# CLINICAL PROTOCOL M16-300

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|---|---|
| Protocol Number | M16-300 |
| Version and Date | Version 3, 01-DEC-2017 |
| Protocol Title | A Phase 1/2 Study on the Safety of Rovalpituzumab Tesirine Administered in Combination with Nivolumab or Nivolumab and Ipilimumab for Adults with Extensive-Stage Small Cell Lung Cancer |
| Investigational Drugs | Rovalpituzumab tesirine (SC16LD6.5)<br>Nivolumab (BMS-936558, MDX1106, ONO-4538, Opdivo®)<br>Ipilimumab (MDX-010, Yervoy®) |
| Phase | 1/2 |
| EUDRA CT Number | 2016-003686-26 |
| CRO Medical Monitors | [redacted] |
| Sponsor | AbbVie*<br>1 North Waukegan Road<br>North Chicago, IL 60064 |
| Sponsor Representative | [redacted] |

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority. "AbbVie" shall mean AbbVie Inc. or its affiliate AbbVie Stemcentrx LLC.

# Synopsis

**TITLE:**
A Phase 1/2 Study on the Safety of Rovalpituzumab Tesirine Administered in Combination with Nivolumab or Nivolumab and Ipilimumab for Adults with Extensive-Stage Small Cell Lung Cancer

**PROTOCOL NUMBER:** M16-300

**PHASE OF DEVELOPMENT:** 1/2

**INVESTIGATORS AND STUDY CENTERS:** Multicenter

**OBJECTIVES:**

Primary:

- To assess the safety of rovalpituzumab tesirine when administered in combination with nivolumab or nivolumab and ipilimumab in adult subjects with extensive-stage small cell lung cancer (SCLC)

Secondary:

- To explore the efficacy of rovalpituzumab tesirine when administered in combination with nivolumab or nivolumab and ipilimumab in adult subjects with extensive-stage SCLC

Exploratory:

- To explore the expression of DLL3 and PD-L1 in SCLC and their relationship to clinical outcome during treatment
- To explore the pharmacokinetics (PK) of and incidence of anti-therapeutic antibodies (ATA) against rovalpituzumab tesirine, nivolumab, and ipilimumab
- To explore the effect of study drug regimen on disease and immune biomarkers

**TEST PRODUCTS, DOSE, AND MODE OF ADMINISTRATION:**

- Rovalpituzumab tesirine 0.3 mg/kg will be administered intravenously (IV) on Day 1 of the first and third 3-week cycle (q6wk x 2), or per other dosing regimen recommended by the safety monitoring committee (SMC)
- Nivolumab 1 mg/kg or 360 mg IV q3wk or 480 mg IV q4wk as monotherapy
- Ipilimumab 1 mg/kg or 3 mg/kg IV q3wk x 4 cycles
- Dexamethasone 8 mg orally (PO) twice daily (BID) on Day –1, Day 1 (the day of dosing), and Day 2 of each cycle in which rovalpituzumab tesirine is administered.

**STUDY DESIGN AND METHODOLOGY:**

This is a multicenter study involving rovalpituzumab tesirine administered in combination with nivolumab or nivolumab and ipilimumab in subjects with SCLC. Planned cohorts are indicated below.

| Cohort | Population | Rovalpituzumab tesirine | Nivolumab | Ipilimumab |
|---|---|---|---|---|
| 1 | 2nd line or later SCLC (Platinum-failure) | 0.3 mg/kg q6wk x 2 | 360 mg q3wk beginning on Week 4 (Cycle 2) x 2 cycles, then 480 mg q4wk | – |
| 2 | 2nd line or later SCLC (Platinum-failure) | 0.3 mg/kg q6wk x 2 | 1 mg/kg q3wk x 4 cycles beginning on Week 4 (Cycle 2), then 480 mg q4wk (monotherapy) after 6 week washout | 1 mg/kg q3wk x 4 beginning on Week 4 (Cycle 2) |
| 3 | 2nd line or later SCLC (Platinum-failure) | 0.3 mg/kg q6wk x 2 | 1 mg/kg q3wk x 4 cycles beginning on Week 4 (Cycle 2), then 480 mg q4wk (monotherapy) after 8 week washout | 3 mg/kg q3wk x 4 beginning on Week 4 (Cycle 2) |

Initially, up to 12 subjects will be enrolled into Cohort 1 in order to obtain 6 evaluable subjects through the DLT evaluation period of 12 weeks, after which an SMC will perform a safety review of the data. The SMC may recommend further evaluation of the safety of a given combination or dose regimen, investigation of alternative dose regimens, a modification of the dosing interval, or a change in the maximum number of doses (or elimination) of any component of the regimen. Based on the tolerability of the initial 6 evaluable subjects in Cohort 1, enrollment may begin of up to 12 subjects into Cohort 2 to obtain 6 evaluable subjects through the DLT evaluation period of 12 weeks. Once Cohort 2 opens, Cohort 1 may continue enrolling (up to 30 subjects total). Similarly, Cohort 3 may enroll up to 12 subjects upon review of the tolerability of the first 6 evaluable subjects in Cohort 2. Once Cohort 3 is open, Cohort 2 may continue enrolling (up to 30 subjects total). Following completion of the DLT evaluation period and SMC review for a given cohort, the SMC may recommend that enrollment into the expansion of the cohort be initiated to gather additional safety data prior to escalation to the next cohort. Based on the tolerability of the initial 6 evaluable subjects in Cohort 3, Cohort 3 may continue enrolling (up to 30 subjects total). If ≤1/6 subjects being evaluated in each cohort experience a DLT within the first 4 cycles of treatment (12 weeks), enrollment beyond 12 subjects may proceed. The SMC will meet at a frequency outlined in the SMC Charter and will periodically monitor the safety and tolerability of the dose regimen to endorse continued enrollment in the cohorts. In general, if a regimen appears intolerable, the dose of rovalpituzumab tesirine may be reduced to dose level -1, 0.2 mg/kg. Such changes will constitute a new cohort, and subsequent cohorts may then carry forward the tolerated dose. For instance, if Cohort 1 is not tolerated, a new Cohort 4 consisting of rovalpituzumab tesirine 0.2 mg/kg and nivolumab 360 mg q3wk could be initiated; if tolerated, a new Cohort 5 consisting of rovalpituzumab tesirine 0.2 mg/kg, nivolumab 1 mg/kg and ipilimumab 1 mg/kg q3wk (nivolumab and ipilimumab doses from Cohort 2) could then be initiated.

For each cohort and dose regimen, up to 30 total subjects may be enrolled as part of an expansion phase after evaluation of the tolerability of the first 6 evaluable subjects. Details regarding enrollment priorities are discussed in Section 3.1.

**MAJOR ELIGIBILITY CRITERIA:**

Subjects with histologically or cytologically confirmed, 2nd line or later extensive-stage SCLC with evaluable or measurable disease; Eastern Cooperative Oncology Group (ECOG) 0-1; adequate hematologic, hepatic, and renal function; no active, known, or suspected autoimmune disease; and no prior exposure to an immuno-oncology or pyrrolobenzodiazepine (PBD)-based drug.

**PLANNED SAMPLE SIZE:**

Up to approximately 90 subjects (up to approximately 30 subjects per cohort)

**STUDY TESTS AND OBSERVATIONS:**

Safety assessments (Section 2.4.1) include physical exam, vital signs, body weight, ECOG performance status, clinical adverse events (AEs), laboratory tests, electrocardiograms (ECGs), echocardiogram, Fluid Retention Questionnaire, and monitoring of concomitant medications.

Efficacy assessments will consist of radiographic imaging. Responses will be categorized by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer, 2009). See Section 6.4.6 for imaging schedule per cohort.

Blood samples for PK, immunogenicity, biomarker, and pharmacodynamics (PD) assessments will be collected at protocol-defined time points to support the study endpoints. Sensitive, validated assays will be used to measure blood concentrations of rovalpituzumab tesirine antibody-drug conjugate (ADC) and related analytes of rovalpituzumab tesirine, such as total antibody and SC-DR002, as applicable. A validated immunoassay will be used to assess ATA against rovalpituzumab tesirine. Analogous assays may be performed for nivolumab and/or ipilimumab.

Pharmacodynamic and biomarker assessments will include analyses of tumor tissue for DLL3 and PD-L1 expression, and of blood samples for tumor markers, circulating tumor cells (CTC), immune, and soluble biomarkers such as soluble DLL3.

**STATISTICAL METHODS:**

As a general strategy, data will be analyzed by cohort and dose regimen.

Safety analysis will include summaries by cohort and dose regimen of: AEs, laboratory measures, physical examinations, ECG, and vital signs using data from subjects in the Safety Analysis set. The incidence of DLTs will be summarized.

Objective response rate (ORR) will be reported with category counts, percentage and 95% confidence interval (CI). Duration of Response (DOR), progression-free survival (PFS) and overall survival (OS) will be evaluated using Kaplan-Meier.

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## Definitions of Abbreviations and Terms

| | |
|---|---|
| ADC | antibody-drug conjugate |
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANA | antinuclear antibodies |
| ANC | absolute neutrophil count |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| AT | aminotransferase |
| ATA | anti-therapeutic antibody |
| BA | bioavailability |
| BE | bioequivalence |
| β-hCG | beta-human chorionic gonadotropin |
| BID | twice daily |
| BSA | Body surface area |
| BUN | blood urea nitrogen |
| $C_{avgss}$ | average concentration in steady-state |
| CBC | complete blood count |
| CBR | clinical benefit rate |
| CFR | Code of Federal Regulations |
| CI | confidence interval |
| $C_{maxss}$ | steady-state peak concentration |
| $C_{min1}$ | minimum trough concentration following the first dose |
| CNS | central nervous system |
| CR | complete response |
| CRP | C-reactive protein |
| CT | computerized tomography |
| CTA | clinical trial agreement |
| CTC | circulating tumor cell |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTLA-4 | cytotoxic T-lymphocyte antigen 4 |
| cTnT | cardiac troponin T |
| cTnI | cardiac troponin I |
| DILI | drug-induced liver injury |
| DLL3 | delta-like protein 3 |
| DLT | dose-limiting toxicity |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic Case Report Form |
| [redacted] | [redacted] |

| | |
|---|---|
| eGFR | estimated glomerular filtration rate |
| EOT | end of treatment |
| ESR | erythrocyte sedimentation rate |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| HBcAb | Hepatitis B core antibody |
| HBsAb | Hepatitis B surface antibody |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |
| IB | Investigator's Brochure |
| ICF | Informed consent form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |
| IHC | Immunohistochemistry |
| IHR | infusion or hypersensitivity reaction |
| IL | Interleukin |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| IV | intravenous(ly) |
| LDH | lactate dehydrogenase |
| LTFU | long-term follow-up |
| LVEF | left ventricular ejection fraction |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| NCI | National Cancer Institute |
| NET | neuroendocrine tumor |
| NSCLC | Non-small cell lung cancer |
| NSE | neuron-specific enolase |
| NYHA | New York Heart Association |
| ORR | objective response rate |
| OS | overall survival |
| PBD | pyrrolobenzodiazepine |
| PBMC | peripheral blood mononuclear cells |
| PCR | polymerase chain reaction |
| PD | progressive disease |
| PD | pharmacodynamic |
| PD-1 | programmed death receptor-1 |
| PD-L1 | anti-PD-L1 antibody |
| PD-L2 | Anti-PD-L2 antibody |
| PET | positron emission tomography |
| PFS | progression-free survival |

| | |
|---|---|
| PK | Pharmacokinetic(s) |
| PO | per os (by mouth/orally) |
| PPK | population pharmacokinetics |
| PR | partial response |
| PT | prothrombin time |
| PTT | partial thromboplastin time |
| q2wk | every 2 weeks |
| q3wk | every 3 weeks |
| q4wk | every 4 weeks |
| q6wk | every 6 weeks |
| q12wk | every 12 weeks |
| QA | quality assurance |
| QTc | QT interval corrected for heart rate |
| QTcF | QT interval corrected for heart rate by Fridericia's formula |
| RBC | red blood cell |
| RCC | Renal cell carcinoma |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RF | rheumatoid factor |
| RP2D | recommended phase 2 dose |
| SAE | serious adverse event |
| SCLC | small cell lung cancer |
| SD | stable disease |
| SMC | safety monitoring committee |
| SPF | sun protection factor |
| TEAE | treatment-emergent adverse event |
| TPC | tumor perpetuating cells |
| ULN | upper limit of normal |
| USP | United States Pharmacopeia |
| [redacted] | [redacted] |

# 1. Introduction

## 1.1 Small Cell Lung Cancer (SCLC)

Small cell lung cancer (SCLC) is an important unmet medical need, representing 15–20% of the 220,000 annual new cases of lung cancer (Govindan, 2006; Siegel, 2012). These cancers arise from epithelial cells with neuroendocrine differentiation and typically are positive for both cytokeratin and neuroendocrine markers; however, the diagnosis is usually made by morphologic examination. Historically, SCLC has been divided into limited versus extensive-stage disease, the former being defined as disease limited to the chest that can be encompassed by a radiation field while the latter includes all other cases. Approximately one-third of newly diagnosed patients will have limited-stage disease while the rest will be extensive. Unlike non-small cell lung cancer (NSCLC), SCLC is rarely cured with local therapy (surgery and/or radiotherapy); systemic chemotherapy remains the cornerstone of therapy for all stages of disease. Standard initial therapy for all patients with a suitable performance status consists of a platinum salt (carboplatin or cisplatin) in combination with a second agent, usually etoposide. For patients with limited-stage disease, concurrent or sequential involved-field thoracic radiotherapy is indicated. Response rates to initial therapy are high, ranging from 70-90% for limited stage and 60–70% for extensive-stage; however, recurrence rates remain high in the limited group and universal in the extensive group, leading to median survivals of only 14-20 months and 9-11 months, respectively (Simon, 2004).

## 1.2 Delta-like Protein 3 and Rovalpituzumab Tesirine

Delta-like protein 3 (DLL3) is an inhibitory ligand of the Notch receptor family. It is highly expressed in high-grade tumors of neuroendocrine origin such as SCLC, including its tumor perpetuating cells (TPCs), but with no detectable surface protein expression in normal tissues or non-neuroendocrine tumor (NET) types (Saunders, 2015; AbbVie data on file). While the function of DLL3 has not been clearly defined, it has been implicated in the regulation of cell development and fate decisions (Dunwoodie, 1997; Chapman, 2011).

Rovalpituzumab tesirine (SC16LD6.5) is a DLL3-targeted antibody-drug conjugate (ADC) consisting of the humanized DLL3-specific IgG1 monoclonal antibody SC16; the DNA cross-linking agent SC-DR002 (D6.5); and a protease-cleavable linker that covalently links SC-DR002 to SC16. The primary mechanism of rovalpituzumab tesirine is binding of the ADC to DLL3 on target-expressing cells, followed by internalization of the ADC-DLL3 complex and release of SC-DR002 via proteolytic cleavage in late endosomes. Interstrand crosslinks of cellular DNA induced by intercalated SC-DR002 leads to cellular cytotoxicity.

In a Phase 1 study (SCRX16-001), rovalpituzumab tesirine exhibited encouraging efficacy in recurrent SCLC, achieving a 31% (8/26) and 85% (22/26) central review-adjudicated confirmed objective response rate (ORR) and clinical benefit rate (CBR) (39% [10/26] and 73% [19/26] by investigator review), respectively, in DLL3 ≥50% tumors dosed at 0.2-0.4 mg/kg. Median overall survival (OS) was 7.7 months in DLL3 ≥50% subjects at all dose levels, with a 1-year survival rate of 30%. In DLL3 ≥50% tumors in the third line setting, rovalpituzumab tesirine achieved a 33% (4/12) and 83% (10/12) central review-adjudicated confirmed ORR and CBR, respectively, with a median survival of 5.8 months and a 1-year survival rate of 37%. Rovalpituzumab tesirine was generally tolerated, with the most common Grade 3 or higher AEs of serosal effusions and thrombocytopenia occurring in 14% and 12% of subjects, respectively (AbbVie data on file). Therefore, rovalpituzumab tesirine appears to be an active anticancer therapy.

### 1.3 Immune Checkpoints and Inhibitors of PD-1 and CTLA-4

Immune checkpoint therapy targets regulatory pathways in T lymphocytes to enhance antitumor immune responses (Sharma, 2015). Agents inhibiting the interaction between programmed death receptor-1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) and their ligands have facilitated considerable progress in the treatment of many solid tumors: ipilimumab, a CTLA-4-blocking antibody, has been approved for the treatment of unresectable or metastatic melanoma (Bristol-Myers Squibb [BMS], 2015), while nivolumab, a PD-1 blocking antibody, has been approved for treatment as a single agent for metastatic NSCLC after platinum-based chemotherapy, advanced renal cell carcinoma (RCC) after prior anti-angiogenic therapy, and as a single agent or in combination with ipilimumab for unresectable or metastatic melanoma (BMS, 2016).

In an ongoing Phase 1/2 study, nivolumab with or without ipilimumab showed antitumor activity with durable responses and manageable safety profiles in previously treated patients with SCLC: nivolumab 3 mg/kg q2wk achieved a PR and SD in 10% (10/98) and 22% (22/98), respectively, while the combination of nivolumab and ipilimumab (1 and 1 mg/kg, 1 and 3 mg/kg, or 3 and 1 mg/kg, respectively) every 3 weeks (q3wk) x 4 followed by nivolumab 3 mg/kg q2wk achieved an ORR and SD in 23% (14/61) and 19% (10/54), respectively (Antonia, 2016). Treatment was generally well tolerated, with grade 3 or higher treatment-related AEs occurring in 13 (13%) patients in the nivolumab 3 mg/kg cohort, 18 (30%) in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohort, and 10 (19%) in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort; the most commonly reported grade 3 or 4 treatment-related adverse events were increased lipase (none vs. 5 [8%] vs. none) and diarrhea (none vs. 3 [5%] vs. 1 [2%]). No patients in the nivolumab 1 mg/kg plus ipilimumab 1 mg/kg cohort had a grade 3 or 4 treatment-related adverse

event. Six (6%) patients in the nivolumab 3 mg/kg group, seven (11%) in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg group, and four (7%) in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg group discontinued treatment due to treatment-related adverse events. Two patients who received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg died from treatment-related adverse events (myasthenia gravis and worsening of renal failure), and one patient who received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg died from treatment-related pneumonitis. Nivolumab and the combination of nivolumab and ipilimumab, therefore, appear to have clinically significant therapeutic potential in SCLC (Antonia, 2016).

### 1.4 Rationale for the Study and Anticipated Risks

Although rovalpituzumab tesirine as well as the checkpoint inhibitors nivolumab and ipilimumab have demonstrated encouraging efficacy in SCLC, neither approach alone appears at this time sufficient to afford a complete clinical benefit or cure in the majority of patients, where medical need remains high. Their mechanisms of actions are complementary and toxicities generally non-overlapping, though, suggesting that combination therapy may be safe, and clinical benefit may be additive or even synergistic. Indeed, preliminary studies indicate that ADCs like rovalpituzumab tesirine may, at least in part, result in immunogenic cell death of tumors, complementing the immuno-regulatory effects of checkpoint inhibitors like nivolumab and/or ipilimumab (Gerber, 2016). However, no formal clinical studies have previously examined the tolerability of rovalpituzumab tesirine administered in combination with checkpoint inhibitors. This study will therefore explore the safety, tolerability, and antitumor activity of rovalpituzumab tesirine administered in combination with nivolumab with or without ipilimumab. Upon completion of the study, decisions to further advance this program will also include review of the ORR rate. The lower bound value of the 95% confidence interval for the ORR rate observed will be compared to the ORR rate of 23% and used as one of the factors in making the decision.

The most frequent treatment-emergent adverse event (TEAE) terms considered related to rovalpituzumab tesirine have included fatigue (35%), peripheral edema (23%), and nausea (19%), while the most frequent, related TEAEs of Grade 3 or higher have included serosal effusions (14%), thrombocytopenia (12%), and skin reactions (8%). In addition, preclinical toxicology studies conducted in the rat and the cynomolgus monkey have identified the bone marrow, lung and kidney as a potential source of clinical AEs (AbbVie data on file).

Warnings for nivolumab include immune-mediated reactions, including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, rash, and encephalitis, as well as infusion reactions and embryo-fetal toxicity. The most common adverse reactions (≥20%) in patients with melanoma were fatigue, rash, musculoskeletal and back pain, pruritus, diarrhea, upper respiratory tract

infection, decreased appetite, and nausea as a single agent, and fatigue, rash, diarrhea, nausea, pyrexia, vomiting, and dyspnea when administered with ipilimumab. In metastatic non-small cell lung cancer (NSCLC), the most common adverse reactions (≥20%) were fatigue, musculoskeletal pain, decreased appetite, cough, and constipation. In advanced renal RCC, they were asthenic conditions, cough, nausea, rash, dyspnea, diarrhea, constipation, decreased appetite, back pain, and arthralgia (BMS, 2016).

Warnings for ipilimumab also include immune-mediated reactions, including hepatitis and endocrinopathies, as well as embryo-fetal toxicity. The most common adverse reactions (≥5%) have been fatigue, diarrhea, pruritus, rash, and colitis. At the 10 mg/kg dose (higher than anticipated in this study), additional common adverse reactions (≥5%) include nausea, vomiting, headache, weight loss, pyrexia, decreased appetite, and insomnia (BMS, 2015).

Accordingly, safety assessments will include regular assessments at protocol-specified time points of routine physical examination, laboratory and imaging tests, as well as echocardiograms, a Fluid Retention Questionnaire, daily weights, and spot urine protein testing.

# 2. Objectives

## 2.1 Primary Objective

- To assess the safety of rovalpituzumab tesirine when administered in combination with nivolumab or nivolumab and ipilimumab in adult subjects with extensive-stage SCLC

## 2.2 Secondary Objective

- To explore the efficacy of rovalpituzumab tesirine when administered in combination with nivolumab or nivolumab and ipilimumab in adult subjects with extensive-stage SCLC

## 2.3 Exploratory Objectives

- To explore the expression of DLL3 and PD-L1 in SCLC and their relationship to clinical outcome during treatment
- To explore the pharmacokinetics (PK) of and incidence of anti-therapeutic antibodies (ATA) against rovalpituzumab tesirine, nivolumab, and ipilimumab
- To explore the effect of study drug regimen on disease and immune biomarkers

## 2.4 Endpoints

### 2.4.1 Safety Endpoints

Analyses of the safety endpoints will include the following measurements or assessments:

- Adverse Events (AEs) and Dose-Limiting Toxicities (DLTs)
- Vital signs (Section 7.7.2)
- Body weight (Section 7.7.2)
- Laboratory abnormalities (Sections 7.7.3 and 8.3.7)
- Electrocardiographic parameters (e.g. QT interval corrected for heart rate [QTc], QT interval corrected for heart rate by Fridericia's formula [QTcF]) (Section 7.7.4)
- Echocardiography (Section 7.7.5)
- Eastern Cooperative Oncology Group (ECOG) performance status (Section 7.7.6)
- Monitoring of concomitant medications

### 2.4.2 Efficacy Endpoints

- Response assessments per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, including ORR and CBR
- Duration of response (DOR)
- Progression-free survival (PFS)
- PFS status after 6 months from the initiation of study treatment
- OS

### 2.4.3 Radiographic imaging, Pharmacokinetics, Biomarker, and Pharmacodynamic Endpoints

Analyses of the endpoints will include the following assessments:

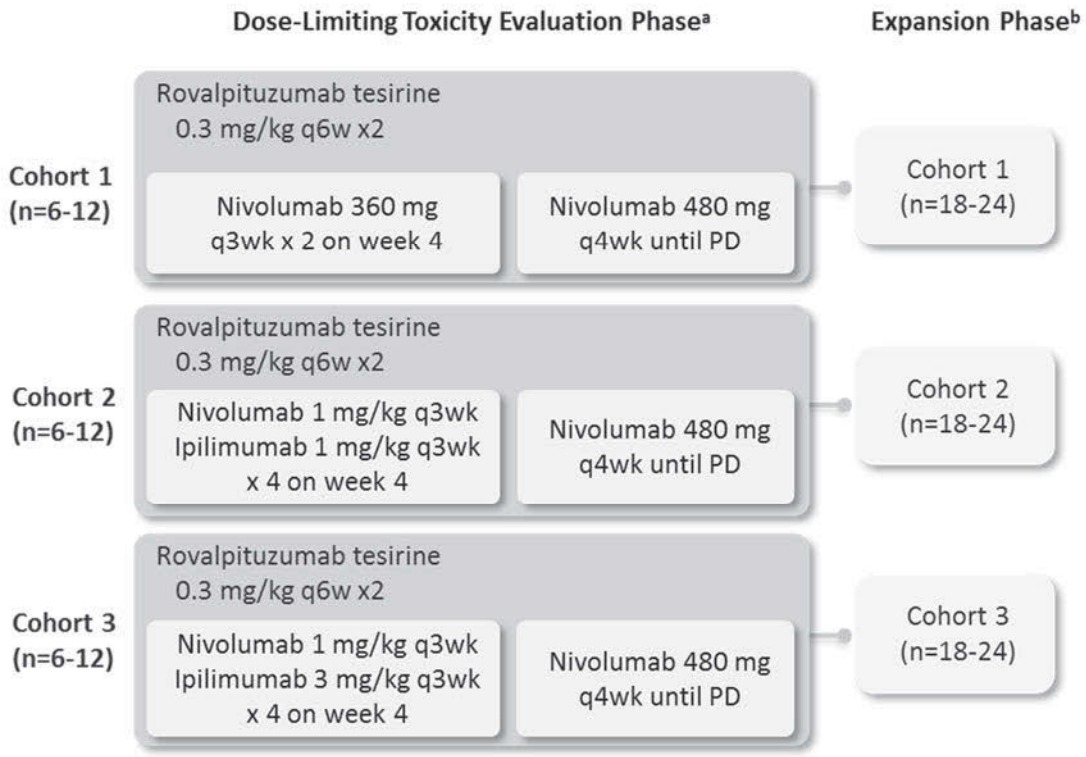
- Specific PK parameters of rovalpituzumab tesirine, nivolumab, and ipilimumab
- ATA incidence and timing
- Tumor DLL3 and PD-L1 expression
- [redacted]
- Blood Soluble Markers
- Immune Markers
- Circulating Tumor Cells (CTCs)

# 3. Investigational Plan

## 3.1 Summary of Study Design

This is a multicenter study involving rovalpituzumab tesirine administered in combination with nivolumab or nivolumab and ipilimumab in subjects with SCLC. The study plans to include 3 cohorts of up to approximately 30 subjects each (Table 1). DLTs will be assessed during the DLT Evaluation Period (Section 3.1.1).

