1.0 Title Page

Clinical Study Protocol M16-289

A Randomized, Open-Label, Multicenter, Phase 3 Study of Rovalpituzumab Tesirine Compared with Topotecan for Subjects with Advanced or Metastatic DLL3^{high} Small Cell Lung Cancer (SCLC) who have First Disease Progression During or Following Front-Line Platinum-Based Chemotherapy (TAHOE)

Incorporating Amendments 1, 2, 3, and 4

AbbVie Investigational Product:	Rovalpituzumab tesirine (Rova-T)
Date:	08 January 2019
Development Phase:	3
Study Design:	A randomized, open-label, multicenter study comparing the efficacy, safety and tolerability of rovalpituzumab tesirine versus topotecan for Subjects with Advanced or Metastatic DLL3^{high} SCLC who have first disease progression during or following front-line platinum-based chemotherapy (TAHOE)
EudraCT Number:	2016-003726-17
Investigators:	Investigator information is on file at AbbVie
Sponsor:	AbbVie Inc.*

Sponsor/Emergency Contact: [redacted] Therapeutic Area Medical Director
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* 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.

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.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	17 November 2016
Amendment 1	09 March 2017
Amendment 2	19 May 2017
Amendment 3	02 July 2018

Following the fourth safety review by the IDMC, on 04 December 2018 the IDMC recommended that enrollment in the study is discontinued due to overall survival concerns associated with the study drug. For patients currently on treatment in Arm A, the IDMC recommends that sites and patients make individual decisions as to whether or not to continue treatment based on patient level response.

- Update Section 1.0, Title Page, with correct title for Sponsor/Emergency Contact.

  Rationale: *Corrected error.*
- Update Section 1.2, Synopsis, Section 5.1, Overall Study Design and Plan, Section 5.3.1.1 Study Procedures, Section 8.1.3, Efficacy Endpoints, Section 8.1.5 Secondary Efficacy Endpoints, Section 8.3, Type 1 Error Adjustment Procedure for Multiple Testing, Appendix C, Study Activities for Arm A (Rovalpituzumab Tesirine), table notes "e" and "t" and Appendix D, Study Activities for Arm B (Topotecan) table notes "d" and "s," to remove CRAC assessment of response and progression.

  Rationale: *Hypothesis testing for the efficacy analysis will not be conducted as the study has stopped enrollment due to failure of OS primary endpoint.*
- Update Section 1.2, Synopsis, Section 5.1, Overall Study Design and Plan, Section 5.3.1.1 Study Procedures, Section 5.5.3, Topotecan (Arm B), Section 5.5.6, Selection and Timing of Dose for Each Subject, to clarify treatment duration will end no later than 04 December 2019 and survival follow up will occur up until and no later than 12 February 2020.

Rationale: *To specify date of last dose and end of safety and survival follow up period for study participants.*

- Update Section 5.3.1.1, Study Procedures, Appendix C, Study Activities for Arm A (Rovalpituzumab Tesirine), and Appendix D, Study Activities for Arm B (Topotecan), footnotes "u" and "t" respectively, to remove collection of PRO post Cycle 1 Day 1.

  Rationale: *PRO analysis will not be conducted due to failure of OS primary endpoint.*

- Update Section 1.2, Synopsis, Section 8.0, Statistical Methods and Determination of Sample Size, and Section 8.4, Determination of Sample Size, to clarify efficacy analysis and sample size.

  Rationale: *Clarify original statistical methodologies will be utilized and final sample size.*

- Update Section 5.3.1.1, Study Procedures, Appendix C, Study Activities for Arm A (Rovalpituzumab Tesirine), and Appendix D, Study Activities for Arm B (Topotecan) when applicable, as follows:
  - to remove performance of echocardiogram at alternating cycles from Cycle 2 for Arm B subjects.
  - to remove collection of Fluid Retention Questionnaire for Arm B subjects

  Rationale: *Removed procedures not required for analysis.*

- Update Section 5.3.1.2, Collection and Handling of Biomarker and/or Optional Exploratory Research, Appendix C, Study Activities for Arm A (Rovalpituzumab Tesirine), footnotes "y," "zz," and Appendix D, Study Activities for Arm B (Topotecan), footnote "v," to remove collection of biomarker and pharmacogenetic samples post Cycle 1 Day 1, End of Treatment or at disease progression

  Rationale: *Removed samples not required for analysis.*

- Removed collection of Health Resource Utilization in Appendix C, Study Activities for Arm A (Rovalpituzumab Tesirine), and Appendix D, Study Activities for Arm B (Topotecan)

  Rationale: *Removed procedures not required for analysis.*

- Removed performance of ECG at End of Treatment visit in Appendix D, Study Activities for Arm B (Topotecan)

  Rationale: *Removed procedure not required for analysis.*

An itemized list of all changes made to this protocol under this amendment can be found in Appendix L.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M16-289
Name of Study Drug: Rovalpituzumab tesirine (Rova-T)	**Phase of Development:** 3
Name of Active Ingredient: Rovalpituzumab tesirine (SC16LD6.5)	**Date of Protocol Synopsis:** 08 January 2019
Protocol Title: A Randomized, Open-Label, Multicenter, Phase 3 Study of Rovalpituzumab Tesirine Compared with Topotecan for Subjects with Advanced or Metastatic DLL3^{high} Small Cell Lung Cancer (SCLC) who have First Disease Progression During or Following Front-Line Platinum-Based Chemotherapy (TAHOE)	
Objectives: Primary • To assess if treatment with rovalpituzumab tesirine improves overall survival (OS) compared to topotecan in subjects with advanced or metastatic DLL3^{high} SCLC who have first disease progression during or following front-line platinum based chemotherapy. Secondary • To assess if the treatment with rovalpituzumab tesirine improves progression free survival (PFS) compared to topotecan in subjects with advanced or metastatic DLL3^{high} SCLC who have first disease progression during or following front-line platinum based chemotherapy. • To assess the effect on patient reported outcomes (i.e., health-related quality of life and symptom assessment) due to treatment with rovalpituzumab tesirine compared to topotecan in subjects with advanced or metastatic DLL3^{high} SCLC who have first disease progression during or following front-line platinum based chemotherapy. • To assess if the treatment with rovalpituzumab tesirine improves objective response rate (ORR) and clinical benefit rate (CBR) compared to topotecan in subjects with advanced or metastatic DLL3^{high} SCLC who have first disease progression during or following front-line platinum based chemotherapy. • To compare the duration of objective response (DOR) between two arms. Exploratory • To compare the safety and tolerability of rovalpituzumab tesirine to topotecan. • To assess the pharmacokinetics (PK) and immunogenicity of rovalpituzumab tesirine. • To evaluate DLL3 expression in circulating tumor cells. • To evaluate pharmacodynamic and predictive biomarkers for association with efficacy and safety.	
Investigators: Multicenter, International	
Study Sites: Approximately 225 globally	
Study Population: Subjects with advanced or metastatic DLL3^{high} SCLC who have first disease progression during or following front-line platinum based chemotherapy. DLL3^{high} is defined as ≥ 75% tumor cells staining positive according to the VENTANA DLL3 (SP347) IHC Assay.	

Number of Subjects to be Enrolled: Approximately 600 subjects

Methodology:

This is a Phase 3, randomized, open-label, multicenter study comparing the efficacy, safety and tolerability of rovalpituzumab tesirine (Arm A) versus topotecan (Arm B) in subjects with advanced or metastatic $DLL3^{high}$ SCLC who have first disease progression during or following front-line platinum-based chemotherapy. Subjects will be randomized in a 2:1 ratio to receive 0.3 mg/kg rovalpituzumab tesirine or 1.5 mg/m^2 (or per the local label) topotecan. Subjects receiving rovalpituzumab tesirine will also receive 8 mg orally (PO) of dexamethasone twice daily on Day –1, Day 1, and Day 2 of each cycle in which rovalpituzumab tesirine is administered.

Randomization will be stratified by prior history of brain metastases (yes versus no), prior PCI (yes vs. no) for subjects with no prior history of brain metastases, sensitivity to first line platinum-based regimen [sensitive (OR/SD after first line therapy and progression/recurrence-free interval ≥ 90 days) versus refractory/resistant (PD as best response to or < 90 days progression/recurrence-free interval after first line therapy)] and LDH (> ULN vs. ≤ ULN) at screening.

