is contraindicated for subjects with known hypersensitivity to either the drug substance or inactive ingredients in the drug product. No overdosages have been reported to date.

ADVERSE EVENTS OF SPECIAL INTEREST (AESI):

AESI include hepatic events that meet the potential Hy's Law criteria (defined as an elevated ALT and/or AST ≥3 × ULN and an elevated TBL >2 × ULN, regardless if it is due to disease progression per investigator assessment, which may occur at different time points during the study conduct), and secondary malignancy, including lymphoid malignancy.

Combined Elevations of Aminotransferases and Bilirubin

Hepatic events (both serious and non-serious) that meet the potential Hy's Law criteria defined as an elevated (ALT and/or AST) ≥3 × ULN and an elevated TBL >2 × ULN, regardless if it is due to disease progression per investigator assessment, that may occur at different time points during the study conduct, should always be reported to the sponsor. These events must be reported by eCRF, with the investigator's assessment of seriousness, severity, causality, and a detailed narrative. These events should be reported within 24 hours of investigator's awareness of the event regardless of seriousness.

If the subject discontinues study drug due to liver enzyme abnormalities, the subject should have additional clinical and laboratory evaluations in order to determine the nature and severity of the potential liver injury (including follow-up ALT, AST, TBL (including fractional), ALP and relevant hepatitis serology).

Secondary Malignancy

A 3-month nonclinical toxicology study in rats administered DS-3201b showed the potential risks of developing lymphoid malignancies. A follow-up 3-month study in older rats performed to further understand the pathogenic mechanisms of this above finding in younger rats showed administration of DS-3201b to aged rats did not induce a lymphoma that had been previously observed with younger rats. In addition, no similar findings were noted in other 3-month animal toxicity studies of DS-3201b. In the ongoing clinical development program cases of secondary malignancies have been reported (see IB version 7 for additional details).

The treatment of subjects with an EZH2 inhibitor may increase the risk of developing a secondary T-cell malignancy. T-cell lymphomas have been observed in animals treated with DS-3201b and other agents that inhibit EZH2 in repeat-dose toxicology studies. A pediatric patient treated with an EZH2 inhibitor (tazemetostat) developed a secondary T-cell lymphoblastic lymphoma after approximately 15 months of therapy. A dose or duration of therapy at which agents that inhibit EZH2 would not increase the risk of a secondary T-cell malignancy is currently unknown.

Subjects receiving DS-3201b should further be monitored for signs and symptoms of toxicities suggestive of secondary malignancy. Any confirmed new diagnosis of secondary malignancy

should be reported as adverse events of special interest and reported to the sponsor in an expedited manner. Generally, these events should be reported as SAEs (with at least a seriousness criterion of important medical event, unless other criteria are met).

11.4 3 Possible Treatment Emergent Adverse Events (TEAEs) for Irinotecan Irinotecan

COMMON:

- Fever
- Alopecia
- Neutropenia
- Leukopenia
- Thrombocytopenia
- Anemia
- Diarrhea
- Abdominal pain
- Asthenia (weakness)
- Anorexia
- Nausea
- Vomiting
- Constipation
- Mucositis
- Pain
- Infection

OCCASIONAL

- Cholinergic like-syndrome (acute)
- Chills
- Dizziness
- Weight loss
- Stomatitis
- Cough
- Dyspnea
- Diaphoresis
- Kidney dysfunction

RARE AND SERIOUS

- Dehydration secondary to diarrhea
- Neutropenic fever
- Anaphylaxis; anaphylactoid reaction

- Renal Failure
- Pulmonary toxicity: Interstitial lung disease or events; discontinue therapy upon diagnosis

11.5 4 Dose Delays and Modifications for DS-3201b

During Cycle 1 of Phase I dose-escalation, which includes the initial 7 days of safety run-in from Day -7 to Day 0, dose delays and modifications for DS-3201b will not be used unless a DLT has been declared for purposes of determining the MTD. The outlined dose delays and modifications for both DS-3201b and irinotecan will be used in all patients in Phase I Cycle 1 if DLT has been declared, in all subsequent cycles of Phase I, and in all cycles of Phase II of this study. If toxicities are encountered, dosing adjustments and delays of DS-3201b and/or irinotecan will be made based on determination of the likely causative agent as outlined above in Sections 11.2 and 11.3. Determination of the likely causative agent will be dependent on the treating physician if they feel that the toxicity is at least possibly related to either or both of the study drugs.

Please refer to Table 2 in Section 9.0 for full details regarding the dose levels for DS-3201b. An abbreviated version of Table 2.0 is shown below for reference.

Dose Level	DS-3201b Dose
Level -1	50 mg once daily
Level 1(Starting Dose)	100 mg once daily
Level 2	150 mg once daily
Level 3	200 mg once daily
Level 4	250 mg once daily
Level 5	300 mg once daily

If dose level reduction below Level -1 is needed to manage toxicity due to DS-3201b, then study treatment with both DS-3201b and irinotecan will be permanently discontinued unless discussed with the study PI.

Table 5.0 Dose Delays and Modifications for Hematologic TEAEs

ADVERSE EVENT GRADE	DOSE MODIFICATION INSTRUCTIONS
≥Grade 4 neutropenia (<0.5 x 10^9/L per NCI CTCAE v5.0) lasting >7 days OR	• Interrupt administration of study drug DS-3201b up to 28 days. • Resume the study drug DS-3201b at the dose before interruption if lasting ≤7 days at a reduced dose (by 1 dose level). If lasting >7 days once resolved to ≤Grade 2