**Figure 1. Study Schema**




* Up to 12 DLL3+ subjects will be enrolled into each cohort in order to obtain 6 evaluable subjects at the end of the 12 week DLT period.

a. Based on the tolerability of the initial 6 DLL3+ subjects in cohort 1, enrollment may begin of up to 12 DLL3+ subjects into cohort 2. The same strategy will be used for cohort 3 enrollment. If a regimen appears intolerable, the dose of rovalpituzumab tesirine may be reduced to 0.2 mg/kg, or 0.1 mg/kg. Such changes will constitute a new cohort, and subsequent cohorts may then carry forward the tolerated dose.

b. For each cohort, up to 30 total subjects may be enrolled as part of an expansion phase after evaluation of the tolerability of the first 6 evaluable subjects.

**Table 1. Planned Cohorts in the Study**

| Cohort | Population | Rovalpituzumab tesirine | Nivolumab | Ipilimumab |
|---|---|---|---|---|
| 1 | 2nd line or later SCLC (Platinum-failure) (Section 4.1) | 0.3 mg/kg q6wk x 2 | 360 mg q3wk beginning on Week 4 (Cycle 2) x 2 cycles, then 480 mg q4wk | – |
| 2 | 2nd line or later SCLC (Platinum-failure) (Section 4.1) | 0.3 mg/kg q6wk x 2 | 1 mg/kg q3wk x 4 cycles beginning on Week 4 (Cycle 2), then 480 mg q4wk (monotherapy) after 6 week washout | 1 mg/kg q3wk x 4 beginning on Week 4 (Cycle 2) |
| 3 | 2nd line or later SCLC (Platinum-failure) (Section 4.1) | 0.3 mg/kg q6wk x 2 | 1 mg/kg q3wk x 4 cycles beginning on Week 4 (Cycle 2), then 480 mg q4wk (monotherapy) after 8 week washout | 3 mg/kg q3wk x 4 beginning on Week 4 (Cycle 2) |

Initially, up to 12 subjects will be enrolled into Cohort 1 in order to obtain 6 evaluable subjects through the DLT evaluation period of 12 weeks If ≤1/6 subjects being evaluated has a DLT, enrollment beyond 12 subjects may proceed (i.e., enrollment into Cohort 1 expansion may begin). Subjects who are considered DLT-inevaluable (e.g., due to withdrawal from study before completing the DLT evaluation period; see Section 3.1.1) will be replaced if required.

Based on the tolerability of the initial 6 evaluable subjects enrolled in Cohort 1, enrollment may begin of up to 12 subjects into Cohort 2. Once Cohort 2 is open, Cohort 1 may continue enrolling (up to 30 subjects total).

Up to 12 DLL3+ subjects may be enrolled into Cohort 2 initially in order to obtain 6 evaluable subjects through the DLT evaluation period of 12 weeks. This will continue for Cohort 3 as well.

Safety will be monitored throughout the trial by the safety monitoring committee (SMC) consisting at least of the medical monitor and biostatistician. After enrollment of up to 12 subjects in Cohort 1, the SMC will perform a safety review of the data. Based on the tolerability of the initial 6 evaluable subjects in Cohort 1, enrollment may begin of up to 12 subjects in Cohort 2. Once Cohort 2 opens, Cohort 1 may continue enrolling (up to 30 subjects total). Similarly, Cohort 3 may enroll up to 12 subjects upon review of the tolerability of the first 6 evaluable subjects in Cohort 2. Once Cohort 3 opens, Cohort 2 may continue enrolling (up to 30 subjects total). Based on the tolerability of the initial 6 subjects in Cohort 3, Cohort 3 may continue enrolling (up to 30 subjects total). The SMC may recommend further evaluation of the safety of a given combination or dose regimen, investigation of alternative dose regimens, a modification of the dosing interval, or a change in the maximum number of doses (or elimination) of any component of the regimen. In general, if a regimen

appears intolerable, the dose of rovalpituzumab tesirine may be reduced to dose level -1, 0.2 mg/kg, or level -2, 0.1 mg/kg. Such changes will constitute a new cohort, and subsequent cohorts may then carry forward the tolerated dose. For instance, if Cohort 1 is not tolerated, a new Cohort 4 consisting of rovalpituzumab tesirine 0.2 mg/kg and nivolumab 360 mg q3wk could be initiated; if tolerated, a new Cohort 5 consisting of rovalpituzumab tesirine 0.2 mg/kg, nivolumab 1 mg/kg and ipilimumab 1 mg/kg (nivolumab and ipilimumab doses from Cohort 2) could then be initiated. The SMC will also review cumulative safety data in order to identify safety concerns that may emerge due to cumulative exposure beyond the DLT window. The process for dose-escalation decisions and dose-interval recommendations, and the roles and responsibilities of the SMC may be detailed separately. The SMC will meet at a frequency defined in the SMC Charter.

Tumor response will be assessed according to the imaging schedule in Section 6.4.6. Treatment decisions by the investigator will be based on RECIST v1.1.

Subjects will be eligible to continue treatment until unacceptable toxicity, progressive disease (PD), withdrawal of consent, study termination, or completion of a planned course of treatment (if a regimen with a limited number of doses is selected), whichever occurs first. Subjects who discontinue study treatment prior to PD will be evaluated for response q6wk until 24 weeks, then q12wk until disease progression or initiation of new anticancer treatment, whichever occurs first, and will afterwards be followed for survival until death or study termination, whichever occurs first.

Blood samples for PK, immunogenicity, biomarker and PD assessments will be collected at protocol-defined time points to support the study endpoints (Sections 7.3 and 7.4).

### 3.1.1 Definition of Dose-Limiting Toxicities

The DLT evaluation period is the first 12 weeks of treatment for all subjects. DLTs are defined as any of the following in the DLT-evaluation period, graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03 (see Appendix 13.6)

- Grade 4 thrombocytopenia (or Grade 3 thrombocytopenia with bleeding) lasting more than 7 days and/or requiring platelet transfusion
- Grade 4 neutropenia lasting more than 7 days, and/or requiring hematopoietic growth factor rescue, or any febrile neutropenia (Grade 3 or 4 neutropenia with concurrent fever ≥38.3°C)
- Grade 4 anemia unrelated to underlying disease

- Clinically-significant Grade 3 or 4 non-hematologic laboratory abnormality that does not resolve to Grade 0/1 or baseline within 7 days
- Grade 3 or 4 non-laboratory AE with the exception of fatigue, asthenia, nausea, or other manageable constitutional symptom

The following events will not be considered DLTs:

- Any AE ≥Grade 3 clearly determined to be unrelated to study drug(s) (e.g., disease progression)
- ≥Grade 3 isolated alkaline phosphatase, amylase, or lipase laboratory abnormality of any duration
- ≥Grade 3 endocrinopathies controlled by hormone replacement
- Grade 3-4 electrolyte abnormalities

### 3.1.2 Retreatment

Retreatment with rovalpituzumab tesirine may be permitted, with medical monitor and sponsor approval, for subjects who tolerate all doses of rovalpituzumab tesirine, achieve clinical benefit as defined by SD or better during the period of receiving rovalpituzumab tesirine, and then experience disease progression at least 12 weeks after the most recent dose of rovalpituzumab tesirine. The retreatment dose level and regimen for each subject will be determined by the medical monitor, sponsor (or designee), and the site investigator, not to exceed the maximum tolerated dose (MTD).

Retreatment with nivolumab, or nivolumab and ipilimumab will not be permitted.

## 3.2 Discussion and Rationale for Study Design

### 3.2.1 Study Design

This is the first formal clinical study of rovalpituzumab tesirine in combination with an inhibitor of PD-1 and CTLA-4. Cohort 1 will first assess the tolerability of doublet rovalpituzumab tesirine and nivolumab, a PD-1 inhibitor; if tolerated, Cohort 2 will assess the tolerability of triplet rovalpituzumab tesirine, nivolumab, and ipilimumab; if tolerated, Cohort 3 will assess the tolerability of the triplet with a higher dose of ipilimumab. Expanded enrollment to each cohort may occur in order to explore further the tolerability of one or more regimen(s).

The evaluation of the study endpoints will inform the safety profile of rovalpituzumab tesirine in combination with nivolumab with or without ipilimumab, and may provide evidence of antitumor activity that could influence the trial design of subsequent studies in SCLC.

### 3.2.2 Method of Assigning Subjects to Cohorts

Upon approval of subject registration by the sponsor or designee, the subject will be enrolled to a cohort. The enrollment confirmation will be documented in the clinical trial master file.

### 3.2.3 Rationale for Selection of Doses

In a recent Phase 1 study with rovalpituzumab tesirine, the MTD was established at 0.4 mg/kg q3wk based on the incidence of Cycle 1 toxicities, while the recommended Phase 2 dose (RP2D) in SCLC was chosen as 0.3 mg/kg q6wk based on the toxicity and efficacy profile during multiple cycle dosing (AbbVie data on file).

In an ongoing Phase 1 study, nivolumab 3 mg/kg q2wk, and nivolumab 1 mg/kg + ipilimumab 3 mg/kg q3wk, were found to be tolerated in SCLC (Antonia, 2015). Since the toxicities of these therapies have been generally non-overlapping, the starting dose regimens in this study will therefore be rovalpituzumab tesirine 0.3 mg/kg q6wk + nivolumab 360 mg q3wk, rovalpituzumab tesirine 0.3 mg/kg q6wk + nivolumab 1 mg/kg q3wk + ipilimumab 1 mg/kg q3wk, and rovalpituzumab tesirine 0.3 mg/kg q6wk + nivolumab 1 mg/kg q3wk + ipilimumab 3 mg/kg q3wk. In all dose levels, nivolumab will be administered at 480 mg q4wk when used as a single agent or after 2 cycles at 360 mg in Cohort 1.

### 3.2.4 Rationale for Nivolumab and Ipilimumab Combination Dose and Schedule

In CA209004, a Phase 1B dose-escalation study of nivolumab in combination with ipilimumab in subjects with unresectable stage III or IV malignant melanoma, the 3 mg/kg nivolumab and 3 mg/kg ipilimumab cohort exceeded the MTD per protocol. While both Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab) and Cohort 2a (3 mg/kg nivolumab + 1 mg/kg ipilimumab) had similar clinical activity, a dose of 3 mg/kg of ipilimumab q3wk for a total of four doses and 1 mg/kg nivolumab q3wk for four doses followed by nivolumab 3mg/kg q2wk until progression was chosen. Exposure-response analysis of nivolumab monotherapy across dose ranges of 1 mg/kg to 10 mg/kg reveals similar clinical activity while exposure-response analysis of 0.3 mg/kg, 3 mg/kg, and 10 mg/kg of ipilimumab monotherapy have demonstrated increasing activity with increase in dose in the phase 2 study CA184022 (Wolchok, 2009). Therefore, theoretically the selection of 3 mg/kg of ipilimumab (Cohort 2) may be more clinically impactful than selection of 3 mg/kg of nivolumab (Cohort 2a).

Data from the phase III study CA209067 in subjects with advanced melanoma showed that the administration schedule of 1 mg/kg of nivolumab q3wk plus 3 mg/kg of ipilimumab q3wk for 4 doses, followed by 3 mg/kg of nivolumab q2wk for cycle 3 and beyond is safe and well tolerated (Larkin, 2015). As described above, current data from study CA209032 showed safety and tolerability of this treatment schedule in heavily pretreated SCLC subjects.

### 3.2.5 Nivolumab Flat Dose Regimens

The safety and efficacy of 240 mg q2wk flat dose of nivolumab is similar to 3 mg/kg q2wk dosing regimen. A flat dose of nivolumab 240 mg q2wk was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab treated cancer patients. The 240 mg q2wk flat dose of nivolumab was recently approved by the FDA. Using a population pharmacokinetic (PPK) model, the overall distributions of nivolumab exposures ($C_{avgss}$, $C_{minss}$, $C_{maxss}$, and $C_{min1}$) are comparable after treatment with either 3 mg/kg or 240 mg nivolumab. The predicted range of nivolumab exposures (median and 90% prediction intervals) resulting from a 240 mg flat dose across the 35 to 160 kg weight range is maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab q2wk dosage. Across the various tumor types in the clinical program, nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy and safety has been found to be relatively flat. Given the similarity of nivolumab PK across tumor types and the similar exposures predicted following administration of 240 mg flat dose compared to 3 mg/kg q2wk regimen, it is expected that the safety and efficacy profile of 240 mg q2wk nivolumab will be similar to that of 3 mg/kg nivolumab.

### 3.2.6 Blinding

This is not a blinded trial.

## 4. Study Population

Subjects must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the investigator and are subject to review in the event of Good Clinical Practice (GCP) audit and/or appropriate health regulatory authority inspection.

To be eligible for retreatment as described in Section 3.1.2, subjects must meet all inclusion and none of the exclusion criteria outlined in this section.

### 4.1 Inclusion Criteria

1) Written informed consent.
   a) Must have signed and dated an IRB/IEC approved written informed consent form (ICF) in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal patient care.
   b) Must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.
2) Target population
   a) Histologically or cytologically confirmed extensive-stage SCLC with PD after at least one platinum-based chemotherapeutic regimen.
   b) Measurable disease, defined as at least 1 tumor lesion ≥10 mm in the longest diameter or a lymph node ≥15 mm in short-axis measurement assessed by computerized tomography (CT) scan (RECIST v1.1) or evaluable disease.
   c) Availability of representative baseline tumor tissue (archived or on-study biopsy) suitable for immunohistochemistry testing. Up to the first 12 subjects of each study cohort must be DLL3 positive per IHC (Immunohistochemistry) assay criteria, based on central assessment prior to enrollment.
   d) ECOG performance status of 0 or 1. See Appendix 13.3 for conversion of performance status using Karnofsky scales, if applicable.
   e) Minimum life expectancy of at least 12 weeks.

f) Asymptomatic central nervous system (CNS) metastases, if present, must be stable, with or without previous treatment, in the absence of corticosteroids for at least 2 weeks prior to initiation of study drugs.

g) Recovery to Grade 1 of any clinically significant toxicity (excluding alopecia) prior to initiation of administration of study drugs.

h) Satisfactory laboratory parameters:

i. Absolute neutrophil count (ANC) ≥1,000/μL.

ii. White blood cell count (WBC) ≥2,500/μL.

iii. Platelet count ≥100,000/μL.

iv. Hemoglobin ≥9.0 g/dL.

v. Total bilirubin ≤1.5 x upper limit of normal (ULN) or ≤3 x ULN for subjects with Gilbert's disease.

vi. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3.0 x ULN (≤5 x ULN if evidence of hepatic involvement by malignant disease).

vii. Creatinine ≤1.5 x ULN or estimated glomerular filtration rate (eGFR) ≥40 mL/min/1.73m$^2$.

viii. Albumin ≥3 g/dL.

iv. Lipase ≤1.5 x ULN. Subjects with Lipase >1.5 x ULN may enroll if there are neither clinical nor radiographic signs of a pancreatitis.

x. Amylase ≤1.5 ULN. Subjects with Amylase >1.5 x ULN may enroll if there are neither clinical nor radiographic signs of a pancreatitis

i) At least two (2) weeks since last dose of any prior systemic anticancer therapy (e.g. chemotherapy, radiation, and/or surgery).

3) Age and Reproductive Status

a) Adult 18 years of age or older.

b) If female, subject must be either postmenopausal, defined as:

- Age >55 years with no menses for 12 or more months without an alternative medical cause.
- Age ≤55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level >40 IU/L.

OR

- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy)

OR

- Woman of Childbearing Potential practicing at least one protocol specified method of birth control, starting at Day 1 through at least 31 weeks following the last dose of study drugs (Section 5.10).

c) If the subject is male and is sexually active with female partner(s) of childbearing potential, he must agree, from Day 1 through 31 weeks following last dose of study drugs, to practice the protocol specified methods of contraception (Section 5.10).

d) Females of childbearing potential must have a negative serum pregnancy test result at Screening and a negative urine pregnancy test prior to dosing on Day 1. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.10) at Screening do not require pregnancy testing.

## 4.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1) Prior treatment with or exposure to:
   a) A pyrrolobenzodiazepine (PBD)-based drug (including rovalpituzumab tesirine unless undergoing retreatment in the context of this protocol)
   b) Other monoclonal antibodies
   c) ADCs
   d) Radioimmmunoconjugates
   e) T-cell or other cell-based or biologic therapies
   f) Experimental anti-tumor vaccines; therapies that target any T cell co-stimulation or checkpoint pathways, such as anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody, including ipilimumab; or other medicines specifically targeting T cells.
2) Any significant medical condition, including any condition suggested by screening laboratory findings that, in the opinion of the investigator or sponsor, may place the subject at undue risk from the study and/or may interfere with interpretation of study results.
3) Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association (NYHA) Class III–IV (Appendix 13.4) within 6 months prior to their first dose of study drugs.

4) Recent or ongoing serious infection, including:
    a) Any active grade 3 or higher (per NCI CTCAE version 4.03) viral, bacterial, or fungal infection within 2 weeks of the first dose of the study drugs. Routine antimicrobial prophylaxis is permitted.
    b) Known seropositivity for or active infection by human immunodeficiency virus (HIV).
    c) Active hepatitis B (by surface antigen expression or polymerase chain reaction [PCR]) or active hepatitis C (by PCR) infection, or subjects taking hepatitis-related antiviral therapy within 6 months of first dose of study drugs.
5) Previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period.
6) Active, known, or suspected autoimmune disease. Vitiligo, type I diabetes mellitus, residual hypothyroidism only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted.
7) A condition requiring systemic treatment with corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days prior to administration of study drugs. Inhaled or topical steroids and adrenal replacement doses >10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.
8) Female subject who is pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 31 weeks after the last dose of study drugs.
9) Male subject who is considering fathering a child or donating sperm during the study for approximately 31 weeks after the last dose of study drugs.
10) Prior participation in a rovalpituzumab tesirine clinical trial, or known hypersensitivity to rovalpituzumab tesirine or excipient contained in the drug formulation, unless undergoing retreatment with rovalpituzumab tesirine in the context of this protocol.
11) Known hypersensitivity to any corticosteroid or excipients contained in the drug formulations.

### 4.3 Removal of Subjects from Therapy or Assessment

The sponsor or its designee must be notified if a subject is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the subject's medical records and electronic case report form (eCRF). When a subject withdraws from treatment, all

safety data normally required at the end of the study (i.e. the End of Treatment (EOT) Visit and long-term follow-up [LTFU]) will be obtained if possible (Sections 6.5 and 6.6).

### 4.3.1 Discontinuation of Study Drug(s)

Treatment with study drug(s) may be discontinued for any of the following reasons:

- PD
- AE
- Investigator decision
- Subject decision, Non-AE
- Other

### 4.3.2 Subject Discontinuation from Study

Any subject may be discontinued from the study for any of the following reasons:

- Subject withdrawal of consent
- AE
- Death
- Investigator decision
- Lost to follow-up
- Significant noncompliance to protocol
- Study termination by sponsor

# 5. Treatments

## 5.1 Treatments Administered

- Rovalpituzumab tesirine 0.3 mg/kg IV on Day 1 of the first and third 3-week cycle (q6wk x 2), or per other dosing regimen recommended by the SMC (all cohorts)
- Nivolumab 360 mg IV q3wk x 2 cycles beginning on Week 4 (Cycle 2) (Cohort 1)
- Nivolumab 1 mg/kg IV q3wk x 4 cycles (Cohorts 2 and 3)
- Nivolumab 480 mg q4wk (all cohorts) – monotherapy to be given after a washout period from ipilimumab. See study drug dosing schedule (Section 5.1.1)
- Ipilimumab 1 mg/kg IV q3wk x 4 cycles beginning on Week 4 (Cycle 2) (Cohort 2)
- Ipilimumab 3 mg/kg IV q3wk x 4 cycles beginning on Week 4 (Cycle 2) (Cohort 3)
- Dexamethasone 8 mg orally (PO) twice daily (BID) on Day -1, Day 1 (the day of dosing), and Day 2 of each cycle in which rovalpituzumab tesirine is administered (all cohorts)

On applicable cycles, rovalpituzumab tesirine will be administered before nivolumab and ipilimumab. Similarly, on applicable cycles, nivolumab will be administered prior to ipilimumab.

Detailed information describing the preparation, administration, and storage of rovalpituzumab tesirine, nivolumab, and ipilimumab is located in the Pharmacy Binder.

### 5.1.1 Treatment Regimen Descriptions for Each Cohort

The schedule, dose, route, and cycle length for the treatment regimens in each of the three cohorts are summarized below in Table 2.

**Table 2. Study Drug Dosing Schedule**

| Cohort | Study Drug(s) | Cycle | | | | | |
|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6+ |
| 1[a] | Rovalpituzumab tesirine 0.3 mg/kg | X | | X | | | |
| | Nivolumab 360 mg q3wk | | X | X | | | |
| | Nivolumab 480 mg q4wk | | | | X | X | X |
| 2[b] | Rovalpituzumab tesirine 0.3 mg/kg | X | | X | | | |
| | Nivolumab 1 mg/kg | | X | X | X | X | |
| | Ipilimumab 1 mg/kg | | X | X | X | X | |
| | Nivolumab 480 mg q4wk[d] | | | | | | X |
| 3[c] | Rovalpituzumab tesirine 0.3 mg/kg | X | | X | | | |
| | Nivolumab 1 mg/kg | | X | X | X | X | |
| | Ipilimumab 3 mg/kg | | X | X | X | X | |
| | Nivolumab 480 mg q4wk[e] | | | | | | X |

a) Cycles 1–3 are 3 weeks. Cycles 4 and beyond are 4 weeks.
b) Cycles 1–5 are 3 weeks. Cycles 6 and beyond are 4 weeks
c) Cycles 1–5 are 3 weeks. Cycles 6 and beyond are 4 weeks
d) Nivolumab 480 mg q4wk (monotherapy) to be started 6 weeks after Cycle 5 Day 1 in Cohort 2.
e) Nivolumab 480 mg q4wk (monotherapy) to be started 8 weeks after Cycle 5 Day 1 in Cohort 3.

## 5.2 Investigational Product (Rovalpituzumab Tesirine)

### 5.2.1 Description

Rovalpituzumab tesirine (SC16LD6.5) drug product is provided in a sterile clear United States Pharmacopeia (USP) Type I 10 mL glass vial as a lyophilized powder containing 30 mg/vial. The lyophilized drug product is reconstituted with 3.2 mL sterile water for injection to deliver 3 mL per vial of 10 mg/mL rovalpituzumab tesirine. The rovalpituzumab tesirine formulation consists of 10 mg/mL rovalpituzumab tesirine in 20 mM histidine hydrochloride, 0.175 M sucrose and 0.4 mg/mL polysorbate 20, pH 6.0. The lyophilized drug product is stored and shipped at 2-8°C prior to its use in clinical trials.