Survival Follow-up will continue until the endpoint of death, the subject becomes lost to follow-up or withdraws consent, termination of the study by AbbVie, or until 12 February 2020 whichever occurs first.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Adult age 18 years or older, who have provided written informed consent.
2. Histologically or cytologically confirmed advanced or metastatic SCLC with documented first disease progression during or following front-line platinum-based systemic regimen.
3. Tumor must have high DLL3 expression ($DLL3^{high}$) defined as having ≥ 75% tumor cells staining positive according to the VENTANA DLL3 (SP347) IHC Assay. Archived or fresh tumor material can be used for the DLL3 testing.
4. Measurable disease, as defined per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 (Refer to Appendix H).
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Subjects with a history of central nervous system (CNS) metastases must have no active CNS disease prior to randomization, defined as radiographically (MRI/CT) confirmed stable or improved status assessed at least 2 weeks after completion of definitive treatment (surgical resection, WBRT or stereotactic RT) and at least 4 weeks following previous radiographic assessment, off or on a stable dose (≤ 10 mg prednisone equivalent) of corticosteroids. No radiographic evidence of progression of definitively treated CNS disease can be present at the baseline tumor assessment. Subjects with history of CNS disease and high resolution MRI-confirmed CNS complete response to front line chemotherapy at least 6 months prior to randomization are eligible with no requirement for local treatment, provided no evidence of CNS disease by high resolution MRI is present at the screening assessment.
7. Recovery to Grade 0 or 1 of any clinically significant toxicity (excluding alopecia) prior to initiation of study drug administration.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

8. Satisfactory laboratory parameters:
   a. Absolute neutrophil count (ANC) ≥ 1,500/μL
   b. Platelet count ≥ 100,000/μL
   c. Hemoglobin ≥ 9.0 g/dL
   d. Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 × ULN for subjects with Gilbert's disease
   e. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5 × ULN if evidence of hepatic involvement by malignant disease)
   f. Calculated creatinine clearance ≥ 40 mL/min by the Cockroft-Gault formula
   g. Albumin ≥ 3 g/dL
9. If female, subject must be either postmenopausal as 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 surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

   OR Women of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control, starting at randomization through at least 6 months after the last dose of Rova-T for subjects in Arm A or at least 1 month after the last dose of topotecan for subjects in Arm B.

   If the male subject is sexually active, he must agree, from randomization through at least 6 months after the last dose of Rova-T for subjects in Arm A or at least 3 months after last dose of topotecan for subjects in Arm B to practice the protocol specified contraception.
10. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at randomization.

    Females of non-childbearing potential (either postmenopausal or permanently surgically sterile) at Screening do not require pregnancy testing.
11. Subject or the subject's legally acceptable representative must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC/Institutional Review Board (IRB)), prior to the initiation of any screening or study-specific procedures and should be willing and able to comply with parameters as outlined in the protocol.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion:

1. Any significant medical condition that, in the opinion of the investigator or Sponsor, may place the subject at undue risk from the study, including but not necessarily limited to uncontrolled hypertension and/or diabetes, clinically significant pulmonary disease or neurological disorder (e.g., seizure disorder active within 6 months).
2. 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 within 6 months prior to their first dose of study drug.
3. Known leptomeningeal metastases.
4. Isolated CNS disease progression with no evidence of progression outside of CNS.
5. More than one prior systemic therapy regimen for SCLC (prior systemic maintenance therapy following front-line platinum based regimen, administered as part of a clinical trial is allowed).
6. Grade 2 or higher pleural or pericardial effusion within 4 weeks of randomization or earlier history of recurrent Grade 2 or higher pleural or pericardial effusions with ongoing requirement for pericardiocentesis or thoracentesis.
7. History of capillary leak syndrome.
8. Serious infection within 2 weeks prior to randomization, including any Grade 3 or higher (per National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) viral, bacterial, or fungal infection.
9. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 6 months, or for protocol specified period of time as per treatment randomization, after the last dose of study drug.
10. Male subject who is considering fathering a child or donating sperm during the study or for approximately 6 months, or for protocol specified period of time as per treatment randomization, after the last dose of study drug.
11. Systemic therapy with corticosteroids at > 10 mg/day prednisone equivalent within 1 week prior to the first dose of study drug for subjects with history of CNS metastases.
12. Subject has a history of active malignancies other than SCLC within the past 2 years prior to study entry, with the exception of in situ cancer which was curatively treated.
13. Treatment with any of the following anti-cancer therapies within the noted time intervals prior to the first dose of study drug:
    - **within 2 weeks:** small molecule targeted agents with half-life of < 7 days; radiation not involving the thoracic cavity.
    - **within 4 weeks:** chemotherapy; radiation involving the thoracic cavity; small molecule targeted agents with half-life of ≥ 7 days; monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, or T-cell or other cell-based therapies
14. Any prior exposure to a pyrrolobenzodiazepine (PBD)-based or indolinobenzodiazepine based drug, or known hypersensitivity to rovalpituzumab tesirine, or excipient contained in the drug formulation.
15. Prior exposure to topotecan, irinotecan or any other topoisomerase I inhibitors.
16. Participation in a previous study with rovalpituzumab tesirine as an investigational agent.
17. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells.

Investigational Product:	Rovalpituzumab tesirine (Rova-T)
Dose:	0.3 mg/kg
Mode of Administration:	Intravenous, on Day 1 of a 42-Day cycle
Co-Medication:	Dexamethasone
Dose:	8 mg
Mode of Administration:	Oral, twice daily on Day –1, Day 1 (the day of dosing Rova-T), and Day 2 of a 42-Day cycle
Reference Therapy or Investigational Product:	Topotecan
Dose:	1.5 mg/m^2 (or per the local label)
Mode of Administration:	Intravenous, on Days 1 – 5 of each 21-Day cycle.

Duration of Treatment:

Regimen of Arm A will be administered for 2 cycles unless earlier discontinuation is warranted due to disease progression, unacceptable toxicity or any other reason; up to two additional cycles of rovalpituzumab tesirine may be permitted however the last dose on study must be administered no later than 04 December 2019 for subjects in Arm A who consent and satisfy all of the protocol defined criteria.

Regimen of Arm B will be administered until disease progression, unacceptable toxicity, any other reason requiring treatment discontinuation, or no later than 04 December 2019, whichever comes first.

Follow up activities, including overall survival assessments, End of Treatment visits and AE/SAE reporting must occur no later than 12 February 2020.

Criteria for Evaluation:

Efficacy:

Overall Survival (OS): After the End of treatment, survival information will be collected at approximately 6-week intervals (or as requested by sponsor to support data analysis) continuing until the endpoint of death, the subject becomes lost to follow-up, AbbVie terminates the study, or until 12 February 2020.

Progression-Free Survival (PFS): will be derived according to progressive disease per RECIST version 1.1 or death. Radiographic tumor assessments for response will be conducted by CT scanning.

Patient-Reported Outcomes (PRO): health-related quality of life (HRQOL) and symptom assessment will be assessed at baseline, during the treatment cycle, at the end of treatment visit and every 6 weeks thereafter until disease progression or initiation of new anti-cancer therapy via the European Organization for Research and Treatment of Cancer QLQ-C15-PAL (EORTC QLQ-C15-PAL), EORTC QLQ-LC13, and EuroQoL Five Dimensions Questionnaire (EQ-5D-5L) questionnaires.

Objective Response Rate (ORR): will be derived per RECIST version 1.1. Radiographic tumor assessments for response will be conducted by CT scanning at baseline, every 6 weeks for 30 weeks, then every 9 weeks until progression or death.

Safety:

Adverse events, laboratory profiles, physical examinations and vital signs will be assessed throughout the study.

Criteria for Evaluation (Continued):

Pharmacokinetic:

Serum concentrations of rovalpituzumab tesirine antibody-drug conjugate (ADC) and the presence of anti-therapeutic antibodies (ATA) will be determined.

Biomarkers/Pharmacogenetics:

Biomarker assessments will include analyses of tumor material and circulating tumor cells for DLL3 expression, blood samples for inflammatory, tumor and safety markers. Samples may also be used for other nucleic acid or protein based exploratory biomarkers to understand the sensitivity or resistance to rovalpituzumab tesirine and biology of SCLC.

Statistical Methods:

Efficacy:

Following the fourth safety review by the IDMC, on 04 December 2018, the IDMC recommended that enrollment in the study is discontinued due to overall survival concerns associated with the study drug. For patients currently on treatment in Arm A, the IDMC recommends that sites and patients make individual decisions as to whether or not to continue treatment based on patient level response. The data collection plan has been minimized given the status change of this study. With all these changes, no statistical testing will be performed for the efficacy endpoints. The efficacy endpoints will be analyzed using the original statistical methodologies as appropriate. The efficacy endpoints for which there is not enough data to implement the statistical models will be summarized by treatment arms. The statistical section remains unchanged to reflect the original analysis plan.

Efficacy analyses will be performed in the randomized set, including all randomized subjects, with subjects grouped according to the treatment assigned at randomization, following intent-to-treat principle, unless otherwise specified. Assessment of response and progression will be determined by the CRAC according to RECIST v1.1.

Overall survival (OS) is the primary efficacy endpoint. OS is defined as the time from the date of randomization to the date of death from any cause (i.e., date of subject's death – date of randomization + 1). For subjects who are alive at the time of the analysis, the data will be censored at the last date they were documented to be alive. Subjects with no post-baseline information will be censored at the date of randomization plus 1 day.

Comparison between the two treatment arms will be performed via a one-sided log-rank test, stratified by the randomization stratification factors, testing the null hypothesis (rovalpituzumab tesirine arm (Arm A) is not superior to topotecan arm (Arm B) in OS). The hazard ratio (HR) of Arm A over Arm B will be estimated using a stratified Cox proportional hazards model. The OS curves for each arm will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% confidence interval for median OS will be computed. Landmark survival rate, defined as the survival rate estimated using the Kaplan-Meier approach at pre-defined timepoints from randomization (e.g., 6, 12 and 18 months), will be summarized, presenting two-sided 95% CIs.