Febrile neutropenia ≥ Grade 3 OR neutropenia requiring supportive G-CSF therapy*	(neutrophil count ≥1.0 × 10^9/L) after discussion with PI and Daiichi. • If a second dose interruption is required for the same event, then the study drug DS-3201b may be reduced 1 additional dose level for subsequent cycles. Further dose reductions must be discussed with the study PI and Daiichi. If patient is already at the lowest dose of study drug DS-3201b, please discuss with the study PI and Daiichi regarding study continuation or discontinuation decision. • If ANC does not recover to ≥1.0 × 10^9/L within 28 days after interrupting study drug DS-3201b and reducing the dose, please discuss with the study PI and sponsor regarding study continuation or discontinuation decision. • Use of G-CSF is allowed for recurrent neutropenia as per treating physician discretion (except in DLT evaluation period in Phase I Dose Escalation). For patients at high-risk of neutropenia as per treatment physician's discretion, G-CSF can be used in the DLT evaluation period in Phase II. • For any dose delays greater than 28 days, decision regarding study continuation or discontinuation should be discussed with the study PI and sponsor.
Grade 4 Thrombocytopenia (<25 x 10^9/L) OR ≥Grade 3 Thrombocytopenia (<50 x 10^9/L) associated with ≥Grade 2 bleeding/ requiring transfusion OR Grade 3 thrombocytopenia (<50 x 10^9/L) lasting >7 days	• For Grade 4 Thrombocytopenia: Interrupt administration of study drug DS-3201b up to 28 days. • For Grade 4 Thrombocytopenia: Resume the study drug DS-3201b at a reduced dose (by 1 dose level) if thrombocytopenia recovers to ≤Grade 2 (platelet count ≥50 x 10^9/L) • For Grade 4 Thrombocytopenia: If a second dose interruption is required due to Grade 4 thrombocytopenia, then the study drug DS-3201b may be reduced 1 additional dose level for subsequent cycles. Further dose reductions must be discussed with the study PI and Daiichi. If patient is already at the lowest dose of study drug DS-3201b, please discuss with the study PI and Daiichi regarding study continuation or discontinuation decision. • For ≥Grade 3 Thrombocytopenia (<50 x 10^9/L) associated with ≥Grade 2 bleeding: First occurrence -

	Interrupt administration of study drug DS-3201b up to 28 days. Resume the study drug at a reduced dose (by 1 dose level) once resolved to ≤Grade 2 (platelet count ≥50 x 10^9/L) or return to baseline levels within 28 days after interrupting study drug, whether transfusion is given or not. The study drug DS-3201b may be resumed at the same dose after discussion with the study PI and Daiichi. • For ≥Grade 3 Thrombocytopenia (<50 x 10^9/L) associated with ≥Grade 2 bleeding: Second occurrence – Discontinue subject from the study • For ≥Grade 3 Thrombocytopenia (<50 x 10^9/L) lasting >7 days: First occurrence - Interrupt administration of study drug DS-3201b up to 28 days. Resume the study drug DS-3201b at a reduced dose (by 1 dose level) once resolved to ≤Grade 2 (platelet count ≥50 x 10^9/L) or return to baseline levels within 28 days after interrupting study drug • For ≥Grade 3 Thrombocytopenia (<50 x 10^9/L) lasting >7 days: Second occurrence – Interrupt administration of study drug DS-3201b up to 28 days. Resume the study drug at a reduced dose (by 1 dose level) once resolved to ≤Grade 2 (platelet count ≥50 x 10^9/L) or return to baseline levels within 28 days after interrupting study drug • For ≥Grade 3 Thrombocytopenia (<50 x 10^9/L) lasting >7 days: Third occurrence - Discontinue subject from the study • For any dose delays greater than 28 days, decision regarding study continuation or discontinuation should be discussed with the study PI and sponsor.
≥Grade 3 anemia (<8.0 g/dL) requiring transfusion	• Interrupt administration of study drug DS-3201b up to 28 days. • Resume the study drug DS-3201b at the dose before interruption once resolved to ≤Grade 2 (hemoglobin levels recovered to ≥8.0 g/dL) at least 7 days since transfusion, or baseline value within 28 days after interrupting study drug, or reduce 1 dose level with after discussion with study PI and Daiichi. • If a second dose interruption is required for the same event, then decrease study drug DS-3201b dose by 1

	dose level for subsequent cycles. Further dose reductions must be discussed with the study PI and sponsor. If patient is already at the lowest dose of study drug, please discuss with the study PI and Daiichi regarding study continuation or discontinuation decision. • Transfusion of red blood cells as per treating physician discretion is allowed. • For any dose delays greater than 28 days, decision regarding study continuation or discontinuation should be discussed with the study PI and Daiichi.

*Please see Section 11.7 for more details on the use of G-CSF in the setting of severe neutropenia or neutropenic fever.

Dose Modifications with Concomitant Strong CYP3A Inhibitors and/or P-gp Inhibitors

When drugs with strong CYP3A inhibitory effect and/or P-gp inhibitory effect are coadministered, the dose of the study drug should be reduced according to table 5.1. The dose of the study drug should be returned to the previous dose level that the subject was given after 3 days from the last dose of the concomitant strong CYP3A inhibitors and/or P-gp inhibitors.

Table 5.1 Dose Delays and Modifications for Concomitant Strong CYP3A Inhibitors and/or P-gp Inhibitors

Inhibitor	DS-3201b Dose	
	200 mg Once Daily	150 or 100 mg Once Daily*
Strong CYP3A inhibitors	Reduce the dose of the study drug to 100 mg once daily	Reduce the dose off the study drug to 50mg once daily
P-gp inhibitors	Reduce the dose of the study drug to 100 mg once daily	Reduce the dose off the study drug to 50mg once daily
Drugs having a strong CYP3A inhibitory effect and a P-gp inhibitory effect	Reduce the dose off the study drug to 50mg once daily	Interrupt the study drug

CYP3A = cytochrome P4503A; P-gp = P-glycoprotein
*When the dose of study drug DS-3201b is 150mg or 100mg once daily, the investigator should consult Daiichi's medical monitor before further reduction of the dose due to concomitant use of strong CYP3A or/and P-gp inhibitors.