A description of the chemistry and formulation may be found in the Investigator's Brochure (IB).

### 5.2.2 Packaging and Labeling

Rovalpituzumab tesirine is provided in sterile clear USP Type I, 10 mL glass vials. The vials and/or primary vial carton will have labels bearing the appropriate label text as required by governing regulatory agencies.

### 5.2.3 Dosing and Administration

Dosing is based on subject actual body weight to the nearest tenth of a kilogram, assessed on Day 1 of each cycle, and administered according to the assigned dose. Detailed information describing the preparation, administration, and storage of rovalpituzumab tesirine is located in the Pharmacy Binder.

Subjects must meet all of the following on each dosing day before receiving rovalpituzumab tesirine:

- ANC ≥1,000/μL
- Platelet count ≥100,000/μL
- Resolution to Grade 0 or 1, or to baseline grade if pre-existing, of any clinically-significant clinical or laboratory AE (excluding alopecia) occurring during the previous cycle, including findings indicative of pleural or pericardial effusions.

## 5.3 Investigational Product (Nivolumab; Opdivo®)

### 5.3.1 Description, Packaging and Labeling

Nivolumab, available in the United States as Opdivo, is a sterile, preservative-free, non-pyrogenic, clear to opalescent, colorless to pale-yellow liquid that may contain light (few) particles. Opdivo injection for intravenous (IV) infusion is supplied in single-dose vials. Each mL of Opdivo solution contains nivolumab 10 mg, mannitol (30 mg), pentetic acid (0.008 mg), polysorbate 80 (0.2 mg), sodium chloride (2.92 mg), sodium citrate dihydrate (5.88 mg), and Water for Injection, USP. May contain hydrochloric acid and/or sodium hydroxide to adjust pH to 6 (BMS, 2016). Additional details or updates may be found in the most recent Prescribing Information.

### 5.3.2 Dosing and Administration

Detailed information describing the preparation, administration, and storage of nivolumab is located in the Pharmacy Binder.

## 5.4 Investigational Product (Ipilimumab; Yervoy®)

### 5.4.1 Description, Packaging and Labeling

Ipilimumab, available in the United States as Yervoy, is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for IV infusion, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is supplied in

single-use vials of 200 mg/40 mL. Each milliliter contains 5 mg of ipilimumab and the following inactive ingredients: diethylene triamine pentaacetic acid (DTPA) (0.04 mg), mannitol (10 mg), polysorbate 80 (vegetable origin) (0.1 mg), sodium chloride (5.85 mg), tris hydrochloride (3.15 mg), and Water for Injection, USP at a pH of 7 (BMS, 2015). Additional details or updates may be found in the most recent Prescribing Information.

### 5.4.2 Dosing and Administration

Detailed information describing the preparation, administration, and storage of ipilimumab is located in the Pharmacy Binder.

## 5.5 Dose Delays/Modifications (Nivolumab and Ipilimumab)

### 5.5.1 Dose Delay Criteria (Nivolumab and Ipilimumab)

Dose reductions for nivolumab and ipilimumab are not permitted in this study. Nivolumab monotherapy or both nivolumab together with combination therapy should be delayed for the following:

- Any Grade ≥1 pneumonitis
- Any Grade ≥ 2 non-skin, drug-related AE, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay.
- Grade 2 drug-related creatinine, AST, ALT, or total bilirubin abnormalities
- Any Grade ≥3 skin drug-related AE
- Any Grade 3 drug-related laboratory abnormality with the following exceptions:
  - Grade 3 or 4 lymphopenia does not require a dose delay
  - Any Grade 3 drug-related amylase and/or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay.

Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication. In the event of isolated CNS progression during study treatment, study drug(s) may be withheld while palliative treatment is administered, e.g. a standard course of whole brain radiotherapy in accordance with institutional practice, and restarted within 1 week after completion of radiotherapy. During this time the subject should be fully evaluated for other sites of disease progression. If more than 6 weeks have elapsed since the previous dose of study drug(s), the subject should undergo a radiographic tumor assessment before restarting study drugs. If additional sites of PD are present, the subject

will be required to discontinue study drugs (but may be eligible for re-treatment as per Section 3.1.2).

If the decision is made to resume nivolumab and/or ipilimumab dosing, the subject should restart treatment on the next regularly scheduled dosing visit. Skipped doses are not to be replaced. If treatment is delayed >6 weeks, the subject must be permanently discontinued from all study therapy, except as specified in Dose Discontinuation Criteria. Tumor assessments for all subjects should continue as per protocol **even if dosing is delayed**.

### 5.5.2 Criteria to Resume Nivolumab/Ipilimumab Dosing

Subjects will be permitted to resume therapy at the same dose level(s) following resolution of the AE to ≤Grade 1 or to baseline within 6 weeks after the last dose, with the exception of subjects who meet criteria for permanent discontinuation as specified in Section 5.5.4 (Dose discontinuation criteria below). Subjects who meet criteria for permanent discontinuation must not receive further study therapy.

Subjects may resume treatment with nivolumab and/or ipilimumab when the drug-related AE(s) resolve(s) to Grade ≤ 1 or baseline, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- For subjects with Grade 2 AST, ALT, or total bilirubin elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 5.5.4) should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for re-treatment if discussed with and approved by the sponsor and/or medical monitor.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the sponsor and/or medical monitor.
- Dose delay of nivolumab or ipilimumab that results in treatment interruption of >6 weeks requires treatment discontinuation, with exceptions as noted in Section 5.5.4. However, if the toxicity resolves to ≤Grade 1 or baseline >6 weeks after the last dose, but the subject does not otherwise meet the criteria for permanent discontinuation (Section 5.5.4), and the investigator

believes that the subject is deriving clinical benefit, then the subject may be eligible to resume the study drug(s) following the approval of the sponsor and/or medical monitor.

### 5.5.3 Rovalpituzumab Tesirine Dose Delays/Modifications

In general, if a subject has a clinically significant, unresolved AE on the next scheduled dosing day, treatment with rovalpituzumab tesirine may be delayed for up to 21 days. The AE must resolve to baseline or ≤Grade 1 prior to proceeding with treatment, unless the AE is determined to be clearly unrelated to rovalpituzumab tesirine. In cases of treatment delays of >21 days for unresolved adverse events, the medical monitor should be contacted regarding the subject's continuation of treatment.

If rovalpituzumab tesirine is delayed at Cycle 3 Day 1, nivolumab and/or ipilimumab are not required to be delayed.

In general, subjects who experience a clinically-significant Grade 3 or 4 AE (unless the AE is determined to be clearly unrelated to rovalpituzumab tesirine) should have a dose reduction(s) of rovalpituzumab tesirine in subsequent treatment cycles to dose level –1 or –2, or as suggested upon discussion with the medical monitor and/or sponsor. If the clinically-significant Grade 3 or 4 AE recurs after dose reduction, rovalpituzumab tesirine should be permanently discontinued.

### 5.5.4 Permanent Treatment Discontinuation Criteria

Subjects meeting any of the following criteria will be required to permanently discontinue all assigned study drug(s).

- PD (see details regarding continuing treatment beyond initial assessment of progression per RECIST v1. 1). See Section 7.2.1 for additional details.
- Clinical deterioration, as assessed by the investigator
- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 6 weeks OR requires systemic treatment
- Any Grade ≥ 2 drug-related pneumonitis or interstitial lung disease that does not resolve following dose delay and systemic steroids (also see Pulmonary Adverse Event Management Algorithm);
- Any Grade 3 non-skin, drug-related AE lasting >7 days or recurs, with the following exceptions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia >7 days or associated with bleeding requires discontinuation
    - Grade ≥3 drug-related AST, ALT or Total Bilirubin requires discontinuation
    - In most cases of Grade 3 AST or ALT elevation, study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the Medical Monitor/designee must occur

- Any Grade 4 drug-related AE or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤7 days
  - Grade 4 lymphopenia or leukopenia
  - Isolated Grade 4 amylase and/or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any AE, laboratory abnormality, or intercurrent illness, which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued treatment.
- Any dosing delay of nivolumab or ipilimumab lasting >6 weeks after the last dose, with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related AEs are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting >6 weeks after the last dose and with no more than 3 missed doses, the medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions >6 weeks after the last dose, which occur for nondrug-related reasons, may be allowed if approved by the medical monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting >6 weeks after the last dose and

with no more than 3 missed doses, the medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted, and subjects must otherwise meet the criteria for continued treatment at the time re-initiation of study therapy is considered.

## 5.6 Required Premedication and Post-medication

All subjects enrolled will receive premedication consisting of dexamethasone orally (PO) at 8 mg BID given on Day –1, Day 1 (the day of dosing), and Day 2 of each rovalpituzumab tesirine cycle. Dexamethasone will be provided through a subject's local prescription by investigator or other provider (i.e., dexamethasone will not be provided by the sponsor). When dexamethasone is not available, the glucocorticoid-equivalent dose of an alternate corticosteroid may be administered. Parenteral (e.g., intravenous, IV) administration may be substituted for per os (by mouth/orally, PO) at the discretion of the investigator.

On Day 1 of each rovalpituzumab tesirine cycle, the first dose of dexamethasone of the day must be taken at least 30 minutes, but no more than 4 hours, prior to the rovalpituzumab tesirine infusion. In the event that a subject arrives for administration of study drugs on Day 1, but has not taken any or all required dexamethasone doses on Day –1 and/or Day 1, study drug administration may proceed, at the investigator’s discretion, after administration of a parenteral corticosteroid dose equivalent to the total missed dexamethasone dose prior to administration of study drugs. For instance, subjects who missed 1, 2, or 3 dexamethasone doses could receive 43 mg, 85 mg, or 128 mg methylprednisolone IV, respectively, prior to proceeding with administration of study drugs. If a subject misses any dose(s) of dexamethasone prior to these visits, the medical monitor may be consulted if additional guidance is needed.

## 5.7 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

Any concomitant therapy given for a study protocol-related AE should be recorded from the time of informed consent.

### 5.7.1 Required Concomitant Therapy

Other than dexamethasone (Section 5.6), there are no required concomitant therapies. However, due to the potential for rovalpituzumab tesirine-related skin photosensitivity, subjects should be

advised to avoid unprotected sun exposure and use a broad spectrum sunscreen (sun protection factor [SPF] of at least 30), protective clothing, a broad-brimmed hat, and sunglasses when outdoors or when driving or riding in the car for more than 1 hour, with re-application of sunscreen as activity-appropriate.

### 5.7.2 Allowed Concomitant Therapy

Standard supportive care for drug-related toxicity is permitted, including growth factors and blood product transfusions per local institutional standards. Other standard supportive care for symptom control or drug-related toxicity is allowed, such as analgesics, anti-emetics, electrolyte replacement, and hydration. Bone modifying agents for bone metastases are also permitted per local institutional standards. Other prescribed medications for non-neoplastic conditions are allowed, as well as vitamins and nutritional supplements.

Concomitant prednisone (or equivalent) may be used at a dose of ≤20 mg/day. The use of intermittent high-dose corticosteroid treatment to prevent or manage hypersensitivity reactions, serosal effusions (Section 8.3.1), or other non-cancer-related symptoms including premedication for known hypersensitivity reactions to contrast for scans is allowed.

Routine prophylaxis with vaccines is permitted; however, vaccines used should not contain live micro-organisms.

If the subject is taking chronic suppressive anti-infectives (antiviral, antifungal, or antibacterial), appropriate investigation must be completed prior to registration and documentation must exclude active infection. The subject should continue suppressive anti-infectives for the duration of study participation.

#### 5.7.2.1 Palliative Therapy

Palliative (limited-field) radiation therapy and palliative surgical resection are permitted if the following criteria are met:

- The subject is considered to have progressed at the time of palliative therapy and meets criteria to continue with treatment beyond progression (Section 7.2.1).
- The case is discussed with the sponsor, medical monitor (or designee). Palliative therapy must be clearly documented as such in the study record.

#### 5.7.2.2 Surgical Resection Following Initial Response

Investigators may choose to resect solitary lesions and render the subject free of macroscopic disease. Subjects enrolled in this study may have such lesions surgically resected only following

consultation with the medical monitor and following the Week 12 re-staging assessments. If tumor shrinkage of the solitary lesion is noted on the re-staging assessment (e.g., Week 12), it is highly encouraged that surgical resection be delayed until subsequent confirmatory scans confirm response, and/or fail to demonstrate further shrinkage. Subjects with a PR who go on to have surgical resection of remaining disease will be considered a PR. Tumor tissue of any resected solitary lesion should be submitted to AbbVie. Detailed instructions of the obtaining, processing, labeling, handling, storage and shipment of these specimens will be provided in a separate Laboratory Manual.

### 5.7.3 Prohibited Concomitant Therapy

Subjects may not receive other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy during the study, other than as allowed in Sections 4 and 5.7.2. Subjects may not have received any systemic anticancer therapy (e.g. chemotherapy, small molecule inhibitors, radiation, and/or other investigational anticancer agents) within two weeks of the Screening Visit.

## 5.8 Treatment Compliance

Study drug administration must be performed by study site staff and documented in source documents and the eCRFs.

## 5.9 Study Drug Accountability

The director of the medical institution should appoint a study drug management director. The investigator and the study drug management director will maintain accurate records of receipt and the condition of all study drugs including dates of receipt. In addition, accurate records will be kept of the weight used to calculate each dispensed rovalpituzumab tesirine dose, and when and how much study drug is dispensed and used by each subject in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

Drug accountability records and inventory will be available. Remaining study drugs (all used, partially used, and unused vials) will be returned to AbbVie or its specified designee/depot or destroyed at the site according to applicable regulations.

Study drugs must not be used for any purpose other than the present study.

Further instructions about study drug accountability are detailed in the Pharmacy Binder.

## 5.10 Contraception Recommendations

If female, subject must be either postmenopausal or permanently surgically sterile (refer to inclusion criteria for definitions of both), OR a Woman of Childbearing Potential, practicing at least one of the following methods of birth control, on Cycle 1 Day 1 (or earlier) through at least 31 weeks after the last dose of study drug.

If subject is a Woman of Childbearing Potential practicing acceptable birth control, one of the following methods must be followed starting on Day 1 (or earlier) through at least 31 weeks following the last dose of study drugs:

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to study Day 1.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to study Day 1.
- Bilateral tubal occlusion/ligation.
- Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the woman of child bearing potential trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse – when this is in line with the preferred and usual lifestyle of the subject. (Note: periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Male subjects who are sexually active with a woman of childbearing potential, even if the male subject has undergone a successful vasectomy, must agree from Study Day 1 through at least 31 weeks after the last dose of study drug to use condoms and his female partner(s) must use at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential).

Male subject agrees not to donate sperm from Study Day 1 through at least 31 weeks after the last dose of study drug.

## 5.11 Documentation of Non-Childbearing Status and Pregnancy Testing

For each female subject, the Investigator will document non-childbearing status (surgically sterile or post-menopausal for at least 1 year) or potential childbearing status.

Should a female study subject become pregnant or suspect she is pregnant while participating in this study, she should inform the treating Investigator immediately (Section 8.3.8).

For female subjects of childbearing potential, the laboratory will perform pregnancy testing according to Appendix 13.1. A serum pregnancy test will be performed at Screening and the results must be available prior to the administration of the first dose of investigational product on C1D1. Subjects with borderline pregnancy tests at Screening must have a serum pregnancy test ≥3 days later to document continued lack of a positive result. Urine pregnancy tests will be performed at Day 1 of each cycle and again at the End of Treatment Visit.

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile) as defined in Section 4 at Screening do not require pregnancy testing. Post-menopausal female subjects ≤55 years of age must have an FSH level >40 IU/L and will have FSH performed at Screening and assessed by the Investigator.

# 6. Study Activities

## 6.1 Enrollment

Subjects who provide informed consent will be screened for eligibility. Once screening procedures have been completed, and for those subjects who meet all of the entry criteria, a Registration and Enrollment Form will be completed and submitted to the sponsor or designee to confirm eligibility. Approved subjects will then be enrolled into a treatment cohort. Refer to the Study Binder for the enrollment form, contact numbers, and other details of enrollment.

Safety assessments (Section 2.4.1) will include physical examinations, vital signs, body weight, ECOG performance status, AE assessments, laboratory tests (Section 7.7.3), ECGs, echocardiograms, Fluid Retention Questionnaire, concomitant medications, AEs, and concomitant therapies will be recorded from Day 1 (pre-dose) through the safety reporting period At the same time, subjects will maintain a diary of daily weights. Any protocol-related AE should be recorded from the time of informed consent as well as any concomitant therapies given for treatment of the AE.

Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7. A schedule of events is provided in Appendix 13.1.

Subjects undergoing retreatment as described in Section 3.1.2 will follow the same study schedule from Screening through EOT and LTFU.

## 6.2 Prescreening Visit

Informed consent for the prescreening portion of this study will be obtained in order to collect and test an archived or fresh tumor tissue specimen for DLL3 expression (Section 7.4.1). Up to the first 12 subjects enrolled into each cohort must test positive for the expression of DLL3, per IHC assay criteria. Demographic information will be collected at this visit (Section 7.1).

## 6.3 Screening Visit (Days -14 to -1)

Informed consent for the main portion of this study will be obtained prior to the performance of any study procedures and may occur within 30 days prior to the Day 1 Visit. All other screening procedures must occur within 14 days prior to Day 1. Imaging performed as standard of care within 14 days prior to Day 1 will be accepted.

The following assessments will occur during Screening:

- Informed consent – omitted for retreatment subjects

- Demographics (Section 7.1) – omitted for retreatment subjects
- Confirmation of study eligibility per inclusion/exclusion criteria (Section 4); if prescreening visit was not conducted, testing of an archived or fresh tumor tissue specimen for DLL3 expression will be conducted during the Screening Visit. Upon enrollment into the study, remaining tumor tissue will be analyzed for PD-L1 expression.
- Medical and surgical history (Section 7.1) – omitted for retreatment subjects
- Malignancy history (Section 7.1) – omitted for retreatment subjects
- Prior anticancer treatments (Section 7.1) – omitted for retreatment subjects
- Physical examination (Section 7.7.1)
- Vital signs (Section 7.7.2)
- Height (Section 7.7.2) (For adult subjects (≥18 years), measurements of height obtained within 6 months prior to Screening Visit may be utilized)
- Urinalysis (Section 7.7.3)
- Triplicate electrocardiogram (ECG)
- ECOG performance status (Section 7.7.6 and Appendix 13.3)
- Procedure-related AEs (Section 7.6)
- Procedure-related concomitant medications
- Disease assessment consisting of CT scans of the chest, abdomen, and pelvis (and neck if indicated) (Section 7.2) – may be omitted for all subjects if recent scans demonstrating PD are within 14 days prior to dosing of study drugs.
- Magnetic resonance imaging (MRI) of the brain – may be omitted for all subjects if recent scans are taken within 14 days prior to dosing of study drugs. CT of the brain with IV contrast may be substituted at the discretion of the investigator. (Section 7.2)
- Paraneoplastic Assessment (Appendix 13.8)
- Blood sample collection for:
  - Complete blood count (CBC) with differential (Section 7.7.3)
  - Serum chemistries (Section 7.7.3)
  - Coagulation tests (Section 7.7.3)
  - Hepatitis B and C tests (Section 7.7.3) – omitted for retreatment subjects
  - Pregnancy test (serum) (Section 7.7.3) for women of child-bearing potential

- Blood [redacted] (Section 7.4.2)
- Blood soluble markers (Section 7.4.3)
- Flow cytometry (Section 7.4.4)
- Peripheral blood RNA (Section 7.4.5)
- Genotyping (Section 7.4.8)
- Endocrinology tests, including ACTH, thyroid stimulating hormone (TSH), and free thyroxine (T4)

## 6.4 Treatment Period

Treatment will be administered in 3-4 week cycles.

### 6.4.1 Peridosing with Dexamethasone

#### 6.4.1.1 Day –1 (Day before Dosing) of Cycle 1 and Cycle 3 Only

- Subjects will take dexamethasone 8 mg PO BID (Section 5.6).
- Dexamethasone may be taken at home or in the clinic.

#### 6.4.1.2 Day 1 (Day of Dosing) of Cycle 1 and Cycle 3 Only

- Subjects will take dexamethasone 8 mg PO BID (the first dose of the day should be at least 30 minutes, but no more than 4 hours, prior to the rovalpituzumab tesirine dose); this dose of dexamethasone will be taken in the clinic.
- All subjects will receive 0.3 mg/kg of rovalpituzumab tesirine at Cycle 1 Day 1 and Cycle 3 Day 1 (Week 7).

#### 6.4.1.3 Day 2 (Day After Dosing) of Cycle 1 and Cycle 3 Only

- Subjects will take dexamethasone 8 mg PO BID (Section 5.6)

### 6.4.2 Day 1 Visit (±2 days) of Each Cycle

If Screening activities occur within 1 calendar day prior to Cycle 1 Day 1, the following pre-dose assessments do not need to be repeated at the Cycle 1 Day 1 Visit: physical examination, ECOG performance status, local safety labs (CBC with differential, chemistries, coagulation tests, urinalysis, and pregnancy test), and disease assessment with tumor response on cycles where imaging is required.

Day 1 procedures may be performed up to 2 calendar days prior to dosing of study drugs. Results from local clinical laboratory tests (at least CBC with differential and serum chemistry panel)

and disease assessment with tumor response on cycles where imaging is required must be available prior to dose administration. All assessments must occur prior to dosing (Appendix 13.1). Imaging report confirming measurable or evaluable disease from the central reader will be provided to determine eligibility prior to enrollment.

The following will be performed on the Day 1 Visit of each cycle:

- Physical examination (Section 7.7.1)
- Vital signs – within 30 minutes prior to the infusion, and then post-infusion at 30 minutes (±10 minutes), 2 hour (±15 minutes), and 4 hour (±30 minutes) for Cycles 1 and 3 only. For all other cycles, vital signs should be collected at least 30 minutes (±10 minutes), but no longer than 4 hours prior to infusion (Section 7.7.2). Post-infusion vitals do not need to include weight. Weight needs to be collected only once prior to infusion and does not need to be collected within 30 minutes prior to infusion.
- Urinalysis (Section 7.7.3)
- Pregnancy test (urine) (Section 7.7.3) for women of child-bearing potential
- Triplicate ECG prior to infusion of rovalpituzumab tesirine and then post-infusion at 30 minutes ± 10 minutes (only done on Cycles 1 and 3) (Section 7.7.4). Triplicate ECG should be performed prior to PK draw.
- Echocardiogram (only performed at Cycles 1and 3 (cycles where rovalpituzumab tesirine is administered) (Section 7.7.5)
- ECOG performance status (Appendix 13.3)
- Fluid Retention Questionnaire with daily weight diary accountability (Cycles 1, 2, 3, and 4) (Section 7.7.7)
- Record all AEs and SAEs (Section 7.6)
- Record concomitant medications
- Blood sample collection for:
  - CBC with differential (Section 7.7.3)
  - Serum chemistries (Section 7.7.3)
  - Coagulation tests (Section 7.7.3)
  - Rovalpituzumab tesirine PK (Section 7.3)
    - Prior to infusion – on Cycle 1 Day 1, Cycle 3 Day 1, and Cycle 5 Day 1

  - Post-infusion at 30 minutes (± 10 minutes), 2 hours (± 15 minutes), and 4 hours (± 30 minutes) – only on Cycle 1 and Cycle 3.
- Rovalpituzumab tesirine ATA –prior to infusion only on Cycle 1 Day 1, Cycle 3 Day 1, and Cycle 5 Day 1
- Nivolumab PK and ATA – all cycles (prior to infusion)
- Ipilimumab PK and ATA (Cohorts 2 and 3 only) – on Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, Cycle 5 Day 1, and Cycle 6 Day 1 (prior to infusion)
- Endocrinology tests, including ACTH, thyroid stimulating hormone (TSH), and free thyroxine (T4)
- Blood [redacted] (Section 7.4.2)
- Blood soluble markers (Section 7.4.3)
- Flow Cytometry (Section 7.4.4)
- Peripheral blood RNA (Section 7.4.5)
- CTCs – (C1D1 and C5D1 pre-infusion only) (Section 7.4.6)
- Plasma for ctDNA (Cycle 1 Day 1, pre-dose only) (Section 7.4.7)

- Administration of study drugs (Section 5.1); on applicable cycles, rovalpituzumab tesirine will be administered before nivolumab and ipilimumab. Similarly, on applicable cycles, nivolumab will be administered prior to ipilimumab.
- Serosal fluid collection, if applicable (Section 7.4.9)

### 6.4.3 Day 2 (Day After Dosing) of Cycle 1 and Cycle 3 Only

- Record AEs and SAEs (Section 7.6) – may be collected by telephone.
- Record concomitant medications – may be collected by telephone.
- A single rovalpituzumab tesirine PK draw will be obtained 24 hours (± 2 hours) after start time of infusion of rovalpituzumab tesirine on Day 1.