Secondary time-to-event endpoints of PFS and DOR will be analyzed using the same statistical method described for the analysis of OS. Analysis of categorical endpoints such as ORR and CBR will be performed for the randomized subjects with measureable disease at baseline. Comparison of the categorical endpoints will be carried out using a one-sided Cochran-Mantel-Haenszel (CMH) test, stratified by the randomization stratification factors.

Statistical Methods (Continued):

Testing Strategy:

To meet global regulatory requirements, a multiple testing strategy will be implemented to control the family-wise type I error for comparisons of rovalpituzumab tesirine arm versus topotecan arm with respect to the primary and secondary endpoints in the order specified below.

The following null hypotheses are considered:

H1: Rovalpituzumab tesirine arm is not superior to topotecan arm in OS.

H2: Rovalpituzumab tesirine arm is not superior to topotecan arm in PFS per CRAC.

H3: Rovalpituzumab tesirine arm is not superior to topotecan arm in PRO physical functioning scale at C2D1 for rovalpituzumab tesirine arm and C3D1 for topotecan arm.

H4: Rovalpituzumab tesirine arm is not superior to topotecan arm in ORR per CRAC.

H5: Rovalpituzumab tesirine arm is not superior to topotecan arm in CBR per CRAC.

H6: Rovalpituzumab tesirine arm is not superior to topotecan arm in DOR per CRAC.

The family of null hypotheses will be tested using a hierarchical procedure, i.e., in a fixed sequence of {H1, H2, H3, H4, H5, H6}. Hypothesis H1 will be tested first, and no further tests will be performed if H1 is not rejected. Thereafter, each hypothesis will be tested in the order specified if and only if H1 and all preceding null hypotheses are rejected. Otherwise testing in the hierarchical sequence will stop.

Safety:

A safety analysis will be performed for all subjects treated with the study drug. For the study as a whole, adverse events will be evaluated and summarized. Laboratory test results and vital signs will be summarized as appropriate.

Sample Size:

Following the fourth safety review by the IDMC, on 04 December 2018 the IDMC recommended that enrollment in the study is discontinued due to overall survival concerns associated with the study drug. 444 subjects were enrolled in the study. The following paragraph describes how the sample size was determined for the study.

The sample size of the study is primarily determined by the analysis of OS. Approximately 600 subjects in total will be randomized to rovalpituzumab tesirine (Arm A) or topotecan (Arm B) in a 2:1 ratio. It is assumed that median overall survival in the topotecan arm (Arm B) will be around 6.5 months. Based on a log-rank test, at a one-sided significance level of 0.025 and a power of 85%, a total of 489 deaths are needed to detect an increase in median OS to 8.67 months in rovalpituzumab tesirine arm (Arm A), corresponding to a hazard ratio of 0.75 (i.e., a reduction in the hazard death of 25%). It is projected that an observed hazard ratio of 0.829 or less, corresponding to 1.34 months or greater improvement in median OS, would result in statistical significance in the final analysis of OS.

Interim Analysis:

No interim analysis is planned.

Biomarkers:

Biomarkers will be measured at baseline and post-treatment, with analyses performed to identify markers associated with rovalpituzumab tesirine response, sensitivity, pharmacodynamics, or safety.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ADC	Antibody-drug conjugate
AE	Adverse event
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibodies
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCL1	Achaete-scute homolog 1
ASTRO	American Society for Radiation Oncology
AST	Aspartate aminotransferase
AT	Aminotransferase
ATA	Anti-therapeutic antibody
ATC	Anatomical therapeutic chemical (codes)
ATEMS	AbbVie Temperature Excursion Management System
β-hCG	Beta-human chorionic gonadotropin
BUN	Blood urea nitrogen
CBR	Clinical benefit rate
CDSM	Clinical Drug Supply Management
CFR	Code of Federal Regulations
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
CR	Complete response
CRF	Case report forms
CRP	C-reactive protein
CS	Clinically significant
CSC	Cancer stem cell
CT	Computerized tomography
CTC	Circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP3A4	Cytochrome P450 3A4

DILI	Drug-induced liver injury
DLL3	Delta-like protein 3
$DLL3^{high}$	DLL3 high expression in tumor
DNA	Deoxyribonucleic acid
DOR	Duration of response
DOT	US Department of Transportation
eCCR	Estimated creatinine clearance rate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic data capture
EFNS	European Federation of Neurological Societies
EGF	Epidermal growth factor
EMEA	European Agency for the Evaluation of Medicinal Products
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
EQ-5D-5L	EuroQoL Five Dimensions Questionnaire
ESR	Erythrocyte sedimentation rate
EU	European Union
FDA	US Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
Gy	Gray
HIPPA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
HRQOL	Health-related quality of life
IATA	International Air Transport Association
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational Medicinal Product

INR	International normalized ratio
IP	Investigational product
IRB	Institutional Review Board
IRT	Interactive response technology
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous(ly)
KM	Kaplan-Meier
LCNEC	Large cell neuroendocrine cancer
LD	Longest diameter
LFT	Liver function tests
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
nAb	Neutralizing antibodies
NASH	Non-alcoholic steatohepatitis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCS	Not clinically significant
NEUROD1	Neurogenic differentiation 1
NSAID	Non-steroidal anti-inflammatory drug
NSE	Neuron-specific enolase
NYHA	New York Heart Association
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PBD	Pyrrolobenzodiazepine
PCI	Prophylactic cranial irradiation
PD	Progressive disease
PDX	Patient-derived xenografts
PET	Positron emission tomography
PET-CT	Positron emission tomography-computed tomography

PFS	Progression-free survival
PK	Pharmacokinetics
PO	Per os (by mouth)
POR	Proof of receipt
PR	Partial response
PRO	Patient reported outcome
PT	Prothrombin time
PTFU	Post-treatment follow up
q3wk	Every 3 weeks
q6wk	Every 6 weeks
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
RF	Rheumatoid factor
Rova-T	Rovalpituzumab tesirine
ROVAT	AbbVie compound number for rovalpituzumab tesirine
RPTD	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC-DR002	DNA cross-linking agent also known as D6.5
SC16	Humanized DLL3-specific IgG1 antibody
SCLC	Small cell lung cancer
SD	Stable disease
SGOT/AST	Serum glutamic-oxaloacetic transaminase
SGPT/ALT	Serum glutamic-pyruvic transaminase
SIADH	Syndrome of Inappropriate Anti-Diuretic Hormone
SMPC	Summary of product characteristics
SPF	Sun protection factor
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA MD	Therapeutic Area Medical Director
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TIC	Tumor-initiating cells
ULN	Upper limit of normal
US	Ultrasound

VALG	Veterans Administration Lung Study Group
VAS	Visual analog scale
VEGF	Vascular endothelial growth factor
WBC	White Blood Cell
WHODRUG	World Health Organization Drug (Dictionary)
WOCBP	Women of Childbearing Potential

2.0 Table of Contents

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3.0 Introduction

3.1 Small Cell Lung Cancer

Small cell lung cancer (SCLC) is an important unmet medical need, representing 15 – 20% of the 220,000 annual new cases of lung cancer.[1,2] SCLC arises from epithelial cells with neuroendocrine differentiation. Historically, SCLC has been staged using Veterans Administration Lung Study Group (VA LG) classification as 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 subjects will have limited stage disease while the rest will be extensive. TNM classification is also used to stage SCLC. Systemic chemotherapy remains the cornerstone of therapy for all stages of SCLC. Standard initial chemotherapy for all subjects with a suitable performance status consists of a platinum salt (carboplatin or cisplatin) in combination with a second agent, usually etoposide or irinotecan. For subjects 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, responses are typically not durable and recurrence rates are high in the limited stage disease and nearly universal in the extensive stage disease, leading to median survivals of 14 – 20 months and 9 – 11 months, respectively.[3]

Options for subjects with relapsed/recurrent SCLC disease are limited. The only agent with several global regulatory approvals is topoisomerase I inhibitor topotecan, but its activity is less than impressive, and associated toxicity is significant.[4] Response rate with topotecan is approximately 14%, while median PFS and OS are 2.7 and 6.5 months, respectively. The strongest predictor of topotecan efficacy is sensitivity to front line therapy: subjects with relapse after more than 90 days from the completion of front line therapy (sensitive) have better results with topotecan compared to subjects that progress while receiving front line therapy or in less than 90 days of its completion (refractory/resistant). Several other single agent or combination regimens used in second line SCLC offer efficacy similar to topotecan.

Therefore, exploration of new therapies in second line SCLC is warranted, with the goals of extending disease control and improving overall survival.

3.2 Delta-Like Protein 3

Delta-like protein 3 (DLL3) is an atypical, inhibitory ligand of the Notch receptor family, discovered by AbbVie Stemcentrx scientists as a novel therapeutic target in SCLC and other high-grade neuroendocrine carcinomas. It was identified by whole transcriptome sequencing of tumor initiating cells (TICs) isolated from SCLC and large cell neuroendocrine cancer (LCNEC) patient-derived xenografts (PDXs), and found to be expressed in the majority of SCLC and LCNEC tumors, but with no detectable protein expression in normal tissues or non-neuroendocrine tumor types.[5] DLL3 has been implicated in the regulation of cell fate decisions during development, and likely acts as an oncogene in high-grade neuroendocrine tumors where it is a downstream transcriptional target of the achaete-scute homolog 1 (ASCL1) transcription factor in SCLC tumor cells, and acts to inhibit the Notch receptor pathway, thereby facilitating neuroendocrine tumorigenesis.[5-7]

3.3 Rovalpituzumab Tesirine

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 pyrrolobenzodiazepine (PBD) 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 (Study SCRX16-001), rovalpituzumab tesirine dosed at 0.2 – 0.4 mg/kg 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), respectively, in subjects whose tumors expressed DLL3 in

≥ 50% of cells. Median overall survival was 7.7 months in DLL3 ≥ 50% subjects at all dose levels, with a 1-year survival rate of 30% (AbbVie Stemcentrx, data on file).