Table 6.0 Dose Delays and Modifications for All Other Non-Hematologic TEAEs

Toxicity Grade	Modification instructions
QTc Grade 3 (QTc >500 ms on 2 separate ECGs, or >60 ms change from baseline, as the average from triplicate), regardless of causality OR Grade 4 (Torsade de Pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia), regardless of causality	• For Grade 3 QTc: Interrupt administration of study drug DS-3201b immediately • For Grade 3 QTc: Check and address any potentially contributing factors: ○ Check and correct electrolytes (potassium, calcium, and magnesium) • For Grade 3 QTc: If possible, stop any concomitant medications that prolong QTc interval • For Grade 3 QTc: Once resolved to ≤Grade 1 (QTc ≤ 480 ms, as the average from triplicate) the study drug DS-3201b may be resumed. • For Grade 3 QTc: If causality is attributed to the study drug DS-3201b, reduce dose by 1 dose level in subsequent cycles • For Grade 3 QTc: If the QTcF increase is assessed to be attributed to a cause other than the study drug DS-3201b, resume the study drug DS-3201b at the dose level before interruption, or at a reduced dose (by 1 dose level) but the subject must be monitored closely for QT prolongation for the first cycle at the increased dose. • For Grade 3 QTc: If a second dose interruption is required due to Grade 3 QTc prolongation, discontinue subject from the study • For Grade 3 QTc: For any dose delays greater than 28 days, decision regarding study continuation or discontinuation should be discussed with the study PI and Daiichi. • For Grade 4 (Torsade de Pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia), regardless of causality: Interrupt the study drug DS-3201b immediately • For Grade 4 (Torsade de Pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia), regardless of causality: Determine if there are any attributing factors such as electrolytes (potassium, calcium and magnesium), concomitant medications, or other factors • For Grade 4 (Torsade de Pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia): If causality is attributed to the study drug DS-3201b, discontinue subject from study • For Grade 4 (Torsade de Pointes, polymorphic ventricular tachycardia, or signs/symptoms of serious arrhythmia): If causality is not attributed to the study drug DS-3201b, study drug administration of DS-3201b can resume at a reduced dose (by 1 dose level) once resolved to ≤Grade 1 (QTc ≤ 480 ms, as the average from triplicate).
Other Non-Laboratory Adverse	• Interrupt administration of study drug DS-3201b up to 28 days.

Events (drug related Grade 3 that require treatment)	• Resume the study drug DS-3201b at the dose before interruption once resolved to ≤Grade 1 or baseline value within 28 days after interrupting study drug. • If a second dose interruption is required for the same drug-related adverse event, then decrease study drug DS-3201b dose by 1 dose level for subsequent cycles. Further dose reductions must be discussed with the study PI and sponsor. If patient is already at the lowest dose of study drug, please discuss with the study PI and Daiichi regarding study continuation or discontinuation decision. Exceptions: o Fatigue (DS-3201b related), Grade 3, that improves within 72 hours after onset o Nausea, vomiting, anorexia, or diarrhea (DS-3201b related), Grade 3, that improves to ≤Grade 2 within 72 hours after onset with appropriate supportive therapy
Other Non-Laboratory Adverse Events (Grade 4, regardless of causality)	• Interrupt administration of study drug DS-3201b up to 28 days. • If causality is attributed to study drug DS-3201b, resume the study drug DS-3201b at a reduced dose (by 1 dose level) for the subsequent cycles once resolved to ≤Grade 1 or baseline condition. • If causality is not attributed to the study drug DS-3201b, resume the study drug DS-3201b at the dose before interruption or at a reduced dose (by 1 dose level). • If second dose interruption is required due to the same drug-related adverse event, discontinue subject from the study. • For any dose delays greater than 28 days, decision regarding study continuation or discontinuation should be discussed with the study PI and sponsor.
Other Laboratory Adverse Events (DS-3201b drug related Grade 3 that require treatment)	• Interrupt administration of study drug DS-3201b up to 28 days. • Resume the study drug DS-3201b at the dose before interruption once resolved to ≤Grade 1 or baseline value within 28 days after interrupting study drug. • If a second dose interruption is required for the same drug-related adverse event, then decrease study drug DS-3201b dose by 1 dose level for subsequent cycles. Further dose reductions must be discussed with the study PI and sponsor. If patient is already at the lowest dose of study drug, please discuss with the study PI and Daiichi regarding study continuation or discontinuation decision. Exceptions: o Transient laboratory abnormalities (DS-3201b-related) that do not involve associated clinical signs or symptoms and that resolve within 72 hours after onset

	• For any dose delays greater than 28 days, decision regarding study continuation or discontinuation should be discussed with the study PI and sponsor.
Other Laboratory Adverse Events (DS-3201b drug related Grade 4)	• Interrupt administration of study drug DS-3201b up to 28 days. • Resume the study drug DS-3201b at a reduced dose (by 1 dose level) for the subsequent cycles once resolved to ≤Grade 1 or baseline condition • If a second dose interruption is required for the same drug-related adverse event, discontinue subject from study • Subjects who experience a ≥Grade 3 laboratory AE who are, in the opinion of the investigator, benefiting from treatment may be allowed to continue study drug.
Other Non-Laboratory and Laboratory Adverse Events (regardless of causality, any AE, lab abnormality or intercurrent illness that presents a substantial clinical risk to the subject with continued dosing per the investigator's opinion)	• Interrupt administration of study drug DS-3201b until there is no longer a substantial clinical risk to the subject with continued dosing of the study drug DS-3201b per the investigator's opinion • Resume the study drug DS-3201b at the same dose level
AEs Grade 1-2	• Proceed with full-dose treatment of all agents.

If DS-3201b needs to be held for any TEAEs as above, irinotecan should be held as well. When both study drugs are held for any particular visit due to TEAEs, counting of dose cycles will held until their TEAEs have resolved or improved enough to meet protocol guidelines to restart treatment with both study drugs. If both drugs are held longer than 1 cycle (21 days), the treating physician must discuss eligibility for the patient to continue treatment on study with the study PI.

11.6 Dose Delays and Modifications for Irinotecan

During Cycle 1 of Phase I dose-escalation, which includes the initial 7 days of safety run-in from Day -7 to Day 0, dose delays and dose modifications of irinotecan will not be used unless a DLT has been declared for purposes of determining the MTD. The outlined dose delays and modifications for both DS-3201b and irinotecan will be used in all patients in Phase I Cycle 1 if DLT has been declared, in all subsequent cycles of Phase I, and in all cycles of Phase II of this study. If toxicities are encountered, dosing adjustments and delays of DS-3201b and/or irinotecan will be made based on determination of the likely causative agent as outlined above

in Sections 11.2 and 11.3. Determination of the likely causative agent will be dependent on the treating physician if they feel that the toxicity is at least possibly related to either or both of the study drugs.

Usual clinical practice for dose delay and modification of irinotecan will be used, and dose adjustments will occur independent of DS-3201b dosing adjustments.

Patients should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm^3, and the platelet count has recovered to ≥100,000/mm^3, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing therapy.