### 6.4.4 Days 8 and 15 Visits (± 2 days) of Cycle 1 and Cycle 3

The following assessments will be performed at Cycle 1 (Day 8), Cycle 1 (Day 15), Cycle 3 (Day 8) and Cycle 3 (Day 15) (± 2 days):

- Physical examination (Section 7.7.1)
- Vital signs (Section 7.7.2)
- Urinalysis (Section 7.7.3)

- Fluid Retention Questionnaire with daily weight diary accountability (Section 7.7.7)
- Record AEs and SAEs (Section 7.6)
- Record concomitant medications
- Serosal fluid collection, if applicable (Section 7.4.9)
- Blood sample collection for:
  - CBC with differential (Section 7.7.3)
  - Serum chemistries (Section 7.7.3)
  - Rovalpituzumab tesirine PK

### 6.4.5 Washout Period Safety Assessments

After the last dose of ipilimumab has been administered on Cycle 5 Day 1 in Cohorts 2 and 3, the subject will undergo a washout period for 6 weeks if in Cohort 2, and 8 weeks if in Cohort 3. During the washout period, subjects will have a Safety Visit in clinic and telephone follow-up calls as described in Table 3 and Table 4.

**Table 3. Cohort 2 Washout Period Schedule**

| Study Drug | Cycle 5 Day 1 | Washout Period | | | | | |
|---|---|---|---|---|---|---|---|
| | | Week 1 | Week 2[a] | Week 3 | Week 4[a] | Week 5 | Cycle 6 Day 1[b] |
| Nivolumab 1 mg/kg | X | | Safety Visit | | Phone Follow-up | | |
| Ipilimumab 1 mg/kg | X | | | | | | |
| Nivolumab 480 mg q4wk | | | | | | | X |

a. Window for visit/telephone follow-up is ±3 days.
b. Window for visit is ±2 days.

**Table 4. Cohort 3 Washout Period Schedule**

| Study Drug | Cycle5 Day 1 | Washout Period | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Week 1 | Week 2[a] | Week 3 | Week 4[a] | Week 5 | Week 6[a] | Week 7 | Cycle 6 Day 1[b] |
| Nivolumab 1 mg/kg | X | | Safety Visit | | Phone Follow Up Visit | | Safety Visit | | |
| Ipilimumab 3 mg/kg | X | | | | | | | | |
| Nivolumab 480 mg q4wk | | | | | | | | | X |

a. Window for visit/telephone follow-up is ±3 days.
b. Window for visit is ±2 days.

**Safety Visit**

The following will be performed during the Safety Visit:

- Physical examination (Section 7.7.1)
- Vital signs (Section 7.7.2)
- ECOG performance status (Appendix 13.3)
- Record AEs and SAEs (Section 7.6)
- Record concomitant medications
- Blood samples for:
- CBC with differential (Section 7.7.3)
- Serum chemistries (Section 7.7.3)

**Telephone Follow-up Calls**

The following will be reviewed during the telephone follow-up call:

- Any new or ongoing AEs
- Any new concomitant medications

### 6.4.6 Efficacy Assessment and Tumor Response

On applicable cycles, disease assessment will occur at least 3 days, but no greater than 7 days, prior to day of dosing.

**Cohort 1 Imaging Schedule:**

- Prior to Cycle 3 Day 1 (6 weeks after Screening imaging)
- Prior to Cycle 5 Day 1 (7 weeks after Cycle 3 Day 1 imaging)
    - If response is noted (CR or PR) on Cycle 5 Day 1 scan, a mandatory 4 week follow up scan will be performed to confirm response. The 4 week follow up scan may be omitted if no response is noted on Cycle 5 Day 1 scan.
- Prior to Cycle 7 Day 1 (8 weeks after Cycle 5 Day 1 imaging)
- After Cycle 5 Day 1, imaging will be collected every 8 weeks (at least 3 days, but no greater than 7 days, prior to day of dosing) during the maintenance therapy stage of the study.

**Cohort 2 Imaging Schedule:**

- Prior to Cycle 3 Day 1 (6 weeks after Screening imaging)
- Prior to Cycle 5 Day 1 (6 weeks after Cycle 3 Day 1 imaging)

- Prior to Cycle 6 Day 1 (6 weeks after Cycle 5 Day 1 imaging given washout period)
- Prior to Cycle 8 Day 1 (8 weeks after Cycle 6 Day 1 Imaging)
- After Cycle 8 Day 1, imaging will be collected every 8 weeks (at least 3 days, but no greater than 7 days, prior to day of dosing) during the maintenance therapy stage of the study.

**Cohort 3 Imaging Schedule:**

- Prior to Cycle 3 Day 1 (6 weeks after Screening imaging)
- Prior to Cycle 5 Day 1 (6 weeks after Cycle 3 Day 1 imaging)
    - If response is noted (CR or PR) on Cycle 5 Day 1 scan, a mandatory 4 week follow up scan will be performed to confirm response. The 4 week follow up scan may be omitted if no response is noted on Cycle 5 Day 1 scan.
- Prior to Cycle 6 Day 1 (8 weeks after Cycle 5 Day 1 imaging given washout period)
- Prior to Cycle 8 Day 1 (8 weeks after Cycle 6 Day 1 imaging)
- After Cycle 8 Day 1, imaging will be collected every 8 weeks (at least 3 days, but no greater than 7 days, prior to day of dosing) during the maintenance therapy stage of the study.

Disease assessment will consist of the following:

- CT scans of the chest, abdomen, and pelvis (and neck if indicated) (Section 7.2)
- MRI of the brain – if clinically indicated (e.g. if CNS progression has been documented previously). CT of the brain with IV contrast may be substituted at the discretion of the study doctor.

Tumor response will be determined and categorized by RECIST v1.1 (Eisenhauer, 2009).

## 6.5 End of Treatment Visit

The EOT Visit occurs within 7 days of documentation of the decision to discontinue treatment. The following procedures will be performed at the EOT Visit:

- Physical examination (Section 7.7.1)
- Vital signs (Section 7.7.2)
- Urinalysis (Section 7.7.3)
- Pregnancy test (urine) (Section 7.7.3) for women of childbearing potential
- Triplicate ECG (Section 7.7.4)

- Echocardiogram (Section 7.7.5)
- ECOG performance status (Appendix 13.3)
- Record AEs and SAEs (Section 7.6)
- Fluid Retention Questionnaire with daily weight diary accountability (Section 7.7.7) if EOT occurs prior to Cycle 5
- Record concomitant medications
- Disease assessment consisting of CT scans of the chest, abdomen, and pelvis (and neck if indicated) – may be omitted if a Disease/Response Assessment was performed within the last 6 weeks (Section 7.2)
- MRI of the brain – if clinically indicated (e.g., if CNS progression has been documented previously); may be omitted if a Disease/Response Assessment was performed within the last 6 weeks. CT of the brain with IV contrast may be substituted at the discretion of the investigator (Section 7.2).
- Blood samples for:
  - CBC with differential (Section 7.7.3)
  - Serum chemistries (Section 7.7.3)
  - Coagulation tests (Section 7.7.3)
  - Rovalpituzumab tesirine PK and ATA
  - Nivolumab PK and ATA
  - Ipilimumab PK and ATA
  - Blood [redacted] (Section 7.4.2)
  - Plasma for ctDNA (Cycle 1 Day 1, pre-dose only) sample
  - Blood soluble markers (Section 7.4.3)
  - Flow Cytometry (Section 7.4.4)
  - Peripheral blood RNA (Section 7.4.5)
  - CTCs (Section 7.4.6)
  - Endocrinology Tests, including ACTH, thyroid stimulating hormone (TSH), and free thyroxine (T4)
- (Optional) fresh tumor tissue, collected at disease progression (Section 7.4.1)
- Serosal fluid, if applicable (Section 7.4.9)

### 6.6 Long-Term Follow-up; Every 6-12 weeks ±1 week

For all subjects who discontinue study drugs for reasons other than disease progression (e.g. due to an AE), the first follow-up visit will occur at 6 weeks (±1 week) after the last dose of study drugs, then q6wk (±1 week) until 6 months, then q12wk (±1 week) until disease progression, initiation of new anticancer therapy, or withdrawal/ termination from the study. Procedures to be conducted on follow-up visits include:

- Record AEs and SAEs (Section 7.6)
- Disease response assessment consisting of CT scans of the chest, abdomen, and pelvis (and neck if indicated) (Section 7.2)
- MRI of the brain – if clinically indicated (e.g. if CNS progression has been documented previously). CT of the brain with IV contrast may be substituted at the discretion of the investigator (Section 7.2).
- (Optional) fresh tumor tissue, collected at disease progression (Section 7.4.1)
- Blood samples for:
  - Blood soluble markers (Section 7.4.3)

Survival status will be followed until death or study withdrawal/termination, whichever occurs first.

At progression, an optional collection of fresh tumor tissue may be conducted (Section 7.4.1).

After disease progression, subjects who are not retreated will be followed for subsequent anticancer therapies and dates, as well as survival status, q6wk (± 1 week) for 24 weeks (6 months), then q12wk (± 1 week) until death or study termination, whichever occurs first.

### 6.7 End of Study/End of Follow-Up

The date the subject met criteria for study discontinuation and the reason for study discontinuation will be recorded. Where available, subsequent anticancer therapies and dates, date of progression (if not already captured on study), and survival status will be recorded.

## 7. Study Assessments

### 7.1 Screening/Baseline Assessments

Only subjects who meet all of the inclusion and none of the exclusion criteria specified in Section 4 will be enrolled in this study.

Screening radiographic assessment must include brain MRI and CT of the chest, abdomen and pelvis (and neck if indicated). CT of the brain with IV contrast may be substituted at the discretion of the investigator. Presence of measureable or evaluable disease at baseline will have to be confirmed by the central reader to determine subject eligibility for the study.

Demographics include age, gender, race, smoking history, and status.

Subject medical and surgical history includes a thorough review of significant past medical and surgical history, current conditions, any treatment for prior malignancies and response to prior treatment, and any concomitant therapies.

Malignancy history should include diagnosis date, tumor type, mutational status, stage, sites of metastases, and prior therapies including dates of treatment and reasons for treatment discontinuation, responses and dates of progression, as available and applicable.

## 7.2 Radiographic Response/Efficacy Assessments

Treatment response will be assessed by radiographic tumor evaluations at protocol-specified time points. Radiographic tumor evaluations include:

- Diagnostic quality, spiral CT scans of the chest, abdomen and pelvis (and neck if indicated)
- MRI of the brain, if indicated. CT of the brain with IV contrast may be substituted at the discretion of the investigator.

Diagnostic quality, spiral CT scans are recommended; other methods may be used if performed consistently throughout the study for each individual subject. Positron emission tomography (PET) scans may be used in an ancillary manner; however, no decisions relating to PD may be made based on PET scans alone. Clinical response will be determined by the investigator at each assessment according to RECIST v1.1 (Appendix 13.5; Eisenhauer, 2009).

For tumors to be assigned a status of responder (PR or CR), changes in tumor measurements must be confirmed by repeat assessments performed no less than 4 weeks, but preferably not more than 6 weeks, after the criteria for response are first met; i.e., two consecutive assessments of PR or CR are required. In instances where a follow-up visit is not otherwise scheduled to occur for more than 6 weeks, repeat radiographic disease assessments should be conducted at least 4 but not more than 6 weeks after the criteria for response are first met, in order to confirm response, whether or not a formal follow-up visit is conducted at the same time.

### 7.2.1 Radiographic Disease Progression

Radiographic disease progression will be defined by RECIST v1.1 (Appendix 13.5).

Accumulating evidence indicates that a minority of subjects with solid tumors treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Subjects will be permitted to continue on treatment with nivolumab and/or ipilimumab beyond initial RECIST v1.1-defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit and without rapid disease progression
- Continue to meet all other study protocol eligibility criteria
- Subject tolerates study drug
- Subject has stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases).

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed with the medical monitor (or designee), and an assessment of the risk/benefit of continuing with study therapy must be documented in the study records.

The tumor burden volume from the time of initial progression should be used as the reference baseline for comparison with the post-progression assessment. Any new lesion considered non-measurable at the time of initial progression may become measurable, and therefore, must be included in the tumor burden measurement as follows:

For solid tumors: New lesions are considered measurable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes, which must have a short axis of at least 15 mm).

For statistical analyses that include the investigator-assessed progression date, subjects who continue treatment beyond the initial investigator-assessed, RECIST v1.1-defined progression will be considered to have investigator-assessed PD at the time of the initial progression event.

Subjects should continue to receive monitoring according to the on-treatment assessments in Appendix 13.1. Radiographic assessment by CT (preferred) or MRI described in Section 7.2 and Appendix 13.1 is required when subjects continue post-progression treatment. For subjects that discontinue post-progression treatment with study therapy, no additional radiographic assessments will be required.

### 7.2.2 Central Radiographic Assessment

Radiological scans will be collected for assessment by a Central Radiographic Assessment Reader. Within 24 hours of each subject's disease assessment, the appropriate scans should be sent by overnight courier or electronically to the central facility. The central reader will make the definitive decision on tumor burden (including measurable disease) and tumor response, which will be relayed to the investigator. All decisions on treatment eligibility, continuation, discontinuation, and retreatment will be made based on the tumor response adjudicated by the central reader.

## 7.3 Pharmacokinetic Assessments

Blood samples for PK and ATA testing will be collected at the time points throughout the study as indicated in Section 6.4, Appendix 13.1, and Appendix 13.2.

Sensitive, validated assays will be used to measure blood concentrations of rovalpituzumab tesirine ADC and related analytes of rovalpituzumab tesirine, such as total antibody and SC-DR002, as applicable. A validated immunoassay will be used to assess ATA against rovalpituzumab tesirine. Analogous assays may be performed for nivolumab and/or ipilimumab.

## 7.4 Pharmacodynamic and Biomarker Assessments

Blood and/or tissue samples for PD and biomarker testing will be collected at the time points throughout the study as indicated in Appendix 13.1. PD and biomarker assessments will include analysis of tumor tissue including but not limited to DLL3 and PD-L1 expression, and of blood samples for tumor markers, CTC, immune, and soluble biomarkers such as DLL3. See the Laboratory Manual for additional details.

### 7.4.1 Tumor Tissue

Tumor tissue, consisting of a representative archived specimen or a fresh tumor biopsy, will be assessed for expression of DLL3 and PD-L1 by methods such as, but not necessarily limited to, immunohistochemistry. Additional studies, such as routine hematoxylin and eosin for morphology and histological classification, immunohistochemistry for confirmation of diagnosis [redacted] may be performed.

At disease progression, an optional tumor biopsy may be performed for the assessment of expression of DLL3 and/or PD-L1, and/or execution of additional studies, such as but not necessarily limited to scoring of immune infiltrates or assessment of molecular pathways related to the response to rovalpituzumab tesirine. Any remaining tissue may be utilized for additional biomarker research and exploratory studies including, but not necessarily limited to, assessment

of tissue for nucleic acid or protein based biomarkers to understand drug sensitivity and resistance, biology of SCLC, and to develop new diagnostic tests.

### 7.4.2 [redacted]

At the indicated times, blood will be collected for testing of [redacted]

### 7.4.3 Blood Soluble Markers

At the indicated times, blood samples will be collected for possible testing of biomarkers that may be related to the PD effects of rovalpituzumab tesirine, nivolumab and/or ipilumumab, such as, but not necessarily limited to, soluble DLL3, or circulating chemokines or cytokines [redacted]

### 7.4.4 Flow Cytometry

At the indicated times, blood will be collected for flow cytometry peripheral blood mononuclear cells (PBMCs) for characterization of immune subsets.

### 7.4.5 Peripheral Blood RNA

Peripheral blood RNA consists of whole blood RNA for assessment of analytes that may reflect the PD effects of rovalpituzumab tesirine, nivolumab, and/or ipilimumab, [redacted]

### 7.4.6 Circulating Tumor Cells

At the indicated times, blood samples will be collected for assessment and characterization of CTCs as a possible reflection of disease burden. This will include a sample for exploratory analyses of CTC-associated biomarkers, such as DLL3, implemented only at specific sites based on feasibility.

### 7.4.7 Cell-Free Circulating Tumor DNA

At the indicated times, blood samples will be collected for possible assessment and characterization of cell free circulating tumor DNA (ctDNA) to potentially assess tumor burden, response to treatment, and PD, and to characterize tumor mutations.

### 7.4.8 Genotyping

At screening, a blood and/or tumor sample will be collected for possible assessment of genes for genetic lesions and/or polymorphisms which may influence the safety or efficacy response to the study drugs. Such genes may include but are not necessarily limited to [redacted]

### 7.4.9 Serosal Fluid

Any pericardial, pleural and/or ascitic fluid collected as part of routine care (e.g. as part of a therapeutic thoracentesis, pericardiocentsis, or paracentesis) will be procured, where feasible, for possible PK, PD, and/or biomarker testing. See the Laboratory Manual for additional details.

## 7.5 Biospecimen Repository

For subjects who provide additional written consent, remaining de-identified unused clinical samples (blood and/or tissue) will be retained by the sponsor and used for the sponsor's future research, including, but not limited to, the evaluation of DLL3 and of additional targets for novel therapeutic agents, the biology of DLL3, and to identify biomarkers. Blood and tissue samples donated for future research may be retained by the sponsor or its designee for up to, but no longer than, 20 years from the end of the main portion of the study. If additional written consent is not provided, any remaining biological samples will be destroyed by sponsor or its designee following study completion.

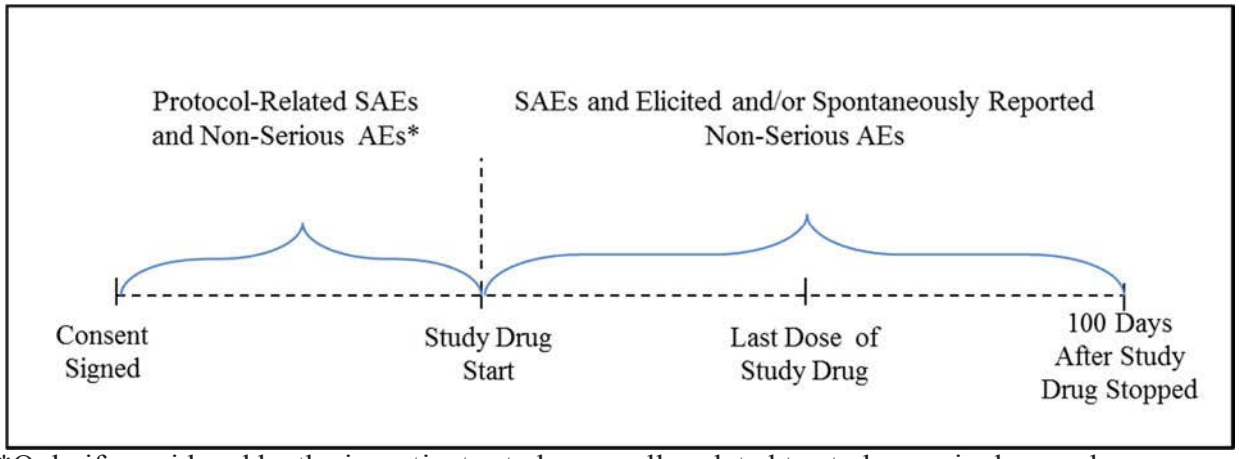
## 7.6 Adverse Event Collection

All AEs reported from the time of study drug administration until 100 days following discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, protocol-related serious and non-serious AEs will be collected from the time the subject signed the study-specific informed consent.

Serious and non-serious AEs occurring after the study-specific informed consent is signed but prior to the initial dose of study drug will be collected **only** if they are considered by the investigator to be causally related to the study-required procedures.

AE information will be collected as shown in Figure 2.

**Figure 2. Adverse Event Collection**




*Only if considered by the investigator to be causally related to study-required procedures.

## 7.7 Other Safety Assessments

In addition to the surveillance and recording of AEs, the assessment of safety during the course of this study will consist of the recording of concomitant therapies; protocol-specified physical examination findings including vital signs; Fluid Retention Questionnaire with daily weight diary; ECOG performance status; disease assessments; and diagnostic testing including laboratory testing, radiographic imaging, ECGs, and echocardiograms.

Safety will be monitored over the course of the study by an SMC.

### 7.7.1 Physical Examination

Physical examinations will include assessments of the head and neck, heart, lungs, abdomen, extremities, neurological, and skin. Complete (comprehensive) physical exam performed at Screening only. A symptom-directed physical examination, including disease progression, will be performed at all other designated visits.

### 7.7.2 Vital Signs, Weight and Height

Vital signs will include heart rate, respirations, blood pressure, and temperature. All vital signs should be measured after the subject has been sitting/resting for at least 5 minutes. For adult subjects (≥18 years), measurements of height obtained within 6 months prior to Screening Visit may be utilized. In the event of an infusion reaction or hypersensitivity reaction (IHR), vital signs should be monitored more frequently than originally scheduled and as clinically indicated.

Weight will be measured at the times indicated, preferably without outer garments such as hats, coats, or shoes. Measurements while in light indoor clothing only, or undergarments only, are

acceptable; but every effort should be made to measure subjects in the same or similar clothing, including any accessories or jewelry, at each assessment.

### 7.7.3 Clinical Laboratory Tests

Laboratory assessments will be performed to evaluate safety at scheduled time points (Appendix 13.1) during the course of the study. The following assessments will be performed at the local laboratory:

- CBC, including white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell (RBC) count, platelet count, hemoglobin, and hematocrit.
- Chemistry panel, including electrolytes (sodium, potassium, chloride, and carbon dioxide), creatinine, blood urea nitrogen (BUN), eGFR, glucose, calcium, magnesium, phosphorus, albumin, total protein, amylase, lipase, and liver function tests (total and direct bilirubin, ALT, AST, alkaline phosphatase, and lactate dehydrogenase [LDH]).
- Coagulation tests, including prothrombin time (PT), partial thromboplastin time (PTT) or activated partial thromboplastin time (aPTT), and INR.
- Endocrine tests, including adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), and free thyroxine (T4).
- Urinalysis, including dipstick results for color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, and protein; as well as spot protein and creatinine.
- Hepatitis B and C tests include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb) and hepatitis C virus (HCV) antibody. Results that may be consistent with chronic or active infection, and/or subjects with known prior active hepatitis B or C infection, should undergo PCR tests for Hepatitis B and/or C, respectively.
- Pregnancy test, consisting of blood or urine testing for beta-human chorionic gonadotropin (β-hCG). Repeat testing may be performed per the investigator.

### 7.7.4 Electrocardiograms

Throughout the study, subjects will be monitored for changes in cardiac conduction through ECGs (Appendix 13.1). ECGs consist of triplicate 12-lead studies, performed within a 5 minute window after at least 10 minutes of quiet rest in a supine position and should be done prior to blood sample for pharmacokinetics, when applicable.

### 7.7.5 Echocardiogram

Echocardiograms will be performed at the indicated times to assess any pericardial effusions, if present, as well as cardiac function (left ventricular ejection fraction [LVEF]). Echocardiograms will only be performed at cycles 1 and 3 (cycles where rovalpituzumab tesirine is administered). Echocardiograms must be reviewed prior to rovalpituzumab tesirine infusions to rule out pericardial effusions. Echocardiograms may be performed up to 72 hours prior to rovalpituzumab tesirine administration.

### 7.7.6 ECOG Performance Status

ECOG performance Status (Appendix 13.3) will be evaluated at protocol-specific time points (Appendix 13.1).

### 7.7.7 Fluid Retention Questionnaire with Daily Weight Diary

Throughout the treatment period, subjects will be asked about the development of any new or worsening peripheral edema or dyspnea (Appendix 13.9). This assessment may take place via telephone.

Throughout the treatment period (starting with Day 1 pre-dose through the end of Cycle 4), subjects will maintain a diary of daily weights.

## 7.8 Paraneoplastic Assessment

Paraneoplastic assessment includes documentation of the presence of an SCLC-related paraneoplastic syndrome, if present (Appendix 13.8).

## 7.9 Appropriateness of Measurements

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications. AEs and, when applicable, clinical laboratory data will be graded using NCI CTCAE, version 4.03 (Appendix 13.6).

Response will be assessed according to RECIST v1.1 (Eisenhauer, 2009), which includes standard criteria for evaluating response in solid tumors. The intervals of evaluation in this protocol are appropriate for disease management.