In a Phase 2 SCRX001-002 (TRINITY) study in patients with SCLC recurrent after at least two systemic chemotherapy regimens, rovalpituzumab tesirine dosed at 0.3 mg/kg every 6 weeks for two cycles (with an option for additional two cycles upon progression occurring ≥ 12 weeks after the second dose) had shown confirmed objective response rate of 16%, progression-free survival of 3.9 months and overall survival of 5.6 months in 3rd line DLL3^{High} patients. Of note, prolonged stable disease with target lesion size reduction has been observed in a significant number of patients receiving additional post-progression cycles of rovalpituzumab tesirine (AbbVie Stemcentrx, data on file).

Therefore, rovalpituzumab tesirine appears to be an active anti-cancer therapy in SCLC.

3.4 Differences Statement

This is the first randomized, open-label, multicenter, Phase 3 study comparing rovalpituzumab tesirine to topotecan in subjects with advanced or metastatic SCLC with high DLL3 expression (DLL3^{high}) in tumor and who have had first disease progression during or following front-line platinum based chemotherapy.

3.5 Benefits and Risks

Activity of the current second line standard of care topotecan is suboptimal and high unmet need in this setting is widely recognized. Based on the Phase 1 results of rovalpituzumab tesirine, this agent may offer improved efficacy over current second line standard. This study will assess the efficacy, tolerability, and safety of rovalpituzumab tesirine in SCLC subjects with first disease progression during or following front-line platinum-based chemotherapy (e.g., cisplatin or carboplatin plus etoposide).

The most frequent treatment-emergent adverse event (TEAE) terms considered related to rovalpituzumab tesirine have included fatigue (37.6%), pleural effusion (29.4%) peripheral edema (29.1%) and decreased appetite (27.3%), while the most frequent,

related TEAE groups of Grade 3 is thrombocytopenia (10.3%), pleural effusions (6.2%), and anaemia (5.4%). In addition, preclinical toxicology studies conducted in the rat and the cynomolgus monkey have identified bone marrow, lung, liver and kidney as potential sources of clinical adverse events (AEs) (AbbVie Stemcentrx data on file). Accordingly, safety assessments will include regular assessments at protocol-specified time points of routine physical examination, laboratory and imaging tests, echocardiograms, a fluid retention questionnaire, daily weights, and spot urine protein testing.

4.0 Study Objectives

The primary objectives of the study are to assess if treatment with rovalpituzumab tesirine improves overall survival (OS) compared to topotecan in subjects with advanced or metastatic DLL3^{high} SCLC who have first disease progression during or following front-line platinum based chemotherapy.

The secondary objectives of the study are as follows: to assess if the treatment with rovalpituzumab tesirine improves progression free survival (PFS) compared to topotecan; to assess the effect on patient reported outcomes (i.e., health-related quality of life and symptom assessment) between two arms; to assess if treatment with rovalpituzumab tesirine improves objective response rate (ORR) and clinical benefit rate (CBR) compared to topotecan; and to compare the duration of objective response between two arms in subjects with advanced or metastatic DLL3^{high} SCLC who have first disease progression during or following front-line platinum based chemotherapy.

The exploratory objectives are to compare the safety and tolerability of rovalpituzumab tesirine to topotecan; to assess the pharmacokinetics (PK) and immunogenicity of rovalpituzumab tesirine; to evaluate DLL3 expression in circulating tumor cells and to evaluate pharmacodynamic and predictive biomarkers for association with efficacy and safety.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

The study was designed to enroll approximately 600 subjects with advanced or metastatic DLL3^{high} SCLC to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. DLL3^{high} is defined as ≥ 75% tumor cells staining positive according to the VENTANA DLL3 (SP347) IHC Assay.

This is a Phase 3, randomized, open-label, multinational, and multicenter study comparing the efficacy, safety and tolerability of rovalpituzumab tesirine versus topotecan in subjects with advanced or metastatic DLL3^{high} SCLC who have first disease progression during or following front-line platinum-based chemotherapy. Approximately 225 clinical sites will participate.

All subjects must have tumor samples analyzed to confirm eligibility. Tumors must be DLL3^{high} as determined by the AbbVie designated central immunohistochemistry (IHC) laboratory. Archived or fresh tumor material can be used for the DLL3 testing. Testing for DLL3 status may occur at any time after initial diagnosis.

Eligible subjects will be randomized in a 2:1 ratio to receive rovalpituzumab tesirine (Arm A) or topotecan (Arm B):

- Subjects assigned to Arm A will receive 0.3 mg/kg rovalpituzumab tesirine (IV) on Day 1 of a 42-Day cycle for 2 cycles, along with 8 mg orally (PO) of dexamethasone twice daily on Day –1, Day 1, and Day 2. Regimen of Arm A will be administered for the 2 cycles planned unless earlier discontinuation is warranted due to disease progression, unacceptable toxicity or any other reason. Up to two additional cycles of rovalpituzumab tesirine may be permitted, however the last dose on study must be administered no later than 04 December 2019 for subjects in Arm A meeting certain criteria, as described in Section 5.3.1.1.

- Arm B subjects will receive 1.5 mg/m^2 topotecan (IV) on Days 1 – 5 of each 21-Day cycle. Topotecan may be administered at a lower dose if required by the local label. The Arm B regimen will be administered until disease progression, unacceptable toxicity or any other reason requiring treatment discontinuation, or no later than 04 December 2019, whichever comes first.

Subjects will be stratified by prior history of brain metastases (yes vs. no), prior PCI (yes vs. no) for subjects with no prior history of brain metastases, sensitivity to first line platinum-based regimen [sensitive (OR/SD after first line therapy and progression/recurrence-free interval ≥ 90 days) vs. refractory/resistant (PD as best response or < 90 days[8] progression/recurrence-free interval after first line therapy)] and LDH level (> ULN vs. ≤ ULN) at screening.

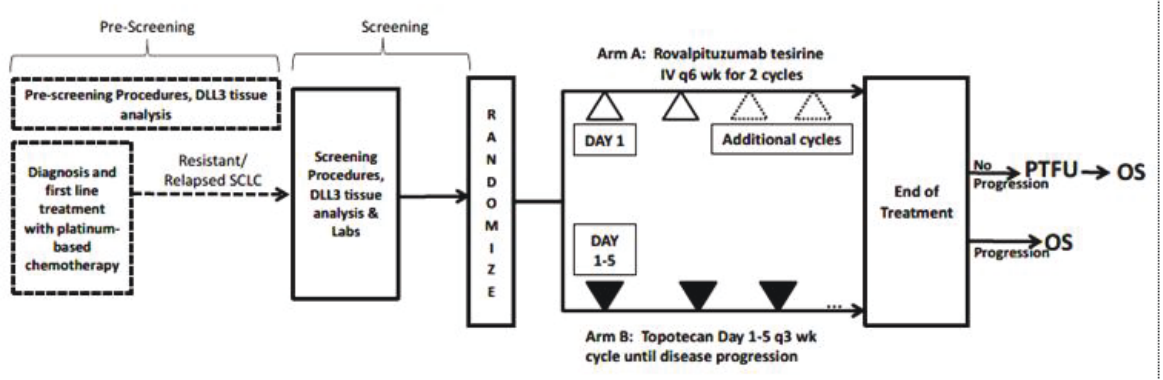
Post-baseline radiographic assessments will be performed every 6 weeks for the first 30 weeks and then every 9 weeks until radiographic progression or death. Radiographic information will be collected to determine response according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. For subjects receiving post-progression doses of rovalpituzumab tesirine radiographic assessments will continue until the second event of disease progression as outlined in Section 5.3.1.1.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved clinically significant laboratory result, the site will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory results or adverse event is achieved.

Subjects no longer undergoing clinical assessments will have survival information reported approximately every 6 weeks (or as requested by sponsor to support data analysis) beginning at the last clinical assessment and continuing until the endpoint of death, the subject has become lost to follow-up, or termination of the study by AbbVie.

A schematic of the study is provided in Figure 1, Study Schema.

Figure 1. Study Schema



Empty arrowhead = Rovalpituzumab tesirine administration cycle; Dotted arrowhead = Additional Rovalpitizumab tesirine administration cycle; Filled arrowhead = Topotecan administration cycle; PTFU = post-treatment follow-up; OS = overall survival

1. Tumor material collection and testing for DLL3 status may occur at any time after initial diagnosis, including outside of the Screening window, depending on completion of the appropriate consent process.
2. Up to two additional cycles of rovalpituzumab tesirine may be permitted for subjects in Arm A meeting certain criteria, as described in Section 5.3.1.1.
3. Topotecan will be administered until disease progression, unacceptable toxicity or any other reason requiring treatment discontinuation.