If both study drugs are held for any particular visit due to TEAEs, then the patient would restart that same visit when their TEAEs have resolved or improved enough to meet protocol guidelines to restart treatment with either one or both study drugs.

If irinotecan needs to be held for any TEAEs as above, patients will have the option to continue DS-3201b as long as the TEAE is not also attributed to DS-3201b. However, counting of dose cycles will held until their TEAEs have resolved or improved enough to meet protocol guidelines to restart treatment with irinotecan, regardless of whether patient continues DS-3201b. If both drugs are held longer than 1 cycle (21 days), the treating physician must discuss eligibility for the patient to continue treatment on study with the study PI.

When administered in combination with other agents, or as a single agent, a reduction in the starting dose by at least one level of irinotecan should be considered for patients known to be homozygous for the UGT1A1*28 allele.

If dose level reduction below Level -2 is needed to manage toxicity due to irinotecan, then study treatment with both DS-3201b and irinotecan will be permanently discontinued.

Table **7.0 Dose** Levels for Irinotecan[a]

Starting Dose	125 mg/m^2
Dose Level -1	100 mg/m^2
Dose Level -2	75 mg/m^2

[a] As per standardized prescribing information in the United States.

Table 8.0 Recommended Dose Modifications for Irinotecan in Combination-Regimens

CTCAE v5.0 Toxicity Grade	During a Cycle of Therapy	At the Start of Subsequent Cycles of Therapy[a]
No toxicity	Maintain dose level	Maintain dose level

Neutropenia*		
1 (1500 to 1999/mm^3)	Maintain dose level	Maintain dose level
2 (1000 to 1499/mm^3)	↓ 1 dose level	Maintain dose level
3 (500 to 999/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
4 (<500/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels
Neutropenic fever	Omit dose until resolved, then ↓ 2 dose levels	
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea[c]		
1 (≤4 stools/day > pretx[b])	Delay dose until resolved to baseline, then give same dose	Maintain dose level
2 (4-6 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 1 dose level	Maintain dose level
3 (≥7 stools/day > pretx; hospitalization indicated)	Omit dose until resolved to baseline, then ↓ 1 dose level	↓ 1 dose level
4 (life-threatening; urgent intervention indicated	Omit dose until resolved to baseline, then ↓ 2 dose levels	↓ 2 dose levels
Other non-hematologic toxicities[d]		
1	Maintain dose level	Maintain dose level
2	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level	Maintain dose level
3	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
4	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels

*Please see Section 11.7 for more details on the use of G-CSF in the setting of severe neutropenia or neutropenic fever.

[a] Relative to the starting dose in the previous cycle.
[b] Pretreatment.
[c] Loperamide as needed can be administered to the patient for relief of symptoms once the toxicity grade has been determined. The dosing and frequency of loperamide can vary per patient and will be determined by the treating physician.
[d] Excludes alopecia, anorexia, asthenia.

11.7 Management Guidelines for Irinotecan-Induced Diarrhea

Early diarrhea (occurring during or shortly after infusion of irinotecan) is usually transient and infrequently severe. It may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Bradycardia may also occur. Early diarrhea and other cholinergic

symptoms may be prevented or treated. Prophylactic or therapeutic administration of 0.25 mg to 1 mg of intravenous or subcutaneous atropine (unless clinically contraindicated) can be used if this occurs.

Late diarrhea (generally occurring more than 24 hours after administration of irinotecan) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. In the clinical studies, the median time to the onset of late diarrhea was 5 days with 3-week dosing and 11 days with weekly dosing. Late diarrhea can be complicated by colitis, ulceration, bleeding, ileus, obstruction, and infection. Cases of megacolon and intestinal perforation have been reported. Patients should have loperamide readily available to begin treatment for late diarrhea. Patients will be instructed to begin loperamide at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normal. One dosage regimen for loperamide is 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. Loperamide is not recommended to be used for more than 48 consecutive hours at these doses because of the risk of paralytic ileus. During the night, the patient may take 4 mg of loperamide every 4 hours.

11.8 7 Use of Granulocyte Colony-Stimulating Factors (G-CSF)

According to guidelines from the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO), primary prophylaxis with granulocyte colony-stimulating factors (G-CSF) is not allowed. However, secondary prophylaxis with G-CSF for neutropenia as per usual standard clinical practice is allowed, even during the initial DLT evaluation period (safety run-in + Cycle 1).[29,30]

11.9 8 Definitions of Dose-Limiting Toxicity (DLT)

Although all toxicities will be closely monitored and graded throughout the entire study treatment, only toxicities occurring during Cycle 1 of treatment (initial 7-day safety run-in plus the first 21 days) that meet the definition of DLT will influence the determination of MTD. Any toxicity during Cycle 1 of treatment that meets the definition of DLT as described below, whether it is attributed to either DS-3201b or irinotecan or both, will affect the determination of MTD during the Phase I portion of the study.

Dose-limiting toxicity (DLT) is defined as a clinically significant non-hematologic treatment-emergent adverse event (TEAE) or abnormal clinical laboratory value that is clearly **NOT** related to disease progression, intercurrent illness, and occurring during the DLT evaluation period (safety run-in + Cycle 1) on study that meets any of the following criteria:

Hematologic dose-limiting toxicity is defined as any:

- All Grade ≥3 adverse event that are at least possibly related to study treatment with the following exceptions:
    - Grade 4 neutropenia lasting less than 7 consecutive days.
    - Grade 3 neutropenia without fever and/or infection where fever is an oral temperature ≥ 38.5˚C.

- Grade 4 thrombocytopenia (platelet count<25,000/mm^3) lasting less than 7 consecutive days. *However, a platelet count <10,000/mm^3 at any time for any duration will count as a DLT.*
- Grade 3 thrombocytopenia without bleeding.

Non-Hematologic dose-limiting toxicity is defined as any:

- All Grade ≥3 adverse events that are at least possibly related to study treatment with the following exceptions:
  - Grade 3 aspartate aminotransferase AST (SGOT) or alanine aminotransferase (ALT) (SGPT) or bilirubin for ≤ 7 days.
  - Grade 3 or 4 nausea, vomiting, and diarrhea that do not require hospitalization or total parenteral nutrition (TPN) support and can be managed with supportive care to ≤ Grade 2 within 48 hours.
  - Electrolyte abnormalities that are corrected to ≤ Grade 2 within 24 hours.
  - Alopecia and study drug-related fever (without Grade 3 neutropenia) will not constitute DLT.
  - Any Grade 5 adverse event proven to be clearly and incontrovertibly related to disease progression or intercurrent illness and not possibly related to study drug DS-3201b.