Standard tests will be performed to detect the possible presence of specific antibodies to study drugs. PK assessments for drug activity are also common in clinical studies.

# 8. Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this study is defined as rovalpituzumab tesirine in combination with nivolumab alone or combined with nivolumab and ipilimumab. Complaints associated with any component of this investigational regimen must be reported to the sponsor (Section 8.2.2.7).

For product complaints, please refer to Section 8.4.

## 8.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The investigator will assess and record any AE in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drugs, and any action(s) taken. For serious adverse events (SAEs) considered as having "no reasonable possibility" of being associated with study drugs, the investigator will provide another cause of the event. For AEs to be considered intermittent, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All AEs will be followed to a satisfactory conclusion.

### 8.1.1 Definitions

#### 8.1.1.1 Adverse Event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are

considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

All protocol-related AEs must be collected from the signing of the study specific informed consent until study drug administration.

In addition, adverse events with onset or worsening reported by a subject from the time that the first dose of study drug is administered until 100 days have elapsed following discontinuation of study drug administration will be considered as treatment-emergent adverse events.

#### 8.1.1.2 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to AbbVie or designee as an SAE within 24 hours of the site being made aware of the SAE.

| | |
|---|---|
| **Death of Subject** | An event that results in the death of a subject. |
| **Life-Threatening** | An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form. |
| **Hospitalization or Prolongation of Hospitalization** | An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit, admission to an outpatient facility, hospitalization for respite care, or admission within the follow-up period for salvage therapy. |
| **Congenital Anomaly** | An anomaly detected at or after birth, or any anomaly that results in fetal loss. |

| | |
|---|---|
| **Persistent or Significant Disability/Incapacity** | An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle). |
| **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome** | An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. |

For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

### 8.2 Adverse Event Severity

The investigator will rate the severity of each AE according to the NCI CTCAE Version 4.03.

For AEs not captured by the Common Terminology Criteria, the following should be used:

| | |
|---|---|
| **Grade 1** | The AE is transient and easily tolerated by the subject (mild). |
| **Grade 2** | The AE causes the subject discomfort and interrupts the subject's usual activities (moderate). |
| **Grade 3/4** | The AE causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening (severe). |
| **Grade 5** | The AE resulted in death of the subject (severe). |

### 8.2.1 Relationship to Study Drugs

The investigator will use the following definitions to assess the relationship of the AE to the use of rovalpituzumab tesirine, nivolumab, or ipilimumab:

| | |
|---|---|
| **Reasonable Possibility** | After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship. |
| **No Reasonable Possibility** | After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship. |

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an investigator's opinion of no reasonable possibility of being related to study drug is given, another cause of event must be provided by the investigator for the SAE.

### 8.2.2 Deaths

For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

Deaths that occur during the protocol specified AE reporting period that are more likely related to disease progression will therefore be considered as expected AE and will not be subject to expedited reporting.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE eCRF. Generally, only one such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a subject with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the AE eCRF. If the cause of death later

becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

#### 8.2.2.1 Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

#### 8.2.2.2 Recording Adverse Events

The following information should be recorded on the AEs and medical history eCRF:

- Description using standard medical terminology, including any onset and resolution dates
- Whether the AE met serious criteria
- Grade or Severity
- Relationship to study drug(s) or alternate causality
- Outcome

#### 8.2.2.3 Diagnosis vs. Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical practice. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, the individual symptom should be reported as a separate AE.

For infusion-related reactions, if multiple signs or symptoms occur with a given infusion-related event, each sign or symptom may be recorded separately with its own level of severity.

#### 8.2.2.4 Recording Serious Adverse Events

For SAEs, record the event(s) on both the eCRF and an SAE form.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both the SAE form and the eCRF.
- For hospitalizations, surgical or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the therapeutic action taken in response to the illness.

#### 8.2.2.5 Adverse Events Expected Due to SCLC or Progression of SCLC

AEs that may be expected from primary SCLC lesions, compression of adjacent thoracic structures or distant metastases are presented in Appendix 13.10, Adverse Events Expected Due to SCLC or Progression of SCLC of the protocol.

These AEs may occur alone or in various combinations and are considered expected AEs in SCLC subjects.

The term “disease progression” alone should not be used when reporting AEs or SAEs, due to its lack of specificity. Rather, symptoms of disease progression should be collected under the unifying diagnosis of "malignant neoplasm progression"; symptoms of progression may be subsumed under this diagnosis.

#### 8.2.2.6 Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from the time of study drug administration (Cycle 1 Day 1) until 100 days following discontinuation of study drug administration. In addition, protocol related serious adverse events and protocol-related nonserious adverse events will be collected from the time the subject signed the study-specific informed consent, only if considered by the Investigator to be causally related to study-required procedures. All SAEs that occur after the safety reporting period and are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor or designee.

Each SAE must be followed until the SAE returns to baseline (resolves or recovers to baseline) or the SAE stabilizes (resolves or recovers with sequelae); the SAE is considered not recovered or not resolved by the investigator; or the subject dies (the SAE end date is equal to the date of death). SAE outcome may not be possible to collect when a subject withdraws consent.

Additionally, all SAEs that occur *after* the safety reporting period (as defined above) that are considered study treatment-related by the investigator, should also be reported to the sponsor or its designee.

All non-serious AEs will be followed through the safety reporting period.

#### 8.2.2.7 Serious Adverse Events Require Immediate Reporting

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the

SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

| | |
|---|---|
| **Email (preferred):** | [redacted] |
| | and |
| | [redacted] |
| **Fax:** | [redacted] |

For general or specific patient safety concerns, please contact the Medical Director listed below:

[redacted]

[redacted]

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (TA MD) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

| | |
|---|---|
| **Phone:** | [redacted] |

## 8.3 Toxicity Management

Subjects will be monitored continuously for toxicity while on study treatment. Toxicity will be assessed using the NCI CTCAE Version 4.03. Adjustments to these guidelines may occur based on the clinical judgment of the investigator with notification to the TA MD.

### 8.3.1 Management of Serosal Effusions/Serositis

Serosal effusions (pleural or pericardial, or ascites) have been observed with rovalpituzumab tesirine, and have the potential to be life-threatening (e.g. pericardial tamponade). Therefore, development of any of these events or worsening from baseline warrants prompt evaluation by the investigator or designee. Alternative causes, such as infection, congestive heart failure, disease progression, and in particular an immune-mediated AE (as might be caused by a checkpoint inhibitor; see Section 8.3.3), should be ruled out. When appropriate, a unifying

diagnosis should be reported, e.g. "heart failure," not simply "pleural effusion" and "edema limbs."

When considered clinically significant (e.g. grade 2 or higher and considered related to study drug):

- Systemic corticosteroids, when initiated promptly, have been reported to be beneficial in some prior cases during treatment with rovalpituzumab tesirine. The investigator should consider initiation of prednisone 1-2 mg/kg/day or equivalent, initiating a taper after improvement to Grade 1 or less, over the following 2-4 weeks.
- Until clinical experience suggests otherwise, guidance for dose delay and/or reduction of rovalpituzumab tesirine, as well as criteria for ongoing dosing, should follow Section 5.2.3 and Section 5.5.

### 8.3.2 Management of Skin Reactions

Skin reactions have been described during single-agent treatment with rovalpituzumab tesirine, nivolumab and ipilimumab. For rovalpituzumab tesirine, these have consisted primarily of photosensitivity, although other reactions such as palmar-plantar erythrodysesthesia and erythema multiforme have been reported. In contrast, for nivolumab and ipilimumab, immune-mediated dermatitis or rash has been described (Section 8.3.3 and Appendix 13.7). As such, development of a skin reaction during treatment warrants prompt evaluation by the investigator or designee:

- If clinically consistent with photosensitivity, the AE may be reported as such (using medically accurate and descriptive AE terminology), and managed as described in Table 5.
- If not clinically consistent with photosensitivity, the following should be done:
  - Photo documentation to facilitate later review by the sponsor or designee.
  - Formal evaluation by a dermatologist, including possible skin biopsy, to rule out alternative etiologies, such as erythema multiforme which may warrant discontinuation of study drug(s), and to facilitate the most appropriate terminology for AE reporting.
  - Immune-mediated skin reactions should consider the guidance of Appendix 13.7.

**Table 5. Recommended Management of Photosensitivity**

| CTCAE v4.03 | | Treatment Recommendations | Dose Modifications |
|---|---|---|---|
| Grade 1 | Painless erythema and erythema covering <10% body surface area (BSA) | Low-potency topical steroid (face)<br>High-potency topical steroid (body) | – |
| Grade 2 | Tender erythema covering 10–30% BSA | Low-potency topical steroid (face)<br>High-potency topical steroid (body)<br>Nonsteroidal anti-inflammatory agents orally as needed | – |
| Grade 3 | Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs) | Low-potency topical steroid (face)<br>High-potency topical steroid (body)<br>Prednisone 0.5 mg/kg x 7 days | Reduce dose |
| Grade 4 | Life-threatening consequences; urgent intervention indicated | Low-potency topical steroid (face)<br>High-potency topical steroid (body)<br>Prednisone 0.5 mg/kg x 7 days<br>Hospitalization | Reduce dose |

### 8.3.3 Management of Potential Drug-Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential DILI is defined as:

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

In general, an increase of AT to >3 x ULN should be followed by repeat testing within 48-72 hours of all four of the usual measures (ALT, AST, alkaline phosphatase, total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing. Inquiry regarding symptoms should also be made (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash). Subjects may be retested locally, but normal laboratory ranges should be recorded and results made to the investigator immediately. All data must be recorded in the eCRF. If symptoms persist or repeat testing shows AT >3 x ULN for subjects with normal baseline measures or 2-fold increases above baseline values for subjects with elevated values

before drug exposure, close observation should be initiated. If close monitoring is not possible, study drugs should be discontinued.

Close observation includes:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease.
- Obtaining a history of exposure to environmental chemical agents.
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., international normalized ratio [INR], direct bilirubin).
- Considering gastroenterology or hepatology consultations.

Discontinuation of study drugs should be considered if potential DILI is suspected and:

- ALT or AST >8 x ULN
- ALT or AST >5 x ULN for more than 2 weeks
- ALT or AST >3 x ULN and (TBL >2 x ULN or INR >1.5)
- ALT or AST >3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia

All subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state. Retreatment of subjects who develop possible DILI and have previously discontinued study drugs may only be permitted upon approval by the sponsor and medical monitor.

### 8.3.4 Immune-Mediated Adverse Events

General guidelines for immune-mediated AEs, which have been described during treatment with nivolumab and/or ipilimumab, but not (to date) with rovalpituzumab tesirine, may be found in Appendix 13.7.

General principles include that differential diagnoses should be diligently evaluated according to standard medical practice, and consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended. These evaluations, in addition to the guidelines of Appendix 13.7 may be supplemented by discussions with the medical monitor. Non-inflammatory etiologies should be considered and appropriately treated.

### 8.3.5 Potential for Infusion-Related Reaction

No infusion-related AEs with rovalpituzumab tesirine have been reported to date. However, as rovalpituzumab tesirine is administered via IV infusion, appropriate precautions should be taken during infusion of the drug with regular monitoring of vital signs per local institutional standards. In the event of a suspected infusion reaction, the infusion should be stopped at least temporarily and institutional standard supportive care administered.

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE version 4.03 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

**For Grade 1 symptoms**: (Mild reaction; infusion interruption not indicated; intervention not indicated)

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

**For Grade 2 symptoms:** (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤24 hours).

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms.

Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

**For Grade 3 or Grade 4 symptoms:** (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life-threatening; pressor or ventilator support indicated).

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

### 8.3.6 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs, including anticipated SAEs, to the sponsor or designee (Section 8.2.2.7).

The sponsor or designee will report all SAEs to the appropriate regulatory authorities as required per local regulatory reporting requirements. In the United States, endpoints that assess disease-related mortality or major morbidity as well as other SAEs that are not study endpoints (but are known consequences of the underlying disease or condition that are anticipated to occur in the study population), should not be reported to Food and Drug Administration (FDA) as individual IND safety reports (per the final rule amending the IND safety reporting requirements under the Code of Federal Regulations 21 CFR 312.32 and FDA guidance, Safety Reporting Requirements for INDs and bioequivalence/ bioavailability (BE/BA) Studies, (FDA, 2012).

### 8.3.7 Laboratory Test Result Abnormalities

Any laboratory test result abnormality should be reported as an AE or SAE, as appropriate, if it:

- is clinically significant or meets the definition of an SAE
- required the subject to have study drugs discontinued or interrupted
- required the subject to receive specific corrective therapy

Wherever possible, the clinical rather than laboratory term should be used by the reporting investigator (e.g. "anemia" rather than "low hemoglobin").

### 8.3.8 Pregnancy

Pregnancy in a study subject must be reported to the sponsor within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued.

All subjects should be informed that contraceptive measures (refer to Section 5.10) should be taken throughout the study and for at least 31 weeks following the last dose of study drug. Male subjects should be informed that contraceptive measures should be taken by their female partner.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. In the event of a pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information, and the pregnancy will be followed to outcome.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

## 8.4 Product Complaint

### 8.4.1 Definition

A Product Complaint is any Complaint related to the biologic or drug component of the products.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, or packaging issues.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

### 8.4.2 Reporting

Product Complaints concerning the investigational product must be reported to the sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product Complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

# 9. Data Quality Control and Quality Assurance

## 9.1 Site Training and Monitoring Procedures

A Study Binder with instructions for study compliance and eCRF completion will be provided. Prior to the enrollment of subjects at the site, the sponsor or its designated clinical and medical personnel will review the following items with the investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration and withdrawal processes
- Current IB
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The eCRF completion process and source documentation requirements
- Monitoring requirements
- Institutional Review Board/Independent Ethics Committee (IRB/IEC) review and approval process
- Informed consent process
- GCP guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labeling, dispensing, and recordkeeping
- Subject coding
- Study samples/specimen collection, handling, and shipping
- Protocol compliance
- Clinical study record keeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the sponsor representative will review regulatory documentation, eCRFs, source documentation, investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study subjects, and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the sponsor or its designated monitors and by quality assurance (QA) auditors, or representatives of regulatory authorities.

## 9.2 Data Management Procedures

The sponsor or its designee will provide eCRF Completion Guidelines for data entry. Study-specific data management procedures will be maintained in the Data Management Plan. Queries resulting from edit checks and/or data verification procedures will be posted in the eCRF.

## 9.3 Access to Source Data

The investigator will permit the sponsor's representatives to monitor the study as frequently as the sponsor deems necessary during or after the completion of the study to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect subject confidentiality are to be employed during monitoring. The eCRFs and related source documents will be reviewed in detail by the sponsor's representative(s) at each site visit. Original source documents or certified copies must be provided to the sponsor's representative for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm that the information contained in the CRFs, such as disease assessments, AEs, and concomitant therapies, is complete and correct. Other study records, such as correspondence with the sponsor and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be made available during or after completion of the study for inspection by representatives of regulatory authorities. In the event of an inspection by regulatory authorities, the sponsor may be available to assist in any preparations. All pertinent study data must be made available as requested to the regulatory authority for verification, audit, or inspection purposes.

## 9.4 Accuracy and Reliability of Data

The sponsor or its designee shall take steps to assure the accuracy and reliability of data including:

- The selection of qualified investigators and appropriate study centers.
- Review of protocol procedures with the investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- Review of eCRFs for accuracy and completeness by the designated monitor(s) during monitoring visits to the study centers. Any discrepancies will be resolved with the investigator or designees as appropriate.

## 9.5 Quality Assurance Procedures

The sponsor's QA group or its designee may conduct audits at the clinical site or other study-related facilities and organizations during or at any time after the study. Audit reports will be retained by the sponsor's QA group or its designee as part of the written record.

## 9.6 Data Handling and Recordkeeping

### 9.6.1 Data Handling

It is the investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the eCRFs and in all required reports. The eCRFs should be captured in the sponsor Electronic Data Capture (EDC) system within five (5) business days of the subject's visit to the site. Data reported on the eCRF that is derived from source documents should be consistent with the source documents or the discrepancies must be explained.

Any change or correction to an eCRF must be maintained in an audit trail within EDC system. Data changes may only be made by those individuals so authorized. Prior to database lock the investigator must review and approve the completed eCRFs to verify their accuracy.

### 9.6.2 Investigator Record Retention

The investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, and in-patient or office subject records) for the maximum period required by the country and institution in which the study will be conducted, or for the following periods, whichever is longer: for at least two (2) years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or for at least two (2) years after the relevant authority has been informed of the discontinuation of clinical development of the study drugs. The investigator may not destroy any records associated with the study without obtaining the prior, written consent of the sponsor. If the investigator withdraws from the study (due to relocation, retirement, etc.), the records shall be transferred to a mutually agreed upon designee, such as another investigator or IRB/IEC. No records shall be transferred without prior, written authorization from the sponsor or its designee.

# 10. Data Analysis and Statistical Methods

This section provides the key details of the statistical analyses to be performed using data captured according to this protocol. Further details on planned analyses for the data captured in this protocol will be provided in the Statistical Analysis Plan.

## 10.1 Determination of Sample Size

Up to approximately 90 subjects are expected to participate in this three-cohort trial (up to approximately 30 per cohort).

The primary objective of this study is to determine the tolerability, adverse event profile, and any DLTs for rovalpituzumab tesirine when given in combination with nivolumab or nivolumab and ipilimumab intravenously in adult subjects with extensive-stage small cell lung cancer. Safety will be monitored throughout the trial by the safety monitoring committee (SMC). The sample size for this study is based on the need to establish safety of the regimens being evaluated and 6 subjects is the minimum number required for the clinical safety evaluation of each cohort and 12 subjects may need to be enrolled in order to evaluate safety after 12 weeks in at least 6 subjects. Enrollment of a minimum of 6 subjects and a maximum of 30 subjects per cohort will allow for a preliminary evaluation of efficacy.

## 10.2 Analysis Populations

The following populations will be considered:

- Full Analysis Set: all enrolled subjects who receive any amount of study drugs.
- Safety Set: all subjects who receive any amount of study drugs.
- PK-Evaluable Set: all subjects who receive at least one dose of study drugs and for whom a baseline measurement and at least one blood sample following a dose of study treatment are available.

## 10.3 Planned Analyses

As a general strategy, continuous efficacy and safety endpoints will be summarized using the five-number summary (mean, standard deviation, median, minimum, and maximum). Frequency distributions (counts and percentages) will be used to summarize categorical endpoints.

### 10.3.1 Disposition of the Study Subjects

The disposition of subjects will be described with summaries by cohort of the number of subjects enrolled, the number of subjects treated, the number of subjects for whom study drugs were permanently discontinued (including the reasons for discontinuation), and the number of subjects who discontinued early from the study.

### 10.3.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by cohort. Results will be reported using subjects in the full analysis set.

### 10.3.3 Exposure to Study Treatment

Frequency distributions of the number of received doses will be presented by cohort. Treatment duration for all enrolled subjects will be described by cohort.

### 10.3.4 Analysis of Efficacy Endpoints

ORR is defined as the proportion of subjects whose best overall response is either CR or PR according to RECIST v1.1. The number and percentage of responders along with the corresponding 95% confidence interval (CI) will be provided for each cohort.

CBR will be analyzed in a way similar to the analysis of the ORR (described above).

DOR will be summarized for responders (i.e., subjects with CR or PR only) by cohort. PFS and OS will be summarized by cohort. Median DOR, PFS, and OS will be obtained by using the Kaplan-Meier approach. The PFS rate at additional time points may also be evaluated (e.g., 26, 39, and 52 weeks). Details of the analysis of efficacy endpoints will be described in the Statistical Analysis Plan.

### 10.3.5 Safety Analyses

Safety endpoints will be summarized using data from the Safety Set. Safety analyses will involve examination of the incidence, severity, and type of TEAEs reported, changes in vital signs and laboratory test results from baseline (the assessment prior to first dose) to specified time points throughout the study, and concomitant medications use.

At least 1 laboratory or other safety-related assessment subsequent to at least 1 dose of study drug is required for inclusion in the analysis of a specific safety parameter. To assess change from baseline, a baseline measurement is also required.

#### 10.3.5.1 Treatment-Emergent Adverse Events

TEAEs reported during the study will be coded using a MedDRA dictionary. Incidence of TEAEs will be summarized by cohort.

#### 10.3.5.2 Clinical Laboratory Evaluation

Laboratory parameters will be summarized by cohort at each visit. Each summary will include the values of the laboratory parameters and their change from baseline. Shift tables from baseline will be presented for laboratory values in the chemistry and hematology panels. A listing will be provided for out of normal range as well as clinically significant abnormal lab values.

#### 10.3.5.3 Vital Signs

Vital signs, including pulse, blood pressure, temperature, height, and body weight will be summarized by cohort and time point. For each assessment of vital signs, change and percent change in vital signs from baseline will be summarized by cohort.

#### 10.3.5.4 ECOG Performance Status

ECOG performance status will be summarized for each visit by cohort. Shifts from baseline to the best and worst post-baseline score may be tabulated.

#### 10.3.5.5 Electrocardiogram

ECG status will be summarized for each scheduled visit by cohort. Shifts from baseline may be tabulated. Additionally, ECG parameters will be described using the five-number summary (mean, standard deviation, median, minimum, and maximum).

#### 10.3.5.6 Echocardiogram

Change from baseline of echocardiogram parameters will be described using the five-number summary (mean, standard deviation, median, minimum, and maximum).

#### 10.3.5.7 Concomitant Medications

Concomitant medications will be classified according to the anatomical therapeutic chemical (ATC) codes in the World Health Organization Drug (WHODRUG) dictionary. The incidence rate of each coded concomitant medication will be tabulated by cohort. The table will be sorted by the incidence use of the entire sample.

### 10.3.6 Pharmacokinetic and Pharmacodynamics Analyses

Concentrations of rovalpituzumab tesirine, nivolumab, and ipilimumab will be summarized using descriptive statistics.

Data from the PK-Evaluable set may also be used in the analysis of PK and exposure-PD analyses. In addition, the PK of rovalpituzumab tesirine, may also be characterized using population methods.

The incidence and timing of ATAs to study drugs will be summarized by descriptive statistics. The possible effects of ATA on PK, efficacy and safety may be explored.

The five-number summary will be used to describe absolute and percent change from baseline in IHC, blood soluble markers (such as soluble DLL3 or [redacted] and CTCs. Regressions may be performed as appropriate. Exploratory analyses may be performed to evaluate a possible correlation between each of these endpoints and disease response and/or toxicities. Additional analyses may also be performed. Details will be provided in the Statistical Analysis Plan.

# 11. Ethical and Regulatory Considerations

GCP requires that the clinical protocol, any protocol amendments, the IB, the ICF and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, ICF, and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any SAEs that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g. ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to the sponsor.

## 11.1 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki.

## 11.2 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the ICF.

In the event a subject withdraws consent to participate from the study, stored biomarker samples will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for research using these samples, the subject may request that their samples be withdrawn. Once AbbVie receives the request, remaining biomarker samples will be destroyed. If the subject changes his/her consent, and the samples have already been tested, those results will still remain as part of the overall research data.

An ICF, approved by an IRB/IEC, must be voluntarily signed and dated before samples are collected for optional exploratory research. The nature of the testing should be explained and the subject given an opportunity to ask questions. The informed consent must be signed before the samples are collected and any testing is performed. If the subject does not consent to provide samples for the optional exploratory research, it will not impact their participation in the study.

In the event a subject withdraws from the main study, optional exploratory research samples will continue to be stored and analyzed unless the subject specifically withdraws consent for the optional samples. If consent is withdrawn for the optional sampling, the subject must inform their study doctor, and once AbbVie is informed, the optional samples will be destroyed. However, if the subject withdraws his/her consent and the samples have already been tested, those results will still remain as part of the overall research data.

### 11.3 Biospecimens

Clinical samples donated by subjects in the study (blood, urine, tissue, etc.) comprise study results of the sponsor and will be collected and processed in accordance with this protocol and delivered to the sponsor or sponsor's designee, as instructed by sponsor. Clinical samples shall not be retained or used by the investigator or institution except as expressly permitted by sponsor in writing. The ICF will contain information on the handling of subject personal information relating to clinical samples, including, if applicable, the labeling of clinical samples with the subject's unique code.

### 11.4 Investigator and Study Personnel Information

The contact information and qualifications of the Principal Investigator, Subinvestigators and name and address of the research facilities shall be included in the Study Binder. The investigator is responsible for the supervision of study conduct in accordance with this protocol, including collection of and maintenance of adequate and appropriate study documentation. The investigator may delegate some of the work involved in the conduct of the study to study staff under his/her supervision. The investigator shall ensure that all study staff are qualified by

education, experience, and training to perform their specific responsibilities in relation to the study. The investigator has final responsibility for the accuracy and authenticity of all study data.