5.2 Selection of Study Population

The study population will consist of adult subjects with histologically or cytologically confirmed advanced or metastatic SCLC with documented disease progression during or following one prior systemic, platinum-based regimen and confirmed DLL3^{high} SCLC.

Subjects must meet all inclusion criteria and none of the exclusion criteria within 28 days of randomization. (Tumor material collection and testing for DLL3 status may occur at any time after initial diagnosis, including outside of the Screening window, depending on completion of the appropriate consent process.) Subjects should be assessed for eligibility based on the most recent data collected prior to randomization. Eligibility criteria may not be waived by the Investigator and are subject to review in the event of a Good Clinical Practice (GCP) audit and/or regulatory authority inspection.

5.2.1 Inclusion Criteria

1. Adult age 18 years or older, who have provided written informed consent.
2. Histologically or cytologically confirmed advanced or metastatic SCLC with documented first disease progression during or following front-line platinum-based systemic regimen.
3. Tumor must have high DLL3 expression ($DLL3^{high}$) defined as having ≥ 75% tumor cells staining positive according to the VENTANA DLL3 (SP347) IHC Assay. Archived or fresh tumor material can be used for the DLL3 testing.
4. Measurable disease, as defined per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 (Refer to Appendix H).
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Subjects with a history of central nervous system (CNS) metastases must have no active CNS disease prior to randomization, defined as radiographically (MRI/CT) confirmed stable or improved status assessed at least 2 weeks after completion of definitive treatment (surgical resection, WBRT or stereotactic RT) and at least 4 weeks following previous radiographic assessment, off or on a stable dose (≤ 10 mg prednisone equivalent) of corticosteroids. No radiographic evidence of progression of definitively treated CNS disease can be present at the baseline tumor assessment. Subjects with history of CNS disease and high resolution MRI-confirmed CNS complete response to front line chemotherapy at least 6 months prior to randomization are eligible with no requirement for local treatment, provided no evidence of CNS disease by high resolution MRI is present at the screening assessment.
7. Recovery to Grade 0 or 1 of any clinically significant toxicity (excluding alopecia) prior to initiation of study drug administration.
8. Satisfactory laboratory parameters:
    a. Absolute neutrophil count (ANC) ≥ 1,500/μL

b. Platelet count ≥ 100,000/μL
c. Hemoglobin ≥ 9.0 g/dL
d. Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 × ULN for subjects with Gilbert's disease
e. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5 × ULN if evidence of hepatic involvement by malignant disease)
f. Calculated creatinine clearance ≥ 40 mL/min by the Cockroft-Gault formula (Refer to Appendix G)
g. Albumin ≥ 3 g/dL

9. 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 surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

OR Women of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control (Section 5.2.4), starting at randomization through at least 6 months after the last dose of Rova-T for subjects in Arm A or at least 1 month after the last dose of topotecan for subjects in Arm B.

If the male subject is sexually active, he must agree, from randomization through at least 6 months after the last dose of Rova-T for subjects in Arm A or at least 3 months after last dose of topotecan for subjects in Arm B to practice the protocol specified contraception (Section 5.2.4).

10. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at randomization.

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing.

11. Subject or the subject's legally acceptable representative must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC/Institutional Review Board (IRB)), prior to the initiation of any screening or study-specific procedures and should be willing and able to comply with parameters as outlined in the protocol.

Rationale for Inclusion Criteria

1 – 6	To select and/or collect data on the subject population
7 – 8	For the safety of the subjects
9 – 10	The impact of rovalpituzumab tesirine on pregnancy in humans is unknown
11	In accordance with Harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

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

1. Any significant medical condition that, in the opinion of the investigator or Sponsor, may place the subject at undue risk from the study, including but not necessarily limited to uncontrolled hypertension and/or diabetes, clinically significant pulmonary disease or neurological disorder (e.g., seizure disorder active within 6 months).
2. 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 within 6 months prior to their first dose of study drug.

3. Known leptomeningeal metastases.
4. Isolated CNS disease progression with no evidence of progression outside of CNS.
5. More than one prior systemic therapy regimen for SCLC (prior systemic maintenance therapy following front-line platinum based regimen, administered as part of a clinical trial is allowed).
6. Grade 2 or higher pleural or pericardial effusion within 4 weeks of randomization or earlier history of recurrent Grade 2 or higher pleural or pericardial effusions with ongoing requirement for pericardiocentesis or thoracentesis.
7. History of capillary leak syndrome.
8. Serious infection within 2 weeks prior to randomization, including any Grade 3 or higher (per NCI CTCAE version 4.0)[9] viral, bacterial, or fungal infection.
9. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 6 months, or for protocol specified period of time as per treatment randomization, after the last dose of study drug.
10. Male subject who is considering fathering a child or donating sperm during the study or for approximately 6 months, or for protocol specified period of time as per treatment randomization, after the last dose of study drug.
11. Systemic therapy with corticosteroids at > 10 mg/day prednisone equivalent within 1 week prior to the first dose of study drug for subjects with history of CNS metastases.
12. Subject has a history of active malignancies other than SCLC within the past 2 years prior to study entry, with the exception of in situ cancer which was curatively treated.
13. Treatment with any of the following anti-cancer therapies within the noted time intervals prior to the first dose of study drug:
    - **within 2 weeks:** small molecule targeted agents with half-life of < 7 days; radiation not involving the thoracic cavity.

- **within 4 weeks:** chemotherapy; radiation involving the thoracic cavity; small molecule targeted agents with half-life of ≥ 7 days; monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, or T-cell or other cell-based therapies

14. Any prior exposure to a pyrrolobenzodiazepine (PBD)-based or indolinobenzodiazepine based drug, or known hypersensitivity to rovalpituzumab tesirine, or excipient contained in the drug formulation.
15. Prior exposure to topotecan, irinotecan or any other topoisomerase I inhibitors.
16. Participation in a previous study with rovalpituzumab tesirine as an investigational agent.
17. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells.

Rationale for Exclusion Criteria

1 – 8, 17	For the safety of the subjects
9 – 10	The impact of rovalpituzumab tesirine on pregnancy in humans is unknown
11 – 16	To select the appropriate subject population

5.2.3 Prior and Concomitant Therapy

Any concomitant medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of study drug administration, or receives during the study through the safety reporting period (Section 6.1.4), 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 protocol-related AE should be recorded from the time of informed consent.

The AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Prior Therapy

Subjects must have received at least one cycle of platinum-based therapy (carboplatin or cisplatin in combination with etoposide) for the treatment of SCLC. Subjects with a history of CNS metastases must have received definitive treatment for CNS disease. Definitive treatment may include surgical resection with negative margins, whole brain irradiation, and/or stereotactic radiation therapy performed in accordance with a regimen endorsed by the NCCN, European Federation of Neurological Societies (EFNS), or American Society for Radiation Oncology (ASTRO).

5.2.3.2 Concomitant Therapy

All subjects randomized to Arm A will receive oral dexamethasone (PO) as premedication at 8 mg twice daily on Day –1, Day 1 (the day of dosing), and Day 2 of each cycle in which rovalpituzumab tesirine is administered. The first dose of the dexamethasone on the day of dosing should be at least 30 minutes but no more than 4 hours prior to the rovalpituzumab tesirine infusion.

In the event that a subject arrives for rovalpituzumab tesirine administration on Day 1, but has not taken any or all required dexamethasone doses on Day –1 and/or Day 1, rovalpituzumab tesirine administration may not proceed, and rovalpituzumab tesirine will be held until the required dexamethasone dosing has occurred.

5.2.3.3 Allowed Concomitant Therapy

Standard supportive care for drug-related toxicity is permitted, including growth factors and blood product transfusions per local institutional standards and per local topotecan label for subjects in the topotecan arm (Arm B). For subjects receiving topotecan (Arm B), myelopoietic growth factors cannot be initiated until 24 hours after completion of treatment with topotecan within a given cycle. 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 (e.g., bisphosphonates, denosumab) 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 ≤ 10 mg/day. The use of intermittent high-dose corticosteroid treatment to prevent or manage infusion reactions, serosal effusions (see Section 6.1.8.1), or other non-cancer-related symptoms including premedication for known hypersensitivity reactions to contrast agent for CT 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 randomization, and documentation must exclude active infection. After exclusion of active infection, otherwise eligible subjects should complete or continue anti-infectives as prescribed.

If a subject requires palliative radiation during the study (e.g., symptomatic worsening of a bone lesion) diagnostic imaging has to be performed to assess for radiographic progression prior to radiation, and documentation of non-progressive status by radiography will be captured in the eCRF. Any cancer-directed therapy a subject receives due to disease improvement will be subject to TA MD approval and must be discussed with the TA MD in advance.

In the event of isolated CNS progression during study treatment for subjects in Arm A, investigational product will be withheld while palliative treatment is administered (e.g., radiotherapy) in accordance with institutional practice. During this time, the subject should be fully evaluated for other sites of progressive disease. If progression is isolated to the CNS, investigational product may be restarted at least 1 week after the completion of local CNS disease-directed therapy if the disease status does not warrant an alternative

treatment strategy due to clinical symptoms or signs indicating threat to vital organs or critical anatomical sites or decline in performance status. If investigator continues treating the subject with rovalpituzumab tesirine after the first event of progressive disease, scans will continue to be collected until second event of progressive disease.