If the treating physician determines that a TEAE occurring during the DLT evaluation period which met the definition for DLT is due to underlying disease progression or intercurrent illness and NOT due to study drug effect from either DS-3201b and irinotecan, a final determination regarding DLT determination will be discussed with the study PI.

Patients who are unable to complete at least 75% of the prescribed dose (i.e., 21 days) of DS-3201b and irinotecan during the DLT evaluation period (safety run-in + Cycle 1) due to non-disease-related ≥ Grade 2 adverse events will be considered to have a DLT. These same DLT definitions detailed above in this section will also apply for the entire duration of the Phase II portion of the study as it pertains to the toxicity stopping rule (please see Section 14.0 for more details).

11.10 9 Excluded Concomitant Medications and Procedures

Because DS-3201b is primarily metabolized by the liver, the following medications and procedures are prohibited during the study:

- Administration of other antineoplastic agents during the study is prohibited.
- Strong CYP3A4/5 inhibitors / inducers, and/or P-gp inhibitors, grapefruit juice, and St. John's wort are prohibited except when prophylactic administration is required for the treatment of symptoms such as infection.
- If strong or moderate CYP3A inducers are medically essential to use as supportive care, concomitant use of moderate and strong CYP3A inducers is permissible after the first dose of DS-3201b. In this case, dose interruption of DS-3201b tosylate is not needed. Avoid the concomitant use as much as possible because drugs having

moderate or strong CYP3A-inducing properties may decrease the plasma concentration of DS-3201b.

- Consumption of herbs/fruits that may have an influence on PK of DS-3201b such as St. John's wort, star fruit, Seville orange or Seville orange-containing foods and beverages, grapefruit or grapefruit-containing food or beverages from 14 days prior to the start of the study and throughout the entire study.

CYP3A Inducers and Inhibitors can be found at the following site:
http://medicine.iupui.edu/clinpharm/ddis/table.aspx

Prohibited Concomitant Medications Due to Known Risk of QT Prolongation
The following drugs are known to prolong QT and to be clearly associated with Torsades de Pointes (TdP). Patients are encouraged to discontinue or refrain from starting any of the following medications while on study with the exception of ondansetron, which is part of the standard pre-medications for irinotecan infusion. For all of the medications listed below,

patients are still allowed to continue or start these medications if truly medically necessary or as part of routine chemotherapy regimen.

- amiodarone
- anagrelide
- azithromycin
- chloroquine
- chlorpromazine
- cilostazol
- ciprofloxacin
- citalopram
- clarithromycin
- disopyramide
- dofetilide
- donepezil
- dronedarone
- droperidol
- erythromycin
- escitalopram
- flecainide
- fluconazole
- haloperidol
- ibutilide
- levofloxacin
- methadone
- moxifloxacin
- ondansetron*
- pentamidine
- pimozide
- procainmide
- propofol
- quinidine
- sevoflurane
- sotalol
- thioridazine

*Excluded from the list of prohibited medicines due to its inclusion as a part of the standard pre-medications for irinotecan infusion

This full list of medications can be found at the following site:
https://crediblemeds.org/new-drug-list/

11.11 Precautions and Restrictions

Pregnancy

It is not known what effects DS-3201b has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients

of reproductive age group and male patients should use highly effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If she is of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception, at the same time, from the time of signing the informed consent through 6 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

Female patients must agree to not donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug(s).

Male patients, even if surgically sterilized (i.e., status post vasectomy), must agree to 1 of the following:

- Practice highly effective barrier contraception during the entire study treatment period and through 6 months after the last dose of study drug, or
- Practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods for the female partner] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Male patients must agree to not donate sperm during the course of this study or 6 months after receiving their last dose of study drug(s).

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Determining the Safety, Tolerability, MTD and RP2D of DS-3201b in Combination with Irinotecan

The Common Terminology Criteria for Adverse Events (CTCAE) 5.0 will be used to determine all adverse events and dose-limiting toxicities.

Determining the Objective Response Rate (ORR) to Treatment with DS-3201b at the RP2D in Combination with Irinotecan

The Response Evaluation Criteria in Solid Tumors Group (RECIST v1.1) criteria will be used to evaluate the response to treatment.[29]

Target Lesions

Change in disease will be assessed by repeat chest/abdomen/pelvis CTs at baseline and at every other cycle thereafter.

Complete Response (CR): Complete absence of all signs of disease without any new lesions or disease-related symptoms.

Partial Response (PR): A reduction of ≥ 30% as compared to the baseline measurement.

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum the longest diameter (LD) since the treatment started.

Progressive Disease (PD): An increase of ≥ 20% over the nadir measurement is defined as progressive disease.

Non-Target Lesions

All other lesions (or sites of disease) not included in the “target lesions,” including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and truly non-measurable lesions, should be identified as non-target lesions and recorded at baseline. Measurements are not required, and these lesions should be followed as defined below.

Lesions that are considered non-measurable include bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Complete response: Disappearance of all non-target lesions.

Non-complete response/Non-progression: Persistence of one or more non-target lesions.

Progression: Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment on Cycle 1 Day 1 until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). If patients remain on treatment with partial response or stable disease past 6 months from the date of Cycle 1 Day 1, the first 6 months of treatment will be used to evaluate the primary endpoint of best overall response. In general, the patient’s best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

Conditions that may define early death include patients that have died without documentation of disease progression and before it was time to conduct the first tumor reassessment. Inevaluable patients include those who have received protocol treatment but did not have any follow-up assessment completed before initiation of alternative treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

Guidelines for Evaluation of Measurable Disease

All patients in this study will be getting a baseline CT scan to include the target lesion (Table 3).

Confirmation Measurement/Duration of Response or Duration of Stable Disease

In patients who are confirmed to have CR/PR, the duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

In patients who are confirmed to have stable disease, the duration of stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Determining the Progression-Free Survival (PFS) and Overall Survival (OS)

Kaplan-Meier analyses will be used to estimate the PFS and OS.