Each Principal Investigator and Subinvestigator (as designated on the Form FDA 1572) will provide a signed Financial Disclosure Form in accordance with 21 CFR 54. Each investigator will notify the sponsor or its authorized representative of any relevant changes to the information included on such Financial Disclosure Form during the conduct of the study and for one (1) year after the study has been completed.

If the study site is located in the European Union, the Principal Investigator and any Subinvestigators must provide their express authorization for the sponsor's collection, use, transfer (including to countries outside of the country where the study is conducted and the EU) and storage of their personal data, including their name, address, phone number for: review by governmental authorities with regard to sponsor's regulatory submissions related to the study; fulfilling regulatory or legal requirements; and publication of the study on the www.clinicaltrials.gov website.

### 11.5 Protocol Amendments and Study Termination

Any investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study subject) must be approved by the sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The investigator is responsible for enrolling subjects who have met protocol eligibility criteria. Protocol deviations must be reported to the sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

The sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

### 11.6 Study Documentation, Privacy and Records Retention

To protect the safety of subjects in the study and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the investigator will provide the sponsor, its licensees and collaborators, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents and certified copies within no more than ten (10) days of request by sponsor (or sooner if required by a regulatory authority).

Records containing subject medical information and other personal data must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of

the subject Authorization contained in the ICF for the study. Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, eCRFs and other documents to be transferred to the sponsor should be completed in strict accordance with the instructions provided by the sponsor, including the instructions regarding the coding of subject identities.

In compliance with local and/or regional regulations, this trial may be registered and trial results may be posted on public registries, such as ClinicalTrials.gov.

### 11.7 Clinical Trial Agreement

A separate written Clinical Trial Agreement (CTA) covering the obligations of the sponsor and of the institution and investigator in relation to the study is required before the study site is initiated. The CTA will include terms for payments by the sponsor to investigators and institutions conducting the trial, requirements for investigators' and institutions' insurance, provisions for reimbursement of the treatment of subject injuries attributable to the study or the study drugs, the publication of clinical trial data, and other relevant provisions.

The investigator and the institution shall collect and record all data and results of the study, including all information, eCRFs, laboratory work sheets, slides, biospecimens, findings and reports ("Results") as required by this protocol, the Sponsor’s instructions and the CTA. Results are the exclusive property of sponsor and are deemed its confidential information. Subject medical records and other source documentation are not included in Results. The written permission of the sponsor is required prior to disclosure by the investigator or the study sites of Results or any other information related to the study or the study drugs. After conclusion of the study at all study sites, the investigator may publish or present the Results that have been generated at the institution, provided that, the Results of the overall study have already been published or disclosed with sponsor's permission in an abstract, manuscript or presentation; or the overall study has been completed at all sites for at least two (2) years; or as otherwise approved by sponsor in writing. The investigator will submit to sponsor for review any proposed publication or presentation along with the name of the applicable scientific journal or presentation forum prior to its submission for publication or presentation. The investigator will comply with the sponsor's request to delete references to its confidential information in any proposed publication or presentation and the investigator or institution will withhold publication or presentation for an additional time period in order to allow the sponsor to obtain patent protection. Investigators will conduct all interactions with third parties, including journal editors and reviewers, in a manner consistent with the confidentiality provisions of the CTA in place with sponsor. The foregoing shall not operate to restrict publication but is intended solely to ensure the accuracy and completeness of data intended for publication, to provide an opportunity

to share with the investigator any new and/or unpublished information of which he/she may be unaware and to ensure that sponsor's confidential information is not disclosed.

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# 13. Appendices

## 13.1 Schedule of Assessments

### 13.1.1 Schedule of Assessments Cohort 1

| Category | Description | Pre-Screening | Screening Day –14 to -1 | Day before dosing[1] Day –1 | Treatment (Each Cycle*) Day 1 (±2 d) | Day 2[1] | Day 8[3] (±2 d) | Day 15[3] (±2 d) | EOT[2] Within ≤7 days of last dose | LTFU q6-12wk[4] (±1 week) |
|---|---|---|---|---|---|---|---|---|---|---|
| Location | Clinic Visit | X | X | | X | | X | X | X | X |
| | Telephone Follow-Up | | | | | X[5] | | | | |
| | Investigator present | X | X | | X | | X | X | X | |
| Screening, Baseline, and Safety Assessments | Informed Consent | X[6] | X[7] | | | | | | | |
| | Demographics | X | X | | | | | | | |
| | Inclusion/Exclusion Criteria[8] | | X | | | | | | | |
| | Medical and Surgical History[9] | | X | | | | | | | |
| | Malignancy History[10] | | X | | | | | | | |
| | Prior Anticancer Treatments[11] | | X | | | | | | | |
| | Physical examination | | X | | X | | X | X | X | |
| | Vital Signs[12] | | X | | X | | X | X | X | |
| | Height | | X | | | | | | | |
| | Complete Blood Count with differential[13] | | X | | X | | X | X | X | |
| | Serum Chemistries[14] | | X | | X | | X | X | X | |
| | Coagulation Tests[15] | | X | | X | | | | X | |
| | Urinalysis[16] | | X | | X | | X | X | X | |
| | Endocrinology Tests[17] | | X | | X | | | | X | |
| | Hepatitis B and C tests[18] | | X | | | | | | | |
| | Pregnancy Test[19] | | X | | X | | | | X | |
| | Electrocardiogram (ECG) | | X | | X[20] | | | | X | |

| Category | Description | Pre-Screening | Screening Day –14 to -1 | Day before dosing[1] Day –1 | Treatment (Each Cycle*) Day 1 (±2 d) | Day 2[1] | Day 8[3] (±2 d) | Day 15[3] (±2 d) | EOT[2] Within ≤7 days of last dose | LTFU q6-12wk[4] (±1 week) |
|---|---|---|---|---|---|---|---|---|---|---|
| | Echocardiogram | | | | X[21] | | | | X | |
| | Performance Status (ECOG) | | X | | X | | | | X | |
| Study Assessments | Fluid Retention Questionnaire[22] | | | | X | | X | X | X | |
| | Adverse Events | | X[23] | | X | X | X | X | X | X |
| | Concomitant Medications[24] | | X[25] | | X | X | X | X | X | |
| | CT Scan[26] | | X | | X[27] | | | | X | X |
| | MRI Brain[28] | | X | | X[29] | | | | X | X |
| | Paraneoplastic Assessment | | X | | | | | | | |
| | Disease Assessment | | X | | | | | | | |
| Treatment | Dexamethasone | | | X | X | X | | | | |
| | Rovalpituzumab tesirine (0.3 mg/kg) | | | | X[30] | | | | | |
| | Nivolumab (360 mg) | | | | X[31, 32] | | | | | |
| | Nivolumab (480 mg) | | | | X[33] | | | | | |
| Response Assessment | Survival Status | | | | | | | | | X |
| | Response Assessment | | | | X[27] | | | | X | X |
| PK and PD | Pharmacokinetics | | | | X[34] | X[35] | X[35] | X[35] | X[34] | |
| | Rovalpituzumab tesirine anti-therapeutic antibodies (ATA) | | | | X[36] | | | | X | |
| | Nivolumab ATA | | | | X[37] | | | | X | |
| | Tumor Tissue[38] | X | X | | | | | | X[39] | X[39] |
| | Blood [redacted] | | X | | X | | | | X | |
| | Blood Soluble Markers[41] | | X | | X | | | | X | X |
| | Flow cytometry[42] | | X | | X | | | | X | |
| | Peripheral blood RNA[43] | | X | | X | | | | X | |

| Category | Description | Pre-Screening | Screening | Day before dosing[1] | Treatment (Each Cycle*) | | | | EOT[2] Within ≤7 days of last dose | LTFU q6-12wk[4] (±1 week) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Day –14 to -1 | Day –1 | Day 1 (±2 d) | Day 2[1] | Day 8[3] (±2 d) | Day 15[3] (±2 d) | | |
| | Circulating Tumor Cells[44] | | | | X[45] | | | | X | |
| | Genotyping[46] | | X | | | | | | | |
| | Serosal Fluid[47] | | | | X | | X | X | X | |
| | Cell Free Circulating Tumor DNA (ctDNA) [48] | | | | X | | | | X | |

**Table Notes**

* **Cycles 1 – 3 are 3 weeks. Cycles 4 and beyond are 4 weeks.**

1) Only applies to Cycle 1 and Cycle 3 when rovalpituzumab tesirine is administered.
2) EOT occurs within 7 days of documentation of the decision to discontinue treatment.
3) Visits on Days 8 and 15 should be done during Cycles 1 and 3 only (may be omitted during cycles that do not include rovalpituzumab tesirine).
4) LTFU includes the 100 day follow up for safety; LTFU also occurs q6wk (±1 week) until 6 months, then q12wk (±1 week) until disease progression, initiation of new anticancer therapy, or withdrawal/termination from the study. Disease/Response Assessment consists of subsequent anticancer therapies and dates, date of progression (if not already captured on study), and survival status. Subjects will be followed for survival until death or study termination, whichever occurs first. After disease progression, subjects who are not retreated will be followed (Section 6.6).
5) This may be a telephone follow-up or performed in clinic.
6) Prescreening ICF only.
7) Informed consent for the main portion of this study will be obtained prior to the performance of any study procedures and may occur within 30 days prior to the Day 1 Visit. All other screening procedures must occur within 14 days prior to Day 1.
8) Confirmation of study eligibility per inclusion/exclusion criteria.
9) Medical and Surgical History includes descriptions of conditions or procedures, and dates of onset - offset.
10) Malignancy History includes tumor type, stage, sites of metastases, mutational status.
11) Prior Anticancer Treatments include names of specific treatments, dates of administration, response to therapy, and DOR, if known.
12) All vitals should be measured after subject has been sitting/resting for at least 5 minutes. Vital signs include temperature, blood pressure, pulse, respiration rate, and weight. Vital signs should be collected at least 30 minutes (but no longer than 4 hours) pre-infusion and then 30 minutes (±10 minutes), 2 hours (±15 minutes), and 4 hours (±30 minutes) post-infusion for Cycles 1 and 3 only. Weight needs to be collected only once prior to infusion and does not need to be collected within 30 minutes prior to infusion. All other cycles, vitals should be collected at least 30 minutes (but no longer than 4 hours) pre-infusion.

13) CBC includes white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell (RBC) count, platelet count, hemoglobin, and hematocrit.

14) Chemistries include electrolytes (sodium, potassium, chloride, and carbon dioxide), creatinine, BUN, eGFR, magnesium, calcium, phosphorus, glucose, albumin, total protein, amylase, lipase, and liver function tests (total and direct bilirubin, ALT, AST, alkaline phosphatase, LDH).

15) Coagulation tests include PT, PTT or aPTT, and INR.

16) Urinalysis includes dipstick results for color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, and protein; as well as spot urine protein and creatinine.

17) Endocrinology Tests include ACTH, thyroid stimulating hormone (TSH), and free thyroxine (T4).

18) Hepatitis B and C tests include HBsAg, HBsAb, HBcAb, and HCV antibody. Results that may be consistent with chronic or active infection must be confirmed by PCR tests for Hepatitis B and/or C.

19) Screening pregnancy test consists of serum testing for β-hCG in women of childbearing potential (Section 5.10 for definition). Urine pregnancy test will be performed at Day 1 of all cycles prior to dosing. Repeat testing may be done per the investigator.

20) ECGs consist of 12-lead studies taken in triplicate, performed within a 5 minute window after at least 10 minutes of quiet rest in a supine position. ECGs will be performed prior to infusion (prior to blood sample collection for pharmacokinetics) and 30 minutes ± 10 minutes post-infusion, when applicable.

21) Echocardiogram includes assessment of LVEF and pericardial effusion, if present; performed only on Cycles 1 and 3 when rovalpituzumab tesirine is administered. ECHO may be performed up to 72 hours prior to Rova-T administration.

22) Fluid Retention Questionnaire includes diary of daily weights and queries for worsening/ new edema or dyspnea; Fluid Retention Questionnaire will be administered on Cycles 1, 2, 3, 4 and EOT visit if occurs prior to Cycle 5. Subjects should record daily weight from Day 1 through the end of Cycle 4.

23) Procedure-related AEs (only).

24) Concomitant Medications include names of all concomitant therapies, including dates of administration, dose regimen, route of administration, and purpose.

25) Procedure related concomitant medications (only).

26) CT imaging of the chest, abdomen, and pelvis, and neck (if indicated), for assessment via RECIST v1.1.

27) On applicable cycles, disease assessment will occur at least 3 days but no greater than 7 days prior to day of dosing. See Section 6.4.6 for imaging schedule per cohort.

28) CT of the brain with IV contrast may be substituted at the discretion of the investigator.

29) MRI brain is only required after screening if clinically indicated (e.g. if CNS progression is documented).

30) Cycles 1 and 3 only.

31) Nivolumab will be administered after rovalpitzumab tesirine on applicable cycles.

32) Cycles 2 and 3 only.

33) Cycles 4 and beyond.

34) See Appendix 13.2 for rovalpituzumab tesirine and nivolumab PK time points.

35) Rovalpituzumab tesirine ***single*** PK will be collected at Cycle 1: Day 2, Day 8, Day 15, Cycle 3: Day 2, Day 8, and Day 15.

36) Prior to infusion on Cycles 1, 3, 5 only.

37) Prior to infusion for all cycles.

38) Tumor Tissue consists of procurement of archived, representative tumor tissue, or an optional fresh tumor biopsy, if accessible for DLL3 and PD-L1 testing. Any remaining tissue may be utilized for additional biomarker research and exploratory studies including, but not necessarily limited to, assessment of tissue for nucleic acid or protein based biomarkers to understand drug sensitivity and resistance, biology of SCLC, and to develop new diagnostic tests. With consent from the subject, tumor tissue may be obtained prior to the screening period (during the prescreening portion of the study) and tested for DLL3 and PD-L1 expression. Up to the first 12 subjects enrolled into each cohort must be DLL3 positive. For any subjects who did not complete a prescreening visit, this will be done at screening.

39) Optional collection of tumor tissue at progression.

40) [redacted]

41) Blood soluble markers sample will be tested for various soluble markers that may include but are not limited to chemokines or cytokines, soluble DLL3, and soluble tumor-specific biomarkers such as [redacted] Samples will be collected pre-dose at designated visits, and again during retreatment cycles at predose of C1D1, C2D1, C3D1.

42) Flow cytometry consists of the collection of blood for characterization of immune cell subsets. Samples will be collected pre-dose at designated visits.

43) Peripheral blood RNA consists of whole blood RNA for assessment of analytes that may reflect the PD effects of rovalpituzumab tesirine and/or nivolumab, including [redacted]. Samples will be collected pre-dose at designated visits.

44) CTC collection includes a sample for exploratory analyses of CTC-associated biomarkers such as DLL3, implemented only at specific sites based on feasibility.

45) CTC collection to occur pre-dose on Day 1 of Cycles 1 and 5.

46) Genotyping includes blood and/or tumor sample for possible assessment of genes for genetic lesions and/or polymorphisms which may influence the safety or efficacy response to the study drugs. Such genes may include but are not necessarily limited to [redacted]

47) Serosal Fluid entails procurement, where feasible, of any pericardial, pleural and/or ascitic fluid collected as part of routine care (e.g. as part of a therapeutic thoracentesis, pericardiocentsis, or paracentesis), for possible PK, PD, and/or biomarker testing.

48) ctDNA collection to occur pre-dose on Day 1 of Cycle 1and EOT .

## 13.1.2 Schedule of Assessments Cohort 2

| Category | Description | Pre-Screening | Screening | Day before dosing[1] | Treatment (Each Cycle*) | | | | Washout Period Safety Assessment[2] | EOT[3] Within ≤7 days of last dose | LTFU q6-12wk[5] (±1 week) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Day –14 to -1 | Day –1 | Day 1 (±2 d) | Day 2[1] | Day 8[4] (±2 d) | Day 15[4] (±2 d) | | | |
| Location | Clinic Visit | X | X | | X | | X | X | X[7] | X | X |
| | Telephone Follow-Up | | | | | X[6] | | | X[7] | | |
| | Investigator present | X | X | | X | | X | X | | X | |
| Screening, Baseline, and Safety Assessments | Informed Consent | X[8] | X[9] | | | | | | | | |
| | Demographics | X | X | | | | | | | | |
| | Inclusion/Exclusion Criteria[10] | | X | | | | | | | | |
| | Medical and Surgical History[11] | | X | | | | | | | | |
| | Malignancy History[12] | | X | | | | | | | | |
| | Prior Anticancer Treatments[13] | | X | | | | | | | | |
| | Physical examination | | X | | X | | X | X | X[14] | X | |
| | Vital Signs[15] | | X | | X | | X | X | X[14] | X | |
| | Height | | X | | | | | | | | |
| | Complete Blood Count with differential[17] | | X | | X | | X | X | X[14] | X | |
| | Serum Chemistries[18] | | X | | X | | X | X | X[14] | X | |
| | Coagulation Tests[19] | | X | | X | | | | | X | |
| | Urinalysis[20] | | X | | X | | X | X | | X | |
| | Endocrinology Tests[21] | | X | | X | | | | | X | |
| | Hepatitis B and C tests[22] | | X | | | | | | | | |
| | Pregnancy Test[23] | | X | | X | | | | | X | |
| | Electrocardiogram (ECG) | | X | | X[24] | | | | | X | |
| | Echocardiogram | | | | X[25] | | | | | X | |
| | Performance Status (ECOG) | | X | | X | | | | X[14] | X | |
| Study Assessments | Fluid Retention Questionnaire[26] | | | | X | | X | X | | X | |
| | Adverse Events | | X[27] | | X | X | X | X | X[16] | X | X |

| Category | Description | Pre-Screening | Screening Day –14 to -1 | Day before dosing[1] Day –1 | Treatment (Each Cycle*) Day 1 (±2 d) | Day 2[1] | Day 8[4] (±2 d) | Day 15[4] (±2 d) | Washout Period Safety Assessment[2] | EOT[3] Within ≤7 days of last dose | LTFU q6-12wk[5] (±1 week) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Concomitant Medications[28] | | X[29] | | X | X | X | X | X[16] | X | |
| | CT Scan[30] | | X | | X[31] | | | | | X | X |
| | MRI Brain[32] | | X | | X[33] | | | | | X | X |
| | Paraneoplastic Assessment | | X | | | | | | | | |
| | Disease Assessment | | X | | | | | | | | |
| Treatment | Dexamethasone | | | X | X | X | | | | | |
| | Rovalpituzumab tesirine (0.3 mg/kg) | | | | X[34] | | | | | | |
| | Nivolumab (1 mg/kg) | | | | X[35, 36] | | | | | | |
| | Nivolumab (480 mg) | | | | X[37, 38] | | | | | | |
| | Ipilimumab (1 mg/kg) | | | | X[39,40] | | | | | | |
| Response Assessment | Survival Status | | | | | | | | | | X |
| | Response Assessment | | | | X[31] | | | | | X | X |
| PK and PD | Pharmacokinetics | | | | X[41] | X[42] | X[42] | X[42] | | X[41] | |
| | Rovalpituzumab tesirine anti-therapeutic antibodies (ATA) | | | | X[43] | | | | | X | |
| | Nivolumab ATA | | | | X[44] | | | | | X | |
| | Ipilimumab ATA | | | | X[45] | | | | | X | |
| | Tumor Tissue[46] | X | X | | | | | | | X[47] | X[47] |
| | Blood [redacted] | | X | | X | | | | | X | |
| | Blood Soluble Markers[49] | | X | | X | | | | | X | X |
| | Flow cytometry[50] | | X | | X | | | | | X | |
| | Peripheral blood RNA[51] | | X | | X | | | | | X | |
| | Circulating Tumor Cells[52] | | | | X[53] | | | | | X | |
| | Genotyping[54] | | X | | | | | | | | |
| | Serosal Fluid[55] | | | | X | | X | X | | X | |

| Category | Description | Pre-Screening | Screening Day –14 to -1 | Day before dosing[1] Day –1 | Treatment (Each Cycle*) Day 1 (±2 d) | Day 2[1] | Day 8[4] (±2 d) | Day 15[4] (±2 d) | Washout Period Safety Assessment[2] | EOT[3] Within ≤7 days of last dose | LTFU q6-12wk[5] (±1 week) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cell Free Circulating Tumor DNA (ctDNA)[56] | | | | X | | | | | X | |

**Table Notes**

* **Cycles 1 – 5 are 3 weeks. Cycles 6 and beyond are 4 weeks.**

1) Only applies to Cycle 1 and Cycle 3 when rovalpituzumab tesirine is administered.
2) Washout Period will occur after Cycle 5 Day 1 and will consist of both telephone follow-up calls and in clinic visits (Section 6.4.5).
3) EOT occurs within 7 days of documentation of the decision to discontinue treatment.
4) Visits on Days 8 and 15 should be done during Cycles 1 and 3 only (may be omitted during cycles that do not include rovalpituzumab tesirine).
5) LTFU includes the 100 day follow up for safety; LTFU also occurs q6wk (±1 week) until 6 months, then q12wk (±1 week) until disease progression, initiation of new anticancer therapy, or withdrawal/termination from the study. Disease/Response Assessment consists of subsequent anticancer therapies and dates, date of progression (if not already captured on study), and survival status. Subjects will be followed for survival until death or study termination, whichever occurs first. After disease progression, subjects who are not retreated will be followed (Section 6.6).
6) This may be a telephone follow-up or performed in clinic.
7) The Safety Visit in clinic should occur 2 weeks (±3 days) after Cycle 5 Day 1. The telephone follow-up call should occur 4 weeks (±3 days) after Cycle 5 Day 1.
8) Prescreening ICF only.
9) Informed consent for the main portion of this study will be obtained prior to the performance of any study procedures and may occur within 30 days prior to the Day 1 Visit. All other screening procedures must occur within 14 days prior to Day 1.
10) Confirmation of study eligibility per inclusion/exclusion criteria.
11) Medical and Surgical History includes descriptions of conditions or procedures, and dates of onset - offset.
12) Malignancy History includes tumor type, stage, sites of metastases, mutational status.
13) Prior Anticancer Treatments include names of specific treatments, dates of administration, response to therapy, and DOR, if known.
14) To be performed at in clinic visit only.
15) All vitals should be measured after subject has been sitting/resting for at least 5 minutes. Vital signs include temperature, blood pressure, pulse, respiration rate, and weight. Vital signs should be collected at least 30 minutes (but no longer than 4 hours) pre-infusion and then 30 minutes (±10 minutes), 2 hours (±15 minutes), and 4 hours (±30 minutes) post-infusion for Cycles 1 and 3 only. Weight needs to be collected only once prior to infusion and does not need to be collected within 30 minutes prior to infusion. All other cycles, vitals should be collected at least 30 minutes (but no longer than 4 hours) pre-infusion.
16) To be performed during both telephone follow-up and in clinic visit.

17) CBC includes white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell (RBC) count, platelet count, hemoglobin, and hematocrit.

18) Chemistries include electrolytes (sodium, potassium, chloride, and carbon dioxide), creatinine, BUN, eGFR, magnesium, calcium, phosphorus, glucose, albumin, total protein, amylase, lipase, and liver function tests (total and direct bilirubin, ALT, AST, alkaline phosphatase, LDH).

19) Coagulation tests include PT, PTT or aPTT, and INR.

20) Urinalysis includes dipstick results for color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, and protein; as well as spot urine protein and creatinine.

21) Endocrinology Tests include ACTH, thyroid stimulating hormone (TSH), and free thyroxine (T4).

22) Hepatitis B and C tests include HBsAg, HBsAb, HBcAb, and HCV antibody. Results that may be consistent with chronic or active infection must be confirmed by PCR tests for Hepatitis B and/or C.

23) Screening pregnancy test consists of serum testing for β-hCG in women of childbearing potential (Section 5.10 for definition). Urine pregnancy test will be performed at Day 1 of all cycles prior to dosing. Repeat testing may be done per the investigator.

24) ECGs consist of 12-lead studies taken in triplicate, performed within a 5 minute window after at least 10 minutes of quiet rest in a supine position. ECGs will be performed prior to infusion (prior to blood sample collection for pharmacokinetics) and 30 minutes ± 10 minutes post-infusion, when applicable.

25) Echocardiogram includes assessment of LVEF and pericardial effusion, if present; performed only on Cycles 1 and 3 when rovalpituzumab tesirine is administered. ECHO may be performed up to 72 hours prior to rovalpituzumab tesirine administration.

26) Fluid Retention Questionnaire includes diary of daily weights and queries for worsening/ new edema or dyspnea; Fluid Retention Questionnaire will be administered on Cycles 1, 2, 3, 4 and EOT visit if occurs prior to Cycle 5. Subjects should record daily weight from Day 1 through the end of Cycle 4.