5.2.3.4 Prohibited Therapy

Subjects may not receive other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy during the study, other than as allowed in Section 5.2.3.2 and Section 5.2.3.3. Additionally, strong inhibitors of cytochrome P450 3A4 (CYP3A4) should be avoided if a subject is randomized to Arm A (refer to Table 1).

Table 1. Examples of Strong CYP3A4 Inhibitors

Enzyme/Transporter	Strong Inhibitor Examples[10]
CYP3A4	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole

(CYP) Cytochrome P450.

Note: This is not an exhaustive list; so if in question, please refer to the appropriate product label.

5.2.4 Contraception Recommendations

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 a FSH level > 40 IU/L.

OR

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

OR For Women of Childbearing Potential (WOCBP)

Practicing at least one of the following methods of birth control, at randomization (or earlier) through at least 6 months after the last dose of investigational product if randomized to Arm A, and at least 1 month after the last dose, if randomized to Arm B.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to randomization.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to randomization.
- Bilateral tubal occlusion/ligation.
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.
- Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the WOCBP 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 (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

If male, subject must be surgically sterile (vasectomy with medical assessment confirming surgical success) or if the male subject has a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), no contraception is required.

If the male subject is sexually active with female partner(s) of childbearing potential, he must agree to use condoms from randomization through 6 months after the last dose of investigational product if randomized to Arm A, and through 3 months after the last dose of topotecan, if randomized to Arm B, and to practice contraception with:

- Female partner(s) must use at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential).
- 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).

Additionally, male subject agrees not to donate sperm from randomization through 6 months after the last dose of investigational product if randomized to Arm A, and through 3 months after the last dose of topotecan, if randomized to Arm B.

5.3 Efficacy, Pharmacokinetic, Biomarker, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C and Appendix D, Study Activities.

5.3.1.1 Study Procedures

Unless otherwise stated, the baseline measurement for any given variable will be defined as the last value obtained for the variable prior to the first dose of investigational product.

The collection of tumor material for DLL3 testing may be done at any time after the informed consent is signed and prior to randomization. Screening procedures and radiographic assessments (CT scan or MRI) must be performed within 28 days prior to randomization. Randomization of the subject in the Interactive Response Technology (IRT) may occur within 3 calendar days prior to C1D1.

Subsequent study procedures should be performed within 3 business days prior to the scheduled treatment visit. For visits where no treatment is administered, procedures may be performed within ± 3 day window relative to due date. Radiographic assessments must be scheduled so that the results are known prior to the treatment visit. Post-treatment follow up, and survival follow up phase visits may occur within ± 1 week window relative to due date unless otherwise indicated.

The results of all screening and evaluations at the time of randomization must be within clinically acceptable limits, upon review by the investigator, before a subject can be randomized. Subjects will not be randomized in the study if laboratory or other screening results are unacceptable. Subjects are allowed to rescreen and have laboratory samples redrawn to meet eligibility within the same 28 day screening window. Subjects who meet the inclusion criteria and do not meet any of the exclusion criteria may be randomized. Therapeutic Area Medical Director (TAMD) review and approval is required in cases where a second rescreen is required.

Subjects receiving additional doses of rovalpituzumab tesirine as described in Section 5.3.1.1 and Section 5.5.2 will follow the same study schedule from Day 1 through EOT and PTFU as in Cycles 1 and 2.

Informed Consent

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken or before any prohibited medications are withheld from the subject in order to participate in this study. Certain standard of care procedures (i.e., ECG) may be utilized as appropriate to prevent repeat protocol-required Screening procedures, but should be discussed with the sponsor. Informed consent may be obtained before the 28-day screening window. Informed consent is also required for tumor biopsy for subjects without archived tumor material at screening. For the optional tumor biopsy at time of disease progression, informed consent must be obtained at the time of initial consent. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Subjects will be considered screen failures if the informed consent has been signed and a study-specific procedure has been performed (e.g., central laboratories drawn), but subject does not randomize into the study. The reason for screen failure will be documented in the source documentation and will be captured in the eCRF.

Tumor Material at Screening

For all subjects, archived or fresh tumor material must be submitted to the AbbVie designated central IHC laboratory for determination of DLL3 expression prior to randomization, as per Appendix C and Appendix D, Study Activities Tables.

Tumor material testing for DLL3 status may occur at any time after initial diagnosis for subjects who provide consent. These subjects must be registered in IRT. Eligibility at the time of tumor progression will depend on DLL3 status (as determined at any time after initial diagnosis), as well as the fulfillment of all other inclusion and exclusion criteria and the trial status (whether the study is still open for accrual).

If archived tissue provided for tumor material testing is not $DLL3^{high}$, re-testing can occur once the subject is re-screened using a fresh tissue biopsy.

Medical and Oncologic History; Adverse Event and Prior/Concomitant Medication Assessment

The following will be collected during the Screening Visit:

- Complete medical history, including demographics and documentation of any clinically significant medical condition and surgical history
- History of tobacco and alcohol use:
  - **current smoker** [subject who has > 100 smoking events in their lifetime and has smoked within the last 12 months] Date of initial cancer diagnosis
  - **past smoker** [subject who has > 100 smoking events in their lifetime and has not smoked in past 12 months]
  - **never smoked** [subject with ≤ 100 smoking events in lifetime]
- Detailed oncology history including:

- Histology
- Date of initial cancer diagnosis
- Date of disease progression
- TNM Stage at diagnosis (if available)
- VALG Stage at diagnosis (Extensive vs. Limited)
- Category of best response to front line platinum-based therapy (PD, SD, PR, CR)
- History of CNS metastases
- History of malignant pleural effusions
- Mutational status, if performed
- Any surgical cancer-related procedures
- Anti-cancer treatments administered (including first and last dose dates and type of modality)

- Detailed prior medication usage including dates of usage and dosing information for all other medications and supplements taken

On Cycle 1 Day 1, any changes observed from the Screening assessments (prior to dosing) will be recorded in the subject's medical history. At each visit, including the End of Treatment (EOT) Visit, the subject's medical history will be reviewed and any changes from baseline will be recorded on the adverse event eCRF.

All medication (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded beginning with first study drug administration through the 70 days following the last dose of investigational product.

Physical Examination

A physical examination, including body weight, will be performed per Appendix C and Appendix D, Study Activities Tables. If the Screening physical examination is performed within 7 days of C1D1, it is not required to be repeated on C1D1 unless clinically indicated. Clinically significant changes from baseline will be documented in the source documentation and eCRFs as adverse events.

Height will be measured at the Screening visit only. For height assessments, the subject should not wear shoes.

Investigators should assess subjects for pleural and pericardial effusion prior to dosing of investigational product on Day 1 of each cycle.

Physical exam will include cardiac, pulmonary (including cardiopulmonary exam for pleural or pericardial effusions), evaluation of extremities for peripheral edema, neurological (sensory, motor, cranial nerves), head and neck, lymphatic, hepatobiliary, gastrointestinal, genitourinary, and skin evaluation per local standard of care.

Vital Signs

Vital signs will be performed per Appendix C and Appendix D, Study Activities Tables. Vital sign determinations include weight, sitting blood pressure, heart rate and body temperature. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections.

Weight will be collected in the clinic prior to dosing at each cycle and the recorded actual weight will be utilized for dosing calculations. For weight assessments, the subject should not wear shoes.

Vital signs should be collected prior to the infusion.

12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be performed per Appendix C and Appendix D, Study Activities Tables. ECGs consist of a single 12-lead study performed within a 5-minute window after at least 5 minutes of quiet rest in a supine position. Additional ECG monitoring may occur as clinically indicated during the study.

A qualified physician will determine whether any findings outside of normal physiological variation are clinically significant (in consultation with a cardiologist if necessary). The physician will document whether findings are clinically significant (CS)

or not clinically significant (NCS) on the tracing and sign and date the tracing. The original annotated ECG tracing containing the physician's assessment will be retained in the subject's records at the study site.

Echocardiogram

Subjects will have echocardiograms performed per Appendix C and Appendix D, Study Activities Tables to assess any pericardial effusion during Screening, and prior to dosing at every cycle for subjects on Arm A, if present, as well as cardiac function (left ventricular ejection fraction, LVEF). Additional echocardiograms may occur as clinically indicated during the study.

ECOG Performance Status

The ECOG performance status will be documented according to Appendix C and Appendix D, Study Activities Tables. Refer to Appendix E, Performance Status Scales Conversion for details.

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 6.1.6).

For female subjects of childbearing potential, pregnancy testing should be performed according to Appendix C and Appendix D, Study Activities Tables. 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, EOT Visit, and PTFU visits until 6 months after the last dose of investigational product.

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing. Postmenopausal female subjects ≤ 55 years of age must have a FSH level > 40 IU/L and will have FSH performed at Screening and assessed by the investigator.

Clinical Laboratory Tests

Samples for chemistry, hematology, coagulation, and urinalysis will be collected per Appendix C and Appendix D, Study Activities Tables. Specific laboratory assessments are outlined in Table 2, Clinical Laboratory Tests.