Correlative Studies

Descriptive analyses as described in Section 10.0 will be used to report all correlative testing results obtained from this study.

13.1 CRITERIA FOR REMOVAL FROM STUDY

Study treatments will be discontinued for all patients in the following situations:

- Disease progression
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Unacceptable adverse event(s)
- Inability of patient to comply with study requirements

In addition to the above, patients may withdraw from the study at any time for any reason. Once decision has been made to stop study drug treatment, the treating physician will report on the date of last treatment and the reason for cessation of study drug treatments. Patients who are no longer receiving study drugs will still be followed clinically for toxicity and survival endpoints, unless the patient explicitly declines.

Procedures for Study Withdrawal

Withdrawal procedures will include an end-of-treatment (EOT) visit within 30 days of the last dose of study drug.

Replacement of Patients

During both Phase I and II of the study (dose-escalation), any patient who discontinues treatment before completing the first cycle of treatment (C1D21) will be considered not evaluable for DLT and will be replaced. Completion of the first cycle of treatment is defined by completion of at least 75% of both study drugs during the initial 28-Day DLT evaluation window (7-day safety run-in + 21-day Cycle 1). The only exception are patients who are unable to complete at least 75% of the prescribed dose of DS-3201b and irinotecan during the DLT evaluation period (safety run-in + Cycle 1) due to non-disease-related ≥ Grade 2 adverse events; these patients will be considered to have a DLT and will not be replaced. Please see Section 11.0 for the full definition of DLTs.

During Phase II of the study, any patient who discontinues treatment before completing two cycles of treatment but has completed the DLT evaluation period will still undergo the first repeat CT scan prior to their scheduled C3D1. If a CT scan evaluation is unable to be obtained, these patients will not be replaced, and they will be considered as not deriving clinical benefit from the study drug.

Re-screening of Patients

Any patient who fails to meet eligibility criteria upon initial screening can undergo re-screening at a later time. The initial screening information, including the reason why the subject was initially ineligible, will be recorded. No data from the initial evaluation will be entered into the clinical database for patients who undergo re-screening and are ultimately enrolled onto the study.

Continuation of Treatment for Patients

Any patient who continues to derive benefit from the study drug combination with either a partial response or stable disease will be eligible to continue study treatment until unacceptable toxicity or progression of disease.

14.0 BIOSTATISTICS

Dose-Escalation Phase I:

We will employ a standard 3-by-3 dose-escalation phase I study design to investigate the maximum tolerated dose (MTD) of DS-3201b in combination with fixed dose irinotecan. The study population for Phase I dose-escalation will include only patients who complete at least 1 full cycle of treatment (including the initial 7-day safety run-in and the complete 21-days of Cycle 1); only these patients will be considered evaluable for DLT and determination of the MTD. Patients who do not receive at least 1 full cycle of study drug for reasons other than toxicity and who also do not meet any definition of DLT will be excluded from analysis and will be replaced.

DS-3201b will be administered at the dose levels of 25%, 50%, 75%, 100%, 125% and 150% of the predicted MTD (200 mg daily). Patients will be assessed for toxicity weekly with cycle 1, and then on day 1 of each subsequent cycle. Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment (initial 7-day safety run-in plus the first 21 days) will necessarily influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Patients will be monitored on day 1 of each subsequent cycle of therapy for treatment emergent adverse events.

If none of the initial cohort of 3 has a DLT, the dose level will be escalated. If one of three patients has a DLT, that dose level will be expanded with 3 more patients. Dose escalation will stop if ≥2 DLTs are seen at a dose level, whether out of 3 or 6 patients. Please see section 11.5 for a full definition of DLTs. The MTD is defined as the highest dose level at which no more than 1 of the 6 patients at that level has a DLT. If no patient in the current 3-patient cohort has a DLT and the dose level is under final consideration for the MTD, an additional three patients will be treated at that level for confirmation. For the Phase I portion of this study, the minimum sample size is 4 patients, and the maximum sample size is 36 patients. The 6 patients treated at the established MTD in Phase I will also count as the initial 6 patients in the Phase II portion of the study.

The probability of escalation is as follows:

True DLT rate	5%	10%	15%	20%	25%	30%	40%	50%
Probability of escalation	0.97	0.91	0.81	0.71	0.60	0.49	0.31	0.17

Adverse events will be graded according to the CTCAE version 5.0, with patients being assessed weekly while on the treatment. Data on pharmacokinetics (PK) of DS-3201b after DS-3201b administered alone or in combination with irinotecan will be collected 7 Days prior to C1D1, on C1D1, on C1D8, on C1D15 and on C2D15 for each patient in the phase I component of this study. Standard plasma PK parameters for each of the above timepoints will include the maximum plasma concentration (Cmax), minimum plasma concentration (Cmin), and time to maximum plasma concentration (Tmax). The area under the plasma concentration versus time curve (AUC) for DS-3201b will be estimated using non-compartmental analysis and/or a population PK approach.

Phase II:

The second phase of this study will be an open-label, single arm, phase II study of DS-3201b at the established RP2D in combination with fixed dose irinotecan. The primary objective of this study is to assess efficacy, ORR defined as CR+PR measured by RECIST v1.1.

Historical control:

We base the sample size calculation on the estimated response rate of 16% as a benchmark, which we derive from the reported study from Le Chevalier et al.[30] A two-stage Simon's minimax design will be employed to test the null hypothesis that the true ORR is 16% versus the alternative hypothesis that the true ORR is at least 35% with a type I error of 0.05 and a power of 0.8. In the first stage, 16 patients will be accrued. The first 6 patients out of this initial 16-patient cohort will be the 6 patients treated at MTD in Phase I.

Efficacy will be measured by RECIST v1.1 assessed response to therapy. If there are 2 or fewer responses in these 16 patients, the study will be stopped early for futility. The probability of stopping the study early for futility is 52% per the two-stage Simon's minimax design. If at least 3 patients show response in this first stage, we will request permission from the sponsor to enroll an additional 15 patients in the second stage. At the end of the study, if ≥9 patients out of total of 31 enrolled patients show a partial response or a complete response, then further investigation of DS-3201b in combination with irinotecan will be considered worthwhile.