27) Procedure-related AEs (only).

28) Concomitant Medications include names of all concomitant therapies, including dates of administration, dose regimen, route of administration, and purpose.

29) Procedure related concomitant medications (only).

30) CT imaging of the chest, abdomen, and pelvis, and neck (if indicated), for assessment via RECIST v1.1.

31) On applicable cycles, disease assessment will occur at least 3 days but no greater than 7 days prior to day of dosing. See Section 6.4.6 for imaging schedule per cohort.

32) CT of the brain with IV contrast may be substituted at the discretion of the investigator.

33) MRI brain is only required after screening if clinically indicated (e.g. if CNS progression is documented).

34) Cycles 1 and 3 only.

35) Nivolumab (1 mg/kg) will be administered after rovalpitzumab tesirine on applicable cycles.

36) Cycles 2 – 5 only.

37) Nivolumab 480 mg (monotherapy) to be started 6 weeks after Cycle 5 Day 1.

38) Cycles 6 and beyond.

39) Ipilimumab will be administered after rovalpitzumab tesirine and nivolumab on applicable cycles.

40) Cycles 2 – 5 only.

41) See Appendix 13.2 for rovalpituzumab tesirine, nivolumab, and ipilimumab PK time points.

42) Rovalpituzumab tesirine ***single*** PK will be collected at Cycle 1: Day 2, Day 8, Day 15, Cycle 3: Day 2, Day 8, and Day 15.

43) Prior to infusion on Cycles 1, 3, 5 only.

44) Prior to infusion for all cycles.

45) Prior to infusion on Cycles 1 – 6 only.

46) Tumor Tissue consists of procurement of archived, representative tumor tissue, or an optional fresh tumor biopsy, if accessible for DLL3 and PD-L1 testing. Any remaining tissue may be utilized for additional biomarker research and exploratory studies including, but not necessarily limited to, assessment of tissue for nucleic acid or protein based biomarkers to understand drug sensitivity and resistance, biology of SCLC, and to develop new diagnostic tests. With consent from the subject, tumor tissue may be obtained prior to the screening period (during the prescreening portion of the study) and tested for DLL3 and PD-L1 expression. Up to the first 12 subjects enrolled into each cohort must be DLL3 positive. For any subjects who did not complete a prescreening visit, this will be done at screening.

47) Optional collection of tumor tissue at progression.

48) [redacted]

49) Blood soluble markers sample will be tested for various soluble markers that may include but are not limited to chemokines or cytokines, soluble DLL3, and soluble tumor-specific biomarkers such as [redacted] Samples will be collected pre-dose at designated visits, and again during retreatment cycles at pre-dose of C1D1, C2D1, C3D1.

50) Flow cytometry consists of the collection of blood for characterization of immune cell subsets. Samples will be collected pre-dose at designated visits.

51) Peripheral blood RNA consists of whole blood RNA for assessment of analytes that may reflect the PD effects of rovalpituzumab tesirine, nivolumab and/or ipilimumab, including [redacted]. Samples will be collected pre-dose at designated visits.

52) CTC collection includes a sample for exploratory analyses of CTC-associated biomarkers such as DLL3, implemented only at specific sites based on feasibility.

53) CTC collection to occur pre-dose on Day 1 of Cycles 1 and 5.

54) Genotyping includes blood and/or tumor sample for possible assessment of genes for genetic lesions and/or polymorphisms which may influence the safety or efficacy response to the study drugs. Such genes may include but are not necessarily limited to [redacted]

55) Serosal Fluid entails procurement, where feasible, of any pericardial, pleural and/or ascitic fluid collected as part of routine care (e.g. as part of a therapeutic thoracentesis, pericardiocentsis, or paracentesis), for possible PK, PD, and/or biomarker testing.

56) ctDNA collection to occur pre-dose on Day 1 of Cycle 1and EOT.

## 13.1.3 Schedule of Assessments Cohort 3

| Category | Description | Pre-Screening | Screening | Day before dosing[1] | Treatment (Each Cycle*) | | | | Washout Period Safety Assessment[2] | EOT[3] Within ≤7 days of last dose | LTFU q6-12wk[5] (±1 week) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Day –14 to -1 | Day –1 | Day 1 (±2 d) | Day 2[1] | Day 8[4] (±2 d) | Day 15[4] (±2 d) | | | |
| Location | Clinic Visit | X | X | | X | | X | X | X[7] | X | X |
| | Telephone Follow-Up | | | | | X[6] | | | X[7] | | |
| | Investigator present | X | X | | X | | X | X | | X | |
| Screening, Baseline, and Safety Assessments | Informed Consent | X[8] | X[9] | | | | | | | | |
| | Demographics | X | X | | | | | | | | |
| | Inclusion/Exclusion Criteria[10] | | X | | | | | | | | |
| | Medical and Surgical History[11] | | X | | | | | | | | |
| | Malignancy History[12] | | X | | | | | | | | |
| | Prior Anticancer Treatments[13] | | X | | | | | | | | |
| | Physical examination | | X | | X | | X | X | X[14] | X | |
| | Vital Signs[15] | | X | | X | | X | X | X[14] | X | |
| | Height | | X | | | | | | | | |
| | Complete Blood Count with differential[17] | | X | | X | | X | X | X[14] | X | |
| | Serum Chemistries[18] | | X | | X | | X | X | X[14] | X | |
| | Coagulation Tests[19] | | X | | X | | | | | X | |
| | Urinalysis[20] | | X | | X | | X | X | | X | |
| | Endocrinology Tests[21] | | X | | X | | | | | X | |
| | Hepatitis B and C tests[22] | | X | | | | | | | | |
| | Pregnancy Test[23] | | X | | X | | | | | X | |
| | Electrocardiogram (ECG) | | X | | X[24] | | | | | X | |
| | Echocardiogram | | | | X[25] | | | | | X | |
| | Performance Status (ECOG) | | X | | X | | | | X[14] | X | |
| Study Assessments | Fluid Retention Questionnaire[26] | | | | X | | X | X | | X | |
| | Adverse Events | | X[27] | | X | X | X | X | X[16] | X | X |

| Category | Description | Pre-Screening | Screening | Day before dosing[1] | Treatment (Each Cycle*) | | | | Washout Period Safety Assessment[2] | EOT[3] Within ≤7 days of last dose | LTFU q6-12wk[5] (±1 week) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Day –14 to -1 | Day –1 | Day 1 (±2 d) | Day 2[1] | Day 8[4] (±2 d) | Day 15[4] (±2 d) | | | |
| | Concomitant Medications[28] | | X[29] | | X | X | X | X | X[16] | X | |
| | CT Scan[30] | | X | | X[31] | | | | | X | X |
| | MRI Brain[32] | | X | | X[33] | | | | | X | X |
| | Paraneoplastic Assessment | | X | | | | | | | | |
| | Disease Assessment | | X | | | | | | | | |
| Treatment | Dexamethasone | | | X | X | X | | | | | |
| | Rovalpituzumab tesirine (0.3 mg/kg) | | | | X[34] | | | | | | |
| | Nivolumab (1 mg/kg) | | | | X[35, 36] | | | | | | |
| | Nivolumab (480 mg) | | | | X[37, 38] | | | | | | |
| | Ipilimumab (3 mg/kg) | | | | X[39,40] | | | | | | |
| Response Assessment | Survival Status | | | | | | | | | | X |
| | Response Assessment | | | | X[31] | | | | | X | X |
| PK and PD | Pharmacokinetics | | | | X[41] | X[42] | X[42] | X[42] | | X[41] | |
| | Rovalpituzumab tesirine anti-therapeutic antibodies (ATA) | | | | X[43] | | | | | X | |
| | Nivolumab ATA | | | | X[44] | | | | | X | |
| | Ipilimumab ATA | | | | X[45] | | | | | X | |
| | Tumor Tissue[46] | X | X | | | | | | | X[47] | X[47] |
| | Blood [redacted] | | X | | X | | | | | X | |
| | Blood Soluble Markers[49] | | X | | X | | | | | X | X |
| | Flow cytometry[50] | | X | | X | | | | | X | |
| | Peripheral blood RNA[51] | | X | | X | | | | | X | |
| | Circulating Tumor Cells[52] | | | | X[53] | | | | | X | |
| | Genotyping[54] | | X | | | | | | | | |
| | Serosal Fluid[55] | | | | X | | X | X | | X | |

| Category | Description | Pre-Screening | Screening | Day before dosing[1] | Treatment (Each Cycle*) | | | | Washout Period Safety Assessment[2] | EOT[3] Within ≤7 days of last dose | LTFU q6-12wk[5] (±1 week) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Day –14 to -1 | Day –1 | Day 1 (±2 d) | Day 2[1] | Day 8[4] (±2 d) | Day 15[4] (±2 d) | | | |
| | Cell Free Circulating Tumor DNA (ctDNA)[56] | | | | X | | | | | X | |

**Table Notes**

* **Cycles 1 – 5 are 3 weeks. Cycles 6 and beyond are 4 weeks.**

1) Only applies to Cycle 1 and Cycle 3 when rovalpituzumab tesirine is administered.
2) Washout Period will occur after Cycle 5 Day 1 and will consist of both telephone follow-up calls and in clinic visits (Section 6.4.5).
3) EOT occurs within 7 days of documentation of the decision to discontinue treatment.
4) Visits on Days 8 and 15 should be done during Cycles 1 and 3 only (may be omitted during cycles that do not include rovalpituzumab tesirine).
5) LTFU includes the 100 day follow up for safety; LTFU also occurs q6wk (±1 week) until 6 months, then q12wk (±1 week) until disease progression, initiation of new anticancer therapy, or withdrawal/termination from the study. Disease/Response Assessment consists of subsequent anticancer therapies and dates, date of progression (if not already captured on study), and survival status. Subjects will be followed for survival until death or study termination, whichever occurs first. After disease progression, subjects who are not retreated will be followed (Section 6.6).
6) This may be a telephone follow-up or performed in clinic.
7) The Safety Visit in clinic should occur 2 weeks (±3 days) and 6 weeks (±3 days) after Cycle 5 Day 1. The telephone follow-up calls should occur 4 weeks (±3 days) after Cycle 5 Day 1.
8) Prescreening ICF only.
9) Informed consent for the main portion of this study will be obtained prior to the performance of any study procedures and may occur within 30 days prior to the Day 1 Visit. All other screening procedures must occur within 14 days prior to Day 1.
10) Confirmation of study eligibility per inclusion/exclusion criteria.
11) Medical and Surgical History includes descriptions of conditions or procedures, and dates of onset - offset.
12) Malignancy History includes tumor type, stage, sites of metastases, mutational status.
13) Prior Anticancer Treatments include names of specific treatments, dates of administration, response to therapy, and DOR, if known.
14) To be performed at in clinic visit only.
15) All vitals should be measured after subject has been sitting/resting for at least 5 minutes. Vital signs include temperature, blood pressure, pulse, respiration rate, and weight. Vital signs should be collected at least 30 minutes (but no longer than 4 hours) pre-infusion and then 30 minutes (±10 minutes), 2 hours (±15 minutes), and 4 hours (±30 minutes) post-infusion for Cycles 1 and 3 only. Weight needs to be collected only once prior to infusion and does not need to be collected within 30 minutes prior to infusion. All other cycles, vitals should be collected at least 30 minutes (but no longer than 4 hours) pre-infusion.

16) To be performed during both telephone follow-up and in clinic visit.

17) CBC includes white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell (RBC) count, platelet count, hemoglobin, and hematocrit.

18) Chemistries include electrolytes (sodium, potassium, chloride, and carbon dioxide), creatinine, BUN, eGFR, magnesium, calcium, phosphorus, glucose, albumin, total protein, amylase, lipase, and liver function tests (total and direct bilirubin, ALT, AST, alkaline phosphatase, LDH).

19) Coagulation tests include PT, PTT or aPTT, and INR.

20) Urinalysis includes dipstick results for color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, and protein; as well as spot urine protein and creatinine.

21) Endocrinology Tests include ACTH, thyroid stimulating hormone (TSH), and free thyroxine (T4).

22) Hepatitis B and C tests include HBsAg, HBsAb, HBcAb, and HCV antibody. Results that may be consistent with chronic or active infection must be confirmed by PCR tests for Hepatitis B and/or C.

23) Screening pregnancy test consists of serum testing for β-hCG in women of childbearing potential (Section 5.10 for definition). Urine pregnancy test will be performed at Day 1 of all cycles prior to dosing. Repeat testing may be done per the investigator.

24) ECGs consist of 12-lead studies taken in triplicate, performed within a 5 minute window after at least 10 minutes of quiet rest in a supine position. ECGs will be performed prior to infusion (prior to blood sample collection for pharmacokinetics) and 30 minutes ± 10 minutes post-infusion, when applicable.

25) Echocardiogram includes assessment of LVEF and pericardial effusion, if present; performed only on Cycles 1 and 3 when rovalpituzumab tesirine is administered. ECHO may be performed up to 72 hours prior to Rova-T administration.

26) Fluid Retention Questionnaire includes diary of daily weights and queries for worsening/ new edema or dyspnea; Fluid Retention Questionnaire will be administered on Cycles 1, 2, 3, 4 and EOT visit if occurs prior to Cycle 5. Subjects should record daily weight from Day 1 through the end of Cycle 4.

27) Procedure-related AEs (only).

28) Concomitant Medications include names of all concomitant therapies, including dates of administration, dose regimen, route of administration, and purpose.

29) Procedure related concomitant medications (only).

30) CT imaging of the chest, abdomen, and pelvis, and neck (if indicated), for assessment via RECIST v1.1.

31) On applicable cycles, disease assessment will occur at least 3 days but no greater than 7 days prior to day of dosing. See Section 6.4.6 for imaging schedule per cohort.

32) CT of the brain with IV contrast may be substituted at the discretion of the investigator.

33) MRI brain is only required after screening if clinically indicated (e.g. if CNS progression is documented).

34) Cycles 1 and 3 only.

35) Nivolumab (1 mg/kg) will be administered after rovalpitzumab tesirine on applicable cycles.

36) Cycles 2 – 5 only.

37) Nivolumab 480 mg (monotherapy) to be started 8 weeks after Cycle 5 Day 1.

38) Cycles 6 and beyond.

39) Ipilimumab will be administered after rovalpitzumab tesirine and nivolumab on applicable cycles.

40) Cycles 2 – 5 only.

41) See Appendix 13.2 for rovalpituzumab tesirine, nivolumab, and ipilimumab PK time points.

42) Rovalpituzumab tesirine ***single*** PK will be collected at Cycle 1: Day 2, Day 8, Day 15, Cycle 3: Day 2, Day 8, and Day 15.

43) Prior to infusion on Cycles 1, 3, 5 only.

44) Prior to infusion for all cycles.

45) Prior to infusion on Cycles 1 – 6 only.

46) Tumor Tissue consists of procurement of archived, representative tumor tissue, or an optional fresh tumor biopsy, if accessible for DLL3 and PD-L1 testing. Any remaining tissue may be utilized for additional biomarker research and exploratory studies including, but not necessarily limited to, assessment of tissue for nucleic acid or protein based biomarkers to understand drug sensitivity and resistance, biology of SCLC, and to develop new diagnostic tests. With consent from the subject, tumor tissue may be obtained prior to the screening period (during the prescreening portion of the study) and tested for DLL3 and PD-L1 expression. Up to the first 12 subjects enrolled into each cohort must be DLL3 positive. For any subjects who did not complete a prescreening visit, this will be done at screening.

47) Optional collection of tumor tissue at progression.

48) [redacted]

49) Blood soluble markers sample will be tested for various soluble markers that may include but are not limited to chemokines or cytokines, soluble DLL3, and soluble tumor-specific biomarkers such as [redacted] Samples will be collected pre-dose on designated visits again during retreatment cycles at pre-dose of C1D1, C2D1, C3D1.

50) Flow cytometry consists of the collection of blood for characterization of immune cell subsets. Samples will be collected during screening, predose of C1D1, C2D1, C3D1 and C4D1.

51) Peripheral blood RNA consists of whole blood RNA for assessment of analytes that may reflect the PD effects of rovalpituzumab tesirine, nivolumab and/or ipilimumab, including [redacted]. Samples will be collected pre-dose at designated visits.

52) CTC collection includes a sample for exploratory analyses of CTC-associated biomarkers such as DLL3, implemented only at specific sites based on feasibility.

53) CTC collection to occur pre-dose on Day 1 of Cycles 1 and 5.

54) Genotyping includes blood and/or tumor sample for possible assessment of genes for genetic lesions and/or polymorphisms which may influence the safety or efficacy response to the study drugs. Such genes may include but are not necessarily limited to [redacted]

55) Serosal Fluid entails procurement, where feasible, of any pericardial, pleural and/or ascitic fluid collected as part of routine care (e.g. as part of a therapeutic thoracentesis, pericardiocentsis, or paracentesis), for possible PK, PD, and/or biomarker testing.

56) ctDNA collection to occur pre-dose on Day 1 of Cycle 1and EOT.

## 13.2 Schedule Peridosing Assessments

| Description | Day -1 | Predose Day 1 | Dosing Day 1 | | | | Day 2 | Day 8 | Day 15 |
|---|---|---|---|---|---|---|---|---|---|
| | | Prior to Infusion | 0 | +30 min (±10 min) | +2 hour (±15 min) | +4 hour (±30 min) | + 24 hours (±2 hours) | ± 2 days | ± 2 days |
| Dexamethasone Peridosing[1] | X | X | | | | | X | | |
| Royalpituzumab Tesirine Administration | | | X | | | | | | |
| Vital Signs[2] | | X | | X | X | X | | X | X |
| ECG[3] | | X | | X | | | | | |
| Pharmacokinetic sample of Royalpituzumab tesirine[4] | | X | | X | X | X | X | X | X |
| Pharmacokinetic sample of Nivolumab[5] | | X | | | | | | | |
| Pharmacokinetic sample of Ipilimumab[6] | | X | | | | | | | |

1) Dexamethasone peridosing as instructed in Section 6.4.1 for Cycles 1 and 3 only (when rovalpituzumab tesirine is administered).
2) Vital signs as per Appendix 13.1.
3) ECG as per Appendix 13.1.
4) PK sample of rovalpituzumab tesirine to be collected at the following cycles (See Section 6.4.2 and 6.4.3):
   - Cycle 1: Day 1, Day 2, Day 8, Day 15
   - Cycle 3: Day 1, Day 2, Day 8, Day 15
   - Cycle 5: Day 1 predose only
5) PK sample of nivolumab to be collected predose beginning at Cycle 1 Day 1 and beyond.
6) PK sample of ipilimumab to be collected predose on Day 1 of Cycle 1, Cycle 2, Cycle 3, Cycle 4, Cycle 5, and Cycle 6 (Cohorts 2 and 3 only)

## 13.3 Performance Status Scales Conversion

| ECOG | | Karnofsky | |
|---|---|---|---|
| **Score** | **Description** | **Percent** | **Description** |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

## 13.4 New York Heart Association (NYHA) Classification

| | |
|---|---|
| Class I | Subjects with no limitation of activities; they suffer no symptoms from ordinary activities. |
| Class II | Subjects with slight, mild limitation of activity; they are comfortable with rest or with mild exertion. |
| Class III | Subjects with marked limitation of activity; they are comfortable only at rest. |
| Class IV | Subjects who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest. |

## 13.5 Response Evaluation Criteria for Solid Tumors (RECIST) v1.1

| Term | Definition |
|---|---|
| Complete response (CR) | Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm. |
| Partial response (PR) | A ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. |
| Progressive disease (PD) | At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 0.5 cm. The appearance of one or more new lesions is also considered progression. |
| Stable disease (SD) | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. |
| New measureable lesions* | Always represents PD. |
| New nonmeasurable lesions | Always represents PD. |
| Non-index lesions | Changes contribute to defining best overall response of CR, PR, SD, and PD. |

From RECIST v1.1 (Eisenhauer, 2009)

* Measureable lesion must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT slice thickness ≤5 mm)

## 13.6 CTCAE v4.03 Grading of Some AEs Relevant to Rovalpituzumab Tesirine

| Group | Adverse Event | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| Effusions | Ascites | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Symptomatic; medical intervention indicated | Severe symptoms; invasive intervention indicated | Life-threatening consequences; urgent operative intervention indicated |
| | Definition: A disorder characterized by accumulation of serous or hemorrhagic fluid in the peritoneal cavity. | | | | |
| | Pericardial effusion | – | Asymptomatic effusion size small to moderate | Effusion with physiologic consequences | Life-threatening consequences; urgent intervention indicated |
| | Definition: A disorder characterized by fluid collection within the pericardial sac, usually due to inflammation. | | | | |
| | Pericardial tamponade | – | – | – | Life-threatening consequences; urgent intervention indicated |
| | Definition: A disorder characterized by an increase in intrapericardial pressure due to the collection of blood or fluid in the pericardium. | | | | |
| | Pleural effusion | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Symptomatic; intervention indicated (e.g., diuretics or limited therapeutic thoracentesis) | Symptomatic with respiratory distress and hypoxia; surgical intervention including chest tube or pleurodesis indicated | Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated |
| | Definition: A disorder characterized by an increase in amounts of fluid within the pleural cavity. Symptoms include shortness of breath, cough and marked chest discomfort. | | | | |
| Edema | Edema face | Localized facial edema | Moderate localized facial edema; limiting instrumental ADL | Severe swelling; limiting self-care ADL | – |
| | Definition: A disorder characterized by swelling due to excessive fluid accumulation in facial tissues. | | | | |
| | Edema limbs | 5–10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection | >10–30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL | >30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self-care ADL | – |
| | Definition: A disorder characterized by swelling due to excessive fluid accumulation in the upper or lower extremities. | | | | |

| Group | Adverse Event | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| Edema cont. | Edema trunk | Swelling or obscuration of anatomic architecture on close inspection | Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL | Gross deviation from normal anatomic contour; limiting self-care ADL | – |
| | Definition: A disorder characterized by swelling due to excessive fluid accumulation in the trunk area. | | | | |
| | Localized edema | Localized to dependent areas, no disability or functional impairment | Moderate localized edema and intervention indicated; limiting instrumental ADL | Severe localized edema and intervention indicated; limiting self-care ADL | – |
| | Definition: A disorder characterized by swelling due to excessive fluid accumulation at a specific anatomic site. | | | | |
| | Periorbital edema | Soft or non-pitting | Indurated or pitting edema; topical intervention indicated | Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative intervention indicated | – |
| | Definition: A disorder characterized by swelling due to an excessive accumulation of fluid around the orbits of the face. | | | | |
| Labs | Hypo-albuminemia | <LLN–3 g/dL; <LLN–30 g/L | <3–2 g/dL; <30–20 g/L | <2 g/dL; <20 g/L | Life-threatening consequences; urgent intervention indicated |
| | Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood. | | | | |
| | Neutrophil count decreased | <LLN–1500/$mm^3$; <LLN–1.5 x 10e9/L | <1500–1000/$mm^3$; <1.5–1.0 x 10e9/L | <1000–500/$mm^3$; <1.0–0.5 x 10e9/L | <500/$mm^3$; <0.5 x 10e9/L |
| | Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen. | | | | |
| | Platelet count decreased | <LLN–75,000/$mm^3$; <LLN–75.0 x 10e9/L | <75,000–50,000/$mm^3$; <75.0–50.0 x 10e9/L | <50,000–25,000/$mm^3$; <50.0–25.0 x 10e9/L | <25,000/$mm^3$;<25.0 x 10e9/L |
| | Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen. | | | | |
| Skin | Erythema multiforme | Target lesions covering <10% BSA and not associated with skin tenderness | Target lesions covering 10-30% BSA and associated with skin tenderness | Target lesions covering >30% BSA and associated with oral or genital erosions | Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated |
| | Definition: A disorder characterized by target lesions (a pink-red ring around a pale center). | | | | |

| Group | Adverse Event | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|---|
| Skin cont. | Palmar-plantar erythrodysesthesia syndrome | Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain | Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL | Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL | - |
| | Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet. | | | | |
| | Photosensitivity | Painless erythema and erythema covering <10% BSA | Tender erythema covering 10-30% BSA | Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs) | Life-threatening consequences; urgent intervention indicated |
| | Definition: A disorder characterized by an increase in sensitivity of the skin to light. | | | | |
| | Rash maculo-papular | Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness) | Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL | Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADL | - |
| | Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus. | | | | |

From CTCAE v4.03. Available from: http://evs nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

## 13.7 Guidance for Management of Immune-Mediated Adverse Events

These general guidelines constitute guidance to the investigator and may be supplemented by discussions with the medical monitor representing the sponsor. The guidance applies to all immuno-oncology agents and regimens.