If the Screening assessment is performed within 7 days of C1D1, it is not required to be repeated on C1D1 unless clinically indicated. All laboratory samples will be assessed using a certified central laboratory and these results will be used for all data analysis. The central laboratory will provide instructions regarding the collection, processing, and shipping of samples. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions as per standard of care.

Qualified medical staff at the site will review, initial and date all local and central laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria as specified in Section 6.1.1.

Table 2. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Urinalysis – Dipstick Only
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands (if indicated) Lymphocytes Monocytes Basophils (if indicated) Eosinophils (if indicated) Platelet count (estimate not acceptable) Mean corpuscular volume Mean corpuscular hemoglobin concentration RBC distribution width	Blood Urea Nitrogen (BUN) Serum Creatinine Total bilirubin Albumin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphate Uric acid Total protein Glucose Chloride Magnesium Amylase Lipase Lactate dehydrogenase (LDH)	Specific gravity Ketones pH Protein Glucose Blood Urobilinogen Bilirubin Leukocyte esterase
Coagulation		**Serum Pregnancy Test**
Activated Partial Thromboplastin Time (aPTT) Prothrombin time (PT) International Normalized Ratio (INR)		Beta-Human Chorionic Gonadotropin (β-hCG) (if applicable) Follicle-stimulating hormone (FSH) (if applicable)

Disease/Response Assessment (Radiographic Imaging)

Treatment response will be assessed by radiographic assessment at protocol-specified time points as outlined in the Appendix C and Appendix D, Study Activities Tables. Diagnostic quality, spiral CT scans are recommended; other CT methods or MRI may be used if performed consistently throughout the study for each individual subject. Scans of the chest and abdomen must be obtained; scans of the neck and pelvis must also be obtained if there is documented or suspected involvement in these regions. Screening radiographic assessment must include brain MRI/CT. Only non-CNS disease will be considered measurable. Disease response will be determined by the investigator at each assessment according to RECIST v1.1 (Appendix H, Response Evaluation Criteria for

Solid Tumors (RECIST) v 1.1).[10] Radiographic assessments must be scheduled so that the results are known prior to the treatment visit.

Effusion (pleural, pericardial, etc.) assessments will be performed at each radiographical assessment and any new findings communicated to the investigator prior to the next dose of investigational product. Effusions should contribute to disease status assessment per RECIST v.1.1 only if confirmed malignant by cytology or otherwise clearly disease-related; if disease progression is suspected solely based on the appearance of new or increase of existing effusions, confirmation of malignant nature of such effusions is strongly recommended prior to making the decision on treatment discontinuation due to known adverse event profile of rovalpituzumab tesirine. If collected, effusion fluid must be tested centrally and/or locally for cytology if disease progression due to appearance/worsening of effusion is suspected.

For subjects whose tumors meet the criteria of partial or complete response (PR or CR), tumor measurements must be confirmed by repeat assessments performed no less than 4 and no more than 6 weeks after the criteria for response are first met.

Isolated CNS-only progression will not require removal of the subject from therapy. Refer to Section 5.2.3.3, Allowed Concomitant Therapy for details associated with CNS only progression.

The EOT radiographic assessment may be omitted if the previous radiographic assessment was performed within the preceding 6 weeks.

Scheduled radiographic assessments will not be affected by delays in therapy and/or drug holidays. Subjects will continue to be monitored by the same diagnostic method throughout the study every 6 weeks after randomization for the first 30 weeks and then every 9 weeks until radiographic disease progression. Subjects who discontinue treatment for reasons other than radiographic disease progression will continue to be followed according to the above schedule, until disease progression occurs.

For subjects in Arm A, if the investigator chooses to continue treating the subject post-progression and the subject consents to additional doses of rovalpituzumab tesirine, scans will continue to be collected every 6 weeks for the first 30 weeks from additional Cycle 3 Day 1 and then again every 9 weeks until the second event of progressive disease. If clinically indicated, radiographic assessments may be performed at times other than those indicated in Appendix C and Appendix D.

MRI/CT of the Brain

MRI of the brain will be assessed at protocol-specified time points as outlined in the Appendix C and Appendix D, Study Activities Tables. Brain MRI may be substituted by CT with intravenous contrast at the discretion of the investigator if MRI testing is clinically contra-indicated or not available. MRI/CT of the brain is required after screening only when clinically indicated (e.g., CNS metastasis history and if CNS progression is suspected).

Randomization and Subject Number Assignment

An Interactive Response Technology system (IRT) will be utilized to register subjects.

Subjects who complete all Screening procedures and meet the eligibility criteria will proceed to randomization. Refer to Section 5.5.5 for details associated with subject assignment to treatment arms.

Patient Reported Outcomes (PRO)

Health-related quality of life and symptom assessments will be performed per Appendix C and Appendix D, Study Assessments using the EORTC QLQ-C15-PAL, the EORTC QLQ-LC13, and the European Quality of Life-5 Dimensions (EQ-5D-5L).

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C15-PAL)[11] is a shortened version of the EORTC QLQ-C30, a widely used instrument for measuring QOL in cancer research. It was developed to ease the difficulty of completing long surveys in subjects who may have a high

symptom burden and short life expectancy. The QLQ-C15-PAL questionnaire contains four multi-item scales (physical & emotional functioning, fatigue and pain) along with six individual items (nausea & vomiting, dyspnea, insomnia, appetite loss, constipation, and global quality of life).

The EORTC QLQ-LC13 is a lung cancer specific module which will supplement the EORTC QLQ-C15-PAL, resulting in a 28-item disease and cancer site-specific quality of life and symptom questionnaire. The QLQ-LC13 module items evaluate symptoms such as cough, haemoptysis, shortness of breath, sore mouth or tongue, dysphagia, tingling hands or feet, hair loss, and pain.

The EuroQol 5 Dimensions 5 Level (EQ-5D-5L) is a generic preference instrument that has been validated in numerous populations. The EQ-5D-5L is composed of 5 questions and a visual analog scale (VAS) assessing overall health that can be converted into a single health status or "utility" score for use in an economic evaluation to adjust life-years gained by the subject's health-related quality of life.

Fluid Retention Questionnaire (Including Subject Daily Weight)

Throughout the treatment period as outlined in the Appendix C and Appendix D, Study Activities Tables, subjects will be asked about the development of any new or worsening peripheral edema or dyspnea (Appendix J, Fluid Retention Questionnaire). The Arm A assessments on Cycle Days 8, 15, 29 and 36 may take place by phone, with the site contacting the subject and reviewing the questionnaire.

Starting on Day 1 through the EOT visit, subjects in Arm A will maintain a diary of daily weight (captured on the Fluid Retention Questionnaire). Subjects should be instructed to use a consistent device throughout the study. The site should advise the subjects in cases where sudden weight gain is observed; the subject should contact the site and possibly be assessed in the clinic.

Additional Two Cycles of Rovalpituzumab Tesirine (Arm A only)

Up to two additional cycles of rovalpituzumab tesirine may be permitted, however the last dose on study must be administered no later than 04 December 2019 for subjects in Arm A who provide consent and who satisfy all of the following criteria:

- achieved clinical benefit defined as stable disease or better with two initial cycles of rovalpituzumab tesirine
- have findings indicative of disease progressing (not limited to CNS) at least 12 weeks after the second dose of rovalpituzumab tesirine
- received no other systemic anti-cancer therapy after two initial cycles of rovalpituzumab tesirine
- had no prior on-study serosal effusions (Appendix I) or edema of > Grade 2 or other non-hematological treatment-related AEs of ≥ Grade 3 or potential DILI and any treatment-related AEs have resolved to Grade 1 or baseline
- have no clinically significant symptoms or signs related to disease progression and/or indicating threat to vital organs and no disease progression at critical anatomical sites necessitating urgent alternative treatment
- have no decline in performance status as compared to the last radiographic assessment at which no progressive disease was identified

Any new or progressing CNS disease of such subject must be definitively treated (radiotherapy or surgery) in order for the subject to be eligible for the two additional cycles of treatment. Subjects remaining in rovalpituzumab tesirine treatment post-progression not limited to CNS will be followed radiographically until the second event of progressive disease. CT/MRI scan must be performed within one week prior to the 4th dose of rovalpituzumab tesirine.

Subjects who do not provide consent for two additional doses of rovalpituzumab tesirine should proceed to the End of Treatment (EOT) visit before continuing on to the Survival Follow Up period.

The last radiographic assessment prior to additional doses of rovalpituzumab tesirine will be used as a new baseline for purposes of subsequent disease assessment.

End of Treatment (EOT) Visit

The visit during which an investigator identifies radiographic disease progression or the subject is not eligible for two additional doses of rovalpituzumab tesirine (Arm A only), or a subject meets other criteria for study treatment discontinuation will be considered the EOT Visit. The EOT visit is the last visit during the treatment phase before a subject enters the Post Treatment Follow Up and/or Survival Follow Up period. The EOT visit should occur within 7 days of documentation of the decision to discontinue treatment and prior to subjects beginning any new anti-cancer therapy, if possible. The reason(s) for the discontinuation from study treatment will be recorded and assessments will be performed per Appendix C and Appendix D, Study Activities Tables.

Disease/Response assessment, including MRI/CT if clinically indicated, may be omitted if performed within the last 6 weeks.

Post-Treatment Follow Up (PTFU)

For all subjects without disease progression (including those who discontinue study treatment for reasons other than disease progression), the first follow-up visit will occur at 6 weeks (± 1 week) after the last Disease/Response Assessment, then every 6 weeks (± 1 week) until disease progression or initiation of new anti-cancer therapy, whichever occurs first. Refer to Appendix C and Appendix D, Study Activities Tables for details of required assessments.

At progression, an optional fresh tumor material sample may be collected from subjects who have provided consent (Section 5.3.1.2, Collection and Handling of Biomarker and Optional Exploratory Research has details regarding tumor material at Time of Disease Progression).

Survival Follow Up (OS)

After disease progression or if a subject stops treatment and declines further study radiographic assessments prior to the endpoint of disease progression, the subject enters the Survival Follow Up period. During this period, the subject will be followed every 6 weeks (± 1 week) for subsequent anti-cancer therapies (dates and responses), and survival status until the endpoint of death, the subject becomes lost to follow-up, termination of the study by AbbVie, or until 12 February 2020 whichever occurs first. If the subject withdraws from study follow-up, the study staff may use a public information source (such as county records) to obtain information about survival status only, as appropriate per local regulations. Refer to Appendix C and Appendix D, Study Activities Tables for details of required assessments.

5.3.1.2 Collection and Handling of Biomarker and/or Optional Exploratory Research Samples

Biomarker Samples

Blood, tumor material, and serosal fluid will be collected as noted in Appendix C and Appendix D, Study Activities Tables and may be utilized to evaluate known and/or novel markers (nucleic acids, peptides/proteins and/or metabolites) of disease status, related conditions or to evaluate the association with pharmacokinetics, safety or efficacy. The biomarker rationale is discussed in the Biomarker Research Variables Section (Section 5.3.6).

All biomarker samples should be labeled and shipped as outlined in the study-specific laboratory manual.

AbbVie (or people or companies working with AbbVie) will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on rovalpituzumab tesirine (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

Tumor Material at Screening

Archived or fresh tumor material remaining after DLL3 IHC testing may be utilized for various biomarkers such as DLL3 expression by additional methodologies, routine hematoxylin and eosin for morphology, IHC for confirmation of diagnosis (e.g., for synaptophysin, chromogranin-A, or CD56), or scoring of immune infiltrates (e.g., IHC for CD3+, CD4+, CD8+, and Foxp3+ cells). Tumor material may also be utilized for exploratory research that includes assessments of nucleic acid or protein based biomarkers of drug sensitivity, resistance, or disease biology and development of a companion diagnostic assay.

Blood (Plasma) for Inflammatory Markers and Circulating Tumor DNA (ctDNA)

At the indicated times noted in Appendix C, Study Activities, blood will be collected, processed to plasma for testing of inflammatory markers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibodies (ANA), rheumatoid factor (RF) and ctDNA. Samples will be collected on Cycle 1 Day 1 (pre-infusion).

Blood (Serum) for Tumor and Soluble Markers

At the indicated times noted in Appendix C, Study Activities, blood will be collected, processed as serum for possible testing of tumor-specific biomarkers that may reflect disease burden such as but not necessarily limited to neuron-specific enolase (NSE) and biomarkers that may be related to the pharmacodynamics effects of rovalpituzumab tesirine such as but not necessarily limited to soluble DLL3, circulating chemokines, or cytokines such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), interleukin (IL)-6, or IL-8. Other biomarkers based on emerging science may also be assessed. Samples will be collected on Cycle 1 Day 1 (pre-infusion).

Blood for Circulating Tumor Cells

At the indicated times noted in Appendix C and Appendix D, Study Activities, blood samples will be collected for assessment and characterization of circulating tumor cells

(CTCs) as a possible reflection of disease burden and DLL3 expression. Whole blood sample will be collected for CTC analysis during screening, and pre-dose on Cycle 1 Day 1.

Serosal Fluid

Any pericardial, pleural, and/or ascitic fluid collected as part of routine care (e.g., as part of a therapeutic thoracentesis, pericardiocentesis, or paracentesis) must be procured for possible PK, pharmacodynamic, and/or biomarker testing. See the laboratory manual for additional details.

Pharmacogenetic Samples

Whole blood samples for DNA and RNA isolation will be collected on Cycle 1 Day 1 (pre-infusion) (–3 business days window is permitted) from each subject. Pharmacogenetic samples should be collected at both timepoints unless precluded by local or national regulations or policies.

Samples will be shipped frozen to AbbVie or a designated laboratory for long-term storage. Instructions for the preparation and shipment of the pharmacogenetic samples will be provided in a laboratory manual.

Optional Exploratory Research Samples

Subjects will have the option to provide samples for exploratory research. Subjects may still participate in the main study even if they decide not to participate in this optional exploratory research.

AbbVie (or people or companies working with AbbVie) will store the exploratory research samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on rovalpituzumab tesirine (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion. The procedure for obtaining and documenting informed consent for exploratory research samples is discussed in Section 9.3.

Tumor Material at the Time of Disease Progression

An optional tumor material collection by biopsy procedure may be obtained at the time of disease progression, from subjects who consent to undergo biopsy procedure. DLL3 expression and other nucleic acid or protein based biomarkers related to the response to rovalpituzumab tesirine and SCLC biology may be assessed.

Biomarker samples will be shipped to AbbVie (or a designated laboratory) for long-term storage. Instructions for the preparation and shipment of the biomarker exploratory research samples will be provided in a laboratory manual.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood Samples for Arm A (Rovalpituzumab Tesirine)

Approximately 6 mL of blood will be collected by venipuncture for pharmacokinetic (PK), Anti-therapeutic antibody (ATA) and neutralizing antibodies (nAb) testing as indicated in Appendix C, Study Activities.

Blood samples should not be drawn from the same arm in which rovalpituzumab tesirine is administered. Samples collected post-infusion should be collected after the full infusion procedure is complete.

The time of each sample collected will be recorded to the nearest minute.

5.3.2.2 Handling/Processing of Samples

Specific instructions for collection of blood/serum samples and subsequent preparation and storage of the samples for the assays will be provided by the central laboratory, AbbVie, or its designee.

5.3.2.3 Disposition of Samples

The frozen serum samples for the rovalpituzumab tesirine ADC, rovalpituzumab tesirine ADC ATA and neutralizing antibodies (nAb) assays will be packed in dry ice sufficient to last during transportation and shipped from the study site to the central laboratory.

An inventory of the included samples will accompany the package and an electronic copy of the manifests (including subject number, study day, the time of sample collection and barcode) will be sent to the contact person at sample.receiving@abbvie.com and/or gprd_lupet@abbvie.com.

5.3.2.4 Measurement Methods

Serum concentrations of rovalpituzumab tesirine ADC and relative titers of rovalpituzumab tesirine ADC ATA will be determined using validated methods. Any additional related analytes may be analyzed using non-validated methods. Serum samples collected for the PK, ATA and nAb analysis may be used for future assay development or validation activities. Rovalpituzumab tesirine ADC nAb samples upon request may be used for the analysis of neutralizing anti-drug antibodies in a validated assay.

5.3.3 Efficacy Variables

The primary objective in the study will be assessed based on the endpoint of OS in subjects with DLL3^{high} SCLC receiving rovalpituzumab tesirine (Arm A) compared to those receiving topotecan (Arm B). To assess the treatment effect of rovalpituzumab tesirine on OS, median OS and OS rates at pre-specified timepoints will be estimated using Kaplan-Meier survival methodology. Estimates of the treatment effect will be presented as hazard ratio through a Cox proportional-hazards analysis.

The secondary objectives of the study are listed in Section 4.0.

5.3.4 Safety Variables

AbbVie will assess adverse events, laboratory data, ECGs and vital signs throughout the study. Adverse events intensity and laboratory evaluation changes will be assessed by utilizing NCI CTCAE Version 4.0.[9]

During the conduct of the study, the AbbVie medical and safety team will be monitoring subject laboratory results and adverse event data as they are reported.

Safety endpoints will be summarized using data from the Safety set. Safety analyses will involve examination of the incidence, severity, and type of treatment-emergent adverse events (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.

5.3.5 Pharmacokinetic Variables

Individual concentrations of rovalpituzumab tesirine ADC and anti-drug antibody will be determined, tabulated and summarized for subjects treated with rovalpituzumab tesirine (Arm A) and summary statistics provided.

5.3.6 Biomarker and/or Optional Exploratory Research Variables

Biomarker Research Variables

Blood, serosal fluid, and tumor material samples will be collected to conduct analyses to investigate biomarkers. The types of biomarkers to be analyzed may include nucleic acids, proteins, lipids or metabolites.

Tumor material and CTCs will be tested for DLL3 expression and analyses will be performed to correlate the expression levels to rovalpituzumab tesirine response.

Enumeration of CTCs, soluble DLL3 in plasma, or markers that are related to the disease or to drug response will be measured at baseline and post-treatment. The information learned from analyzing these samples may be used to investigate factors influencing response to treatment, pharmacodynamics, PK, safety, scientific questions related to

SCLC, and/or in the development of new therapies and diagnostic tests. The results of biomarker testing may not be included with the study summary.

Whole blood for pharmacogenetic analysis may include but not be limited to DLL3, ASCL1, or NEUROD1.

Exploratory