Study enrollment of the 17th patient will be suspended until the determination of the first-stage results, unless the benchmark of 3 patients with radiographic response is achieved by then. All patients will be included in the primary analysis, even if there are major protocol deviations. Patients are considered non-responses (PD) if they are not evaluable (including if CT scan evaluation not available) or died during the study. This study requires accrual of a minimum of 16 patients and up to a maximum of 31 patients if the cohort is expanded to the second stage. The accrual time is estimated to be between 10-24 months at the rate of 3 patients per month and a likely planned 4 months suspension between the first and second stages of this Phase II study.

To protect patients from excessive toxicity, a stopping rule for toxicity will be implemented during Phase II. Since the 6 patients treated at RP2D in Phase I will be included in the Phase II portion of the study, the early stopping rule for toxicity is calculated based on 31-

6=25 newly recruited patients. This toxicity rule will apply for the entire duration of the Phase II portion of the study.

Stopping rule:

Number of recruited patients	5	10	15	20	25
Number of DLT to stop the trial	≥2	≥3	≥3	≥3	≥4

Operating characteristics of the stopping rule:

True DLT rate	0.05	0.09	0.13	0.17	0.21	0.25
Probability of stopping the trial	0.09	0.30	0.54	0.74	0.87	0.94

The ORR is defined as the proportion of patients with CR, or PR at any reassessment after start based on RECIST v1.1 criterion. The time frame for evaluating the primary endpoint of ORR for this portion of the study will be 6 months from the date of Cycle 1 Day 1 for each patient. The ORR and corresponding exact 95% CI will be reported. Progression-free survival will be measured from the start of treatment until the documentation of disease progression or death due to any cause, whichever occurs first, and censored on the date of last tumor assessment. In addition, we will document absence of tumor progression for patients who are still alive prior to data cutoff, dropout, or the initiation of alternate anticancer treatment. Overall survival will be determined as the time from the start of DS-3201b treatment to death, and censored on the last follow-up date. PFS and OS will be evaluated using the Kaplan-Meier method. The duration of response (for those with CR or PR) and durable of stable disease while on treatment (for those with SD) will also be evaluated using the Kaplan-Meier method.

All recorded toxicity data and adverse events of DS-3201b will be listed and tabulated by system organ class, preferred term and treatment. Any significant vital signs and clinical laboratory test results will be listed and summarized. Any significant physical examination findings and clinical laboratory results will be listed.

As secondary objectives, we will explore downstream mechanistic biomarkers of DS-3201b including SLFN11 expression and H3k27me3 signature by descriptive and graphical summaries of assays performed on tissue samples obtained during the study. The Wilcoxon rank sum test will be used to assess SLFN11 expression by immunohistochemistry as a potential predictive biomarker of response to DS-3201b and to correlate with trimethylation of H3K27 as measured by immunohistochemistry in pretreatment, on-treatment and post-treatment tissue samples as well as in circulating tumor cells (CTCs). In addition, next-generation sequencing (NGS) will also be performed on pre-treatment, on-treatment and post-treatment tissue samples obtained from the study. This data will be analyzed using descriptive

and graphic summaries of the assays performed, including use of gene expression heat maps and advanced computational biostatistics with collaborators in the Rudin laboratory.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

This is a multicenter, Phase I/II non-randomized, single-arm study.

16.1 DATA MANAGEMENT ISSUES

A Clinical Research Associate (CRA), Regulatory Research Associate (RRA) and Clinical Research Coordinator (CRC) will be assigned to the study. The responsibilities of these staff members include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinating the activities of the protocol study team.

The data collected for this study will be entered into a secure database (Medidata). Source documentation will be available to support the computerized patient record. The principal investigator will maintain ultimate responsibility for the clinical trial. Data from JHU will be entered into the Medidata database maintained by MSKCC.

FDA regulations require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

16.2 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be

monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated

16.3 Data and Safety Monitoring

The Data and Safety Monitoring Plan utilized for this study must align with the MSK DSM Plan where applicable.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering were approved by the National Cancer Institute in August 2018. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials.”

There are several different mechanisms by which clinical studies are monitored for data safety and quality. At a departmental/PI level, there exist procedures for quality control by the research team(s). Institutional processes in place for quality assurance include protocol monitoring, compliance and data verification audits, staff education on clinical research QA, and two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Deputy Physician-in-Chief of Clinical Research.

The degree of monitoring required will be determined based on level of risk and documented.

The MSK DSMB monitors phase III trials and the DSMC monitors non-phase III trials. The DSMB/C have oversight over the following trials:

- MSK Investigator-Initiated Trials (IITs; MSK as sponsor)
- External studies where MSK is the data coordinating center
- Low risk studies identified as requiring DSMB/C review

The DSMC will initiate review following the enrollment of the first participant, or by the end of the year one if no accruals, and will continue for the study lifecycle until there are no participants under active therapy and the protocol has closed to accrual. The DSMB will initiate review once the protocol is open to accrual..

17.1 PROTECTION OF HUMAN SUBJECTS

Human Subjects Involvement, Characteristics, and Design

This study involves the treatment of human subjects with DS-3201b in combination with irinotecan on a phase I/II protocol.

The subject population will include patients, age 18 or over, with progressive or recurrent SCLC who have received at least one prior line of platinum-based chemotherapy. Patients must have a Karnofsky Performance Status ≥70%. Other inclusion and exclusion criteria will be specified in the protocol to ensure enrollment of patients with adequate hematologic and biochemical function, and no other serious medical conditions. Patients who are pregnant or lactating are excluded, and all patients must use appropriate methods of contraception. Up to 61 patients will be enrolled for both the Phase I and Phase II portions of the study across all sites.

Vulnerable populations will not be targeted for this research.

This study will be conducted at MSKCC and JHU. Participation of additional sites will require a protocol amendment.

Sources of Materials

The data collected from patients on the study will include demographics, medical history, medication records, toxicities, radiologic responses, and outcomes such as time to progression and survival.

Archived tissue samples as well as fresh biopsy samples will be collected for correlative studies to elucidate the mechanism of drug action.

The data collected for this study will be entered into a secure database (Medidata) at MSKCC. Source documentation will be available to support the computerized patient record.

The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

Potential Risks of DS-3201b

There are potential risks in the DS-3201b program that require monitoring. While these toxicities may be severe or life threatening, it is anticipated that they can be managed by clinical monitoring and intervention. Patients will be monitored for these potential toxicities and for unanticipated toxicities while they are receiving DS-3201b and for at least 30 days after their last dose of DS-3201b.

Potential Risks of DS-3201b Based on Current Ongoing Phase 1 Studies

- myelosuppression (thrombocytopenia, anemia, decreased lymphocyte count, decreased neutrophil count)
- dysgeusia
- alopecia
- diarrhea
- decreased appetite
- non-severe (Grade 1) QTc interval prolongation
- *Pneumocystis jirovecii* pneumonia

Potential Risks of DS-3201b Based on Findings from Animal Studies

- Dose-dependent QTc interval prolongation

It is possible that DS-3201b will have toxicities that were not observed in or predicted from the studies completed in rats and dogs, or have not yet been identified in patients, which may be severe or fatal.

For more detailed information, please consult the current Investigator's Brochure.

Subject participation is voluntary. The proposed study does not include patients under 18 years old. All patients will be required to sign a statement of informed consent that conforms to IRB guidelines. Informed consent will be documented by the use of a written consent form which has been approved by the IRB. Before protocol specified procedures are carried out, a study investigator or their staff explains the full details of the protocol and study procedures, as well as the risks involved to patients prior to their inclusion in the trial. Patients will also be informed that they are free to withdraw from the study at any time. The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks and discomforts. This consent is obtained in the clinic by one of the physician investigators whose name is indicated on the face page of the protocol. All patients must read, discuss with consenting physician, and sign an IRB approved consent form indicating their consent to participate. This consent form conforms to the applicable requirements of 21 CFR 50.25 elements of informed consent. Written consent will be obtained by either the principal investigator, co-principal investigators, or participating investigators. The original signed consent forms will become part of the patient's medical record. Each patient will receive a copy of the signed consent form. There is absolutely no waiver of the consent. Consent must be documented in the medical record of each patient.

Protections Against Risk: Procedures for protecting against and minimizing risks to treatment and other clinical interventions will be described within the text of the protocol. This includes toxicity monitoring, dose modification guidelines, and indications for removing patients from the study.

Potential Benefits of the Proposed Research to Human Subjects and Others

The potential benefits of the research to the patients are not known and there may be no benefit to the research subject. Administration of DS-3201b with irinotecan could potentially cause disease regression. The potential benefits of the research to others are not known but may include development of new therapies.

The risks to patients are reasonable in relation to the anticipated potential benefits for patients and others based on the preclinical and clinical data derived on the study drug to date.

Importance of the Knowledge to be Gained

The treatment of SCLC is an important unmet need that could impact thousands of potential patients. This approach would also provide a proof of concept for targeting the EZH2-SLFN11 pathway in patients with other tumor types that develop resistance to chemotherapy.

The risks to patients are reasonable in relation to the anticipated potential benefits for the patients and others, particularly given the broad potential of this therapy for SCLC and the impact on possible future therapies.

17.2 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

The consent indicates that individualized de identified information collected for the purposes of this study may be shared with other qualified researchers. Only researchers who have received approval from MSK will be allowed to access this information which will not include protected health information, such as the participant's name, except for dates. It is also stated in the Research Authorization that their research data may be shared with other qualified researchers.

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
- Secondary malignancy as defined in section 11.2

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant starts investigational treatment/intervention. SAE reporting is required for 30-days after the participant's last investigational treatment/intervention. Any event that occurs after the 30-day period that is unexpected and at least possibly related to protocol treatment must be reported.

Please note: Any SAE that occurs prior to the start of investigational treatment/intervention and is related to a screening test or procedure (i.e., a screening biopsy) must be reported.

All SAEs must be submitted in PIMS. If an SAE requires submission to the HRPP office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be submitted within 5 calendar days of the event. All other SAEs must be submitted within 30 calendar days of the event.

The report should contain the following information:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment(s)
- If the AE was expected
- Detailed text that includes the following
    - An explanation of how the AE was handled
    - A description of the participant's condition
    - Indication if the participant remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office

17.2.1 External SAE Reporting to Daiichi Sankyo

Please refer to the current Pharmacovigilance Agreement (PVA) for the exchange of safety information between MSKCC and Daiichi Sankyo Inc. Pharmacovigilance department.

The SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the IND Office.

For multicenter trials where MSK is the data coordinating center, please refer to the MSK Multicenter Trial Addendum. All required SAE reporting to the funders and/or drug suppliers will be completed by MSK only.

17.2.2 Non Serious Adverse event of Special Interest Reporting to Daiichi Sankyo

Please refer to the current Pharmacovigilance Agreement (PVA) for the exchange of safety information between MSKCC and Daiichi Sankyo Inc. Pharmacovigilance department.

17.2.3 Pregnancy Reporting

Daiichi requests to be notified of any female subject or partner of a male subject who becomes pregnancy while receiving or within 90 days of discontinuing DS-3201b, using the Exposure in Utero (EIU) Reporting form. Please contact Daiichi to receive the EIU Reporting Form upon

learning of a pregnancy if pregnancy information is being shared. A pregnant partner of a protocol participant is neither a study patient nor a human research participant, so participating institutions will not obtain consent from, or submit data to sponsors that originates from, pregnant partners of research participants. Participating institutions may obtain notice from participants whose partners become pregnant during the study and if so, will record that information in the participant's research record.

Although pregnancy is not technically an AE, all pregnancies may be followed to conclusion to determine their outcome. MSK and JHU may provide Daiichi contact information to the participant, so that the participant or partner may contact Daiichi directly if she wishes. However, MSK and JHU will not be involved in the consent of, or data oversight of, the pregnant individual. Any adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the investigator should follow the procedures for reporting SAEs.

Pregnancy Test

For women of childbearing potential (as defined in section 11.10), document the results of a negative serum pregnancy test. For eligibility, if not performed as part of routine care within 14 days of Cycle 1 Day 1, a serum pregnancy test must be performed, with the results available prior to Cycle 1 Day 1 (as noted in section 6.2).

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition

to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix A: Drug Diary - 7-day Safety Run-In

Appendix B: Drug Diary – All Cycles

Appendix C: Lab Manual

Appendix D: MSK Multicenter Trial Addendum

Appendix E: Multicenter External Site SAE Report Form