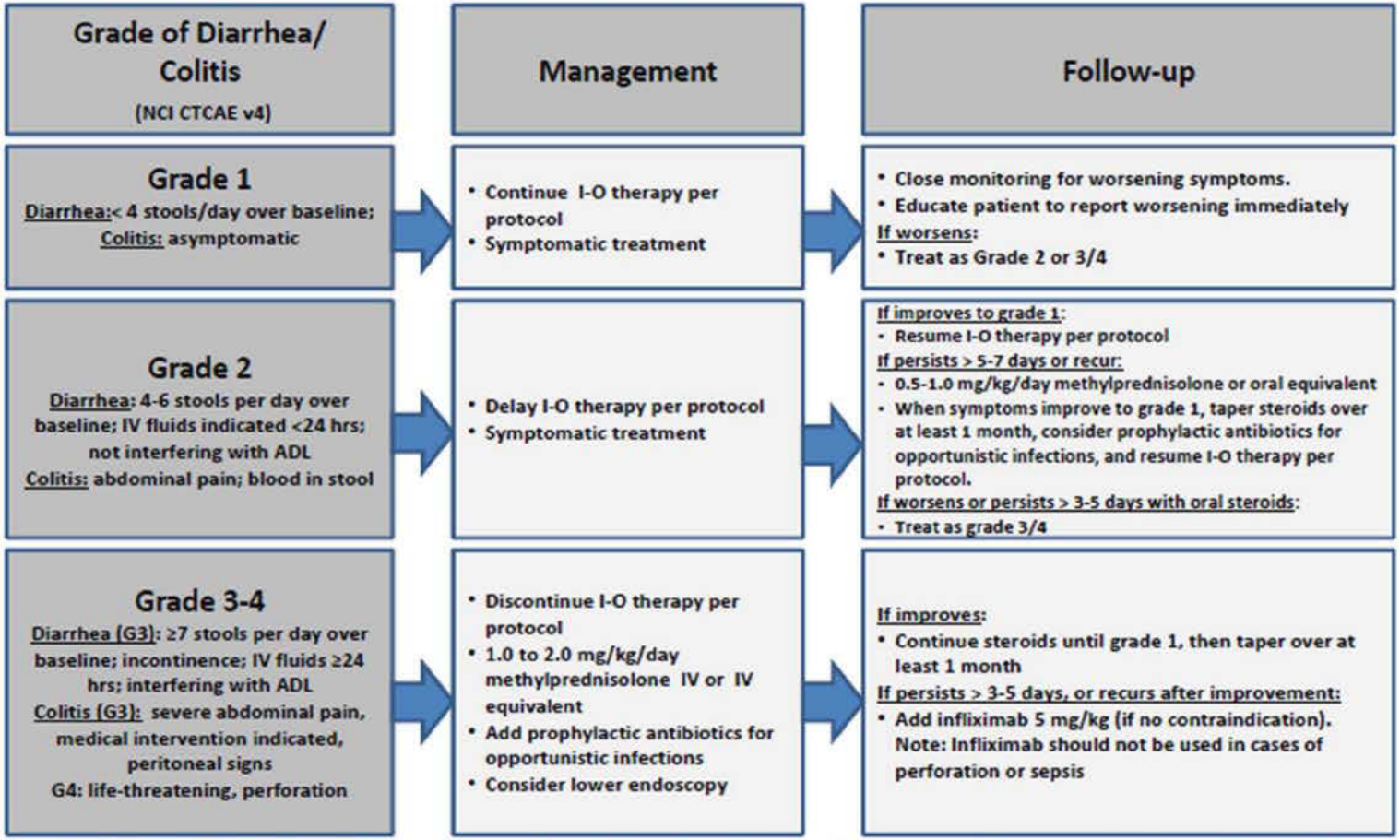
A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended. The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

# GI Adverse Event Management Algorithm

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

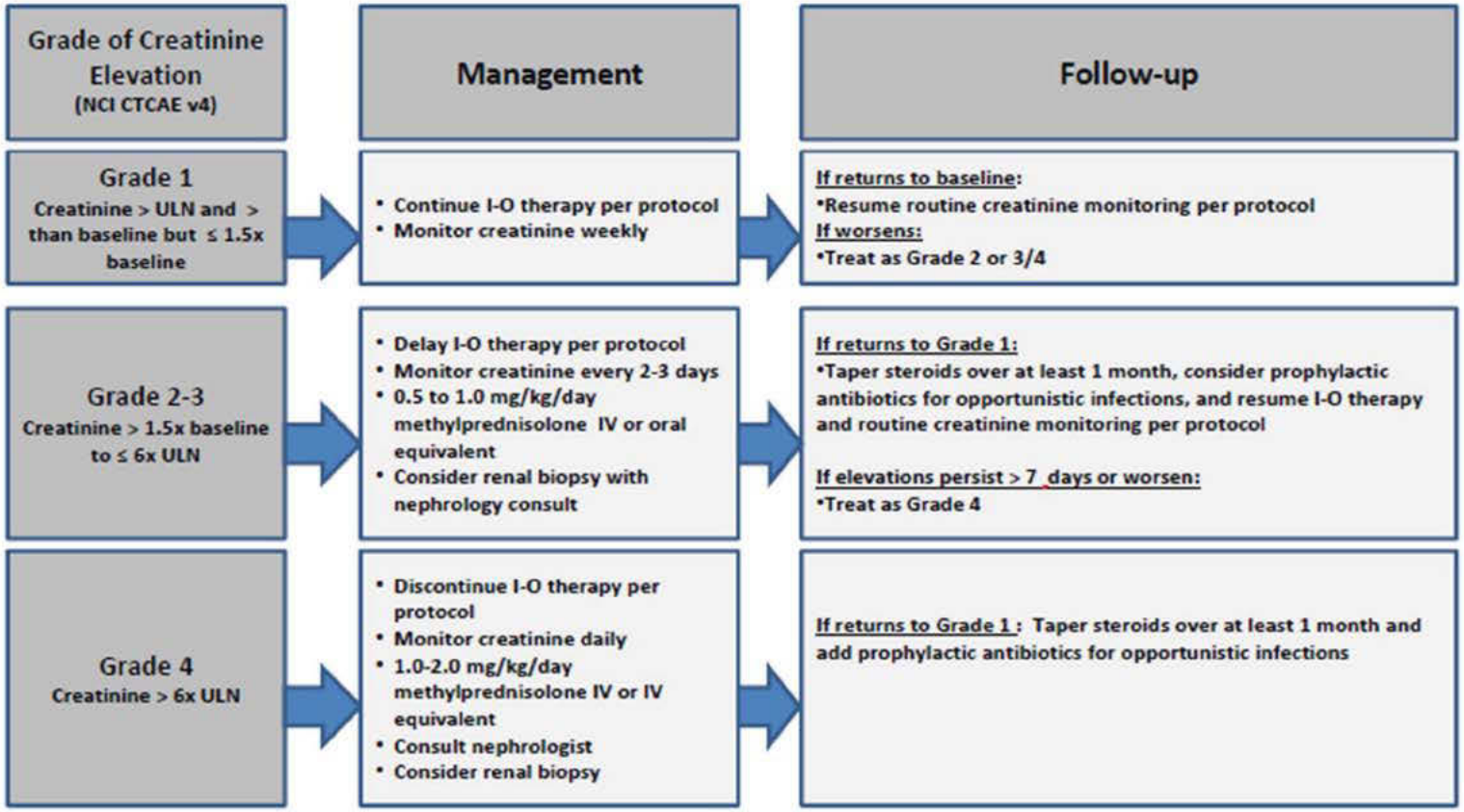



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

# Renal Adverse Event Management Algorithm

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

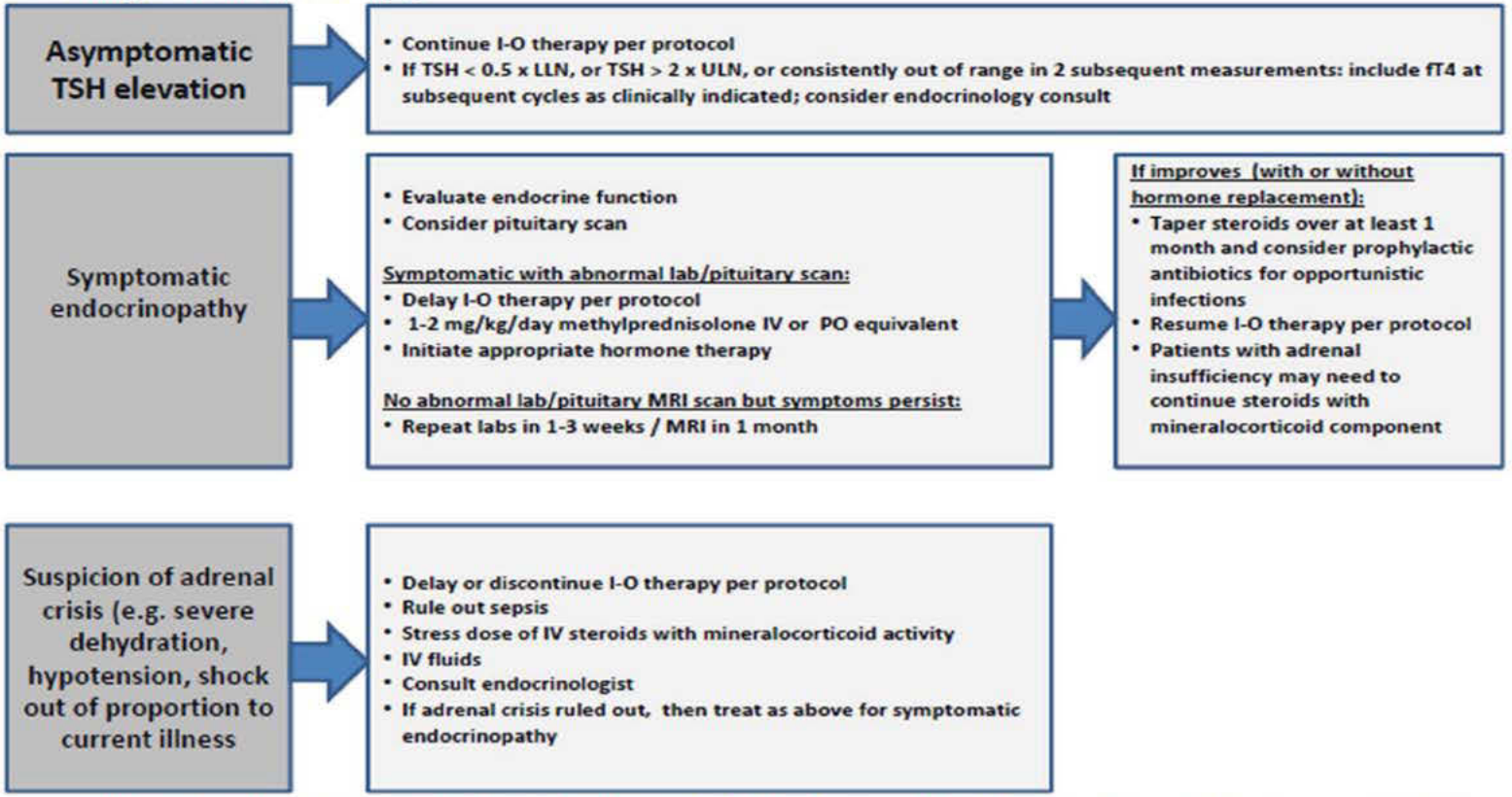



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

# Endocrinopathy Management Algorithm

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




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

Updated 05-Jul-2016

# Hepatic Adverse Event Management Algorithm

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

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

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Updated 05-Jul-2016

# Pulmonary Adverse Event Management Algorithm

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

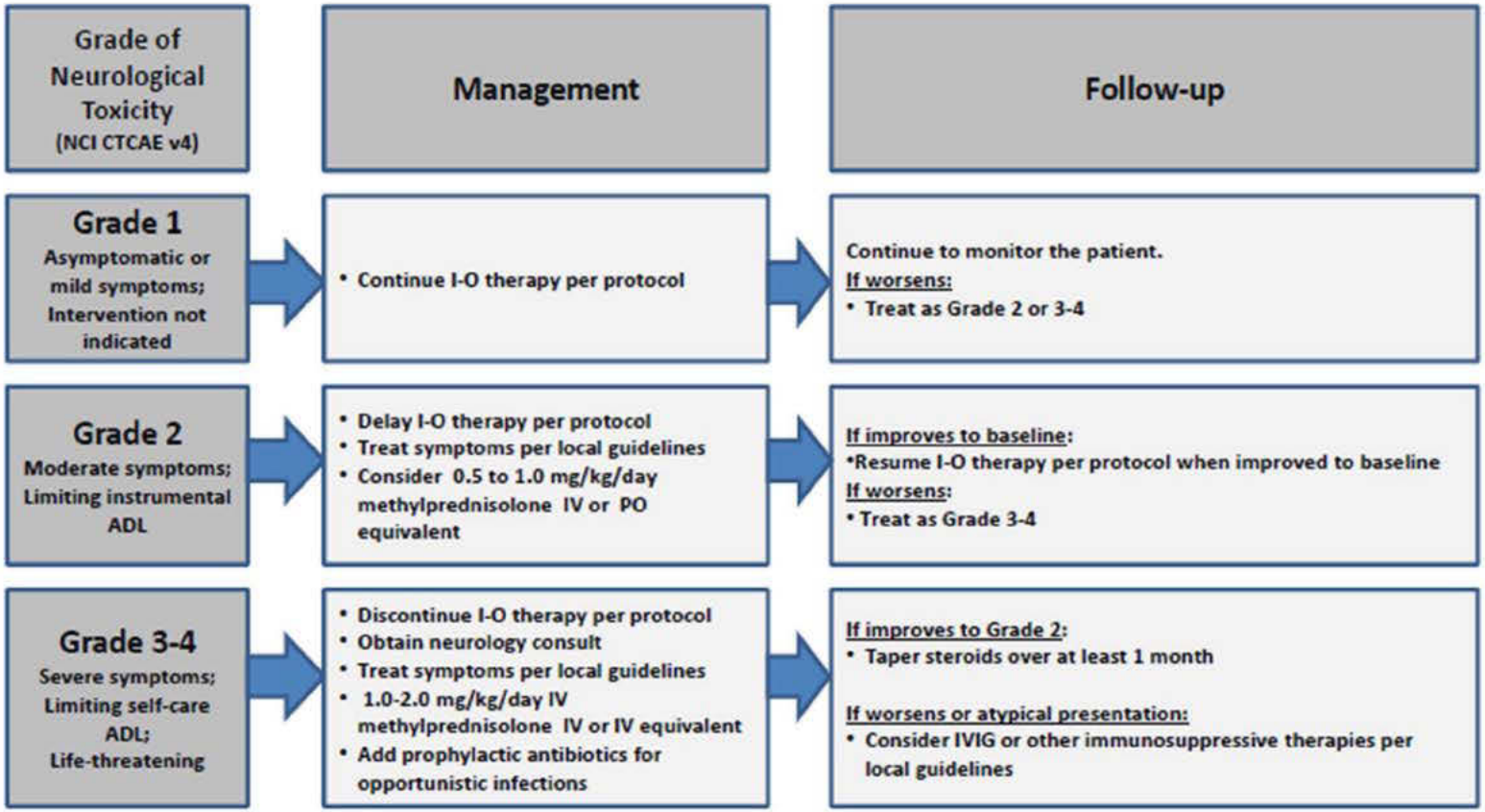
| Grade of Pneumonitis (NCI CTCAE v4) | Management | Follow-up |
|---|---|---|
| Grade 1<br>Radiographic changes only | • Consider delay of I-O therapy<br>• Monitor for symptoms every 2-3 days<br>• Consider Pulmonary and ID consults | • Re-image at least every 3 weeks<br>If worsens:<br>• Treat as Grade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

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

Updated 05-Jul-2016

# Neurological Adverse Event Management Algorithm

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

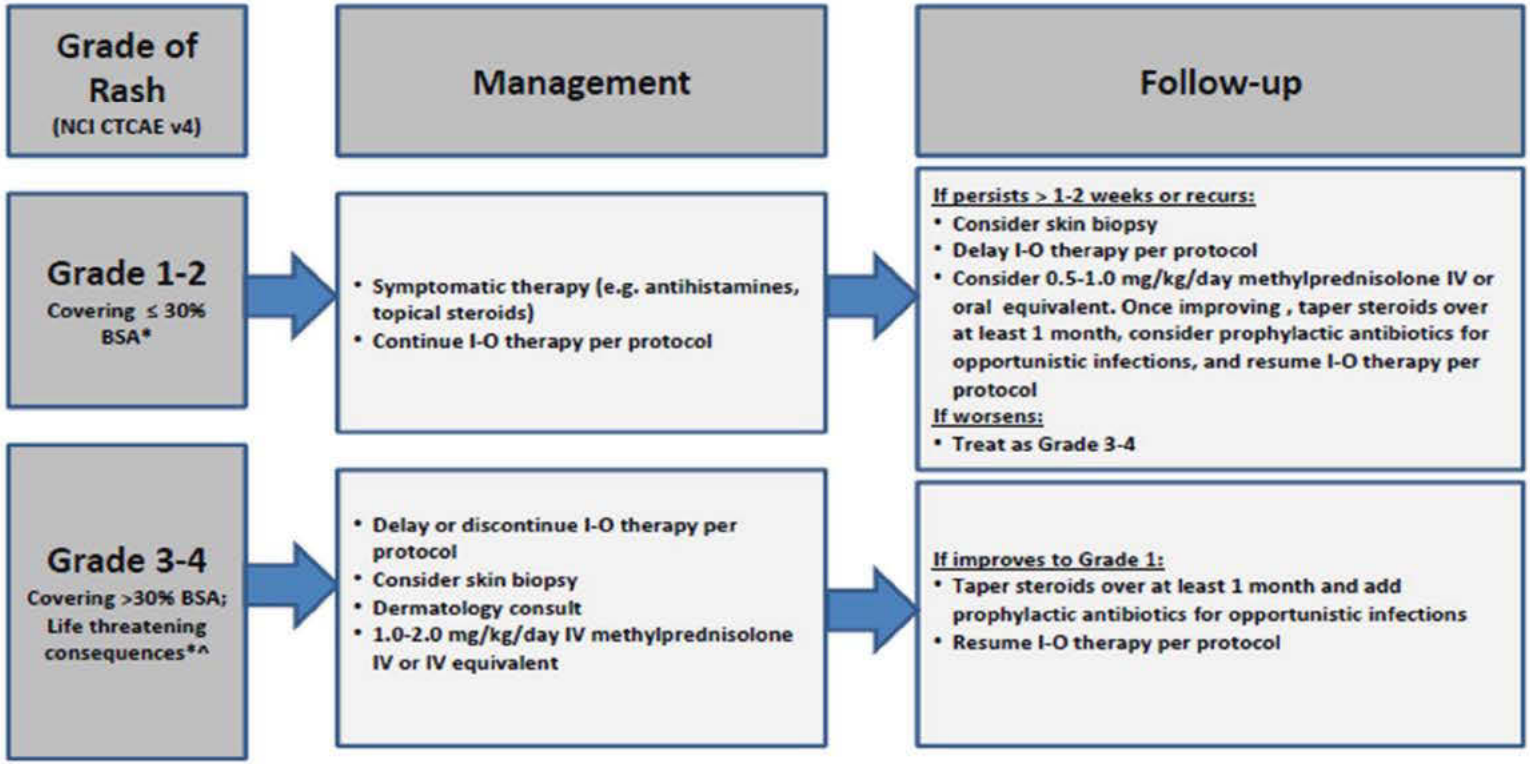



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

# Skin Adverse Event Management Algorithm

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




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

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

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

Updated 05-Jul-2016

## 13.8 Paraneoplastic Assessment

**[EXAMPLE: see Study Binder for actual document]**

**Paraneoplastic Assessment for Study M16-300**

Subject ID: _____

| Does this subject have a history of any of the following? | | Date of Onset DD/MMM/YYYY | Ongoing? | Clinically Significant? |
|---|---|---|---|---|
| Hypercalcemia | ☐Yes ☐No | / / | ☐Yes ☐No | ☐Yes ☐No |
| Lambert-Eaton Myasthenic Syndrome (LEMS) | ☐Yes ☐No | / / | ☐Yes ☐No | ☐Yes ☐No |
| Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) | ☐Yes ☐No | / / | ☐Yes ☐No | ☐Yes ☐No |
| Cerebellar Ataxia | ☐Yes ☐No | / / | ☐Yes ☐No | ☐Yes ☐No |
| Sensory Neuropathy | ☐Ye s ☐No | / / | ☐Yes ☐No | ☐Yes ☐No |
| Limbic Encephalitis | ☐Yes ☐No | / / | ☐Yes ☐No | ☐Yes ☐No |
| Encephalomyelitis | ☐Yes ☐No | / / | ☐Yes ☐No | ☐Yes ☐No |
| Autonomic Neuropathy | ☐Yes ☐No | / / | ☐Yes ☐No | ☐Yes ☐No |
| Opsomyoclonus | ☐Yes ☐No | / / | ☐Yes ☐No | ☐Yes ☐No |
| Retinopathy | ☐Yes ☐No | / / | ☐Yes ☐No | ☐Yes ☐No |
| Other: | ☐Yes ☐No | / / | ☐Yes ☐No | ☐Yes ☐No |

Investigator Signature: _____ Date: _____

## 13.9 Fluid Retention Questionnaire

**[EXAMPLE: see Study Binder for actual document]**

**Fluid Retention Questionnaire for Study M16-300**

Subject ID: _____

Over the past 7 days, or since the last time this questionnaire was asked:

1. What has your daily weight been?

   - Please weigh yourself at the same time each day and record the date and your weight for that day below.
   - Please complete one questionnaire for every 7-day/1-week period.

| Date (DD/MMM/YYYY) | Weight (circle one: lb or kg) |
|---|---|
| | lb or kg |
| | lb or kg |
| | lb or kg |
| | lb or kg |
| | lb or kg |
| | lb or kg |
| | lb or kg |

2. Have you noticed any new or worsening edema – e.g., swelling of the ankles or legs during the days above?
   ☐Yes ☐No

3. Have you noticed any new or worsening shortness of breath during the days above?
   ☐Yes ☐No

4. Please sign below to confirm that you have completed this questionnaire.

_____ Date: _____

## 13.10 Adverse Events Expected Due to SCLC or Progression of SCLC

| Preferred Term |
|---|
| Pleural effusion |
| Malignant pleural effusion |
| Metastases to pleura |
| Dyspnoea |
| Cough |
| Non-cardiac chest pain |
| Haemoptysis* |
| Oesophageal obstruction |
| Pneumonia* |
| Vocal cord paralysis |
| Dysphonia |
| Dysphagia |
| Superior vena cava syndrome |
| Horner's syndrome |
| Metastases to bone |
| Metastases to lymph nodes |
| Metastases to liver |
| Metastases to spine |
| Metastases to the mediastinum |
| Metastases to pleura |
| Metastases to adrenals |
| Metastases to meninges |
| Metastases to central nervous system |
| Metastatic pain |
| Cancer pain |
| Tumour pain |
| Fatigue |
| Asthenia |
| Pulmonary embolism* |
| Shock* |
| Septic shock* |
| Deep vein thrombosis* |
| Lower respiratory tract infection* |
| Respiratory tract infection* |
| Upper respiratory tract infection* |
| Opportunistic infection* |
| Viral infection* |
| Fungal infection* |
| Bacterial infection* |
| Pulmonary haemorrhage* |

| **Preferred Term** |
|---|
| Lung abscess* |
| Empyema* |
| Sepsis* |
| Lymphadenopathy |
| Decreased appetite |
| Malaise |
| Weight decreased |
| Headache |
| Pain excluding chest pain |
| Pyrexia |

*Includes life-threatening or fatal events.

## 13.11 Investigator Signature Page

### Investigator Statement and Signature

I have read the attached protocol entitled, A Phase 1/2 Study on the Safety of Rovalpituzumab Tesirine Administered in Combination with Nivolumab or Nivolumab and Ipilimumab for Adults with Extensive-Stage Small Cell Lung Cancer.

I understand and agree to the provisions of the protocol. I accept the responsibilities included herein in my role as Principal Investigator for the study and I will ensure that all Subinvestigators and study personnel comply with the provisions of this protocol.

Protocol M16-300 Version 3

Dated: 01-DEC-2017

| Investigator Signature | Date |
|---|---|

Investigator Name, Printed

## 13.12 Document History

| Version | Date |
|---|---|
| 1 | 01-DEC-2016 |
| 2 | 16-DEC-2016 |
| 3 | 01-DEC-2017 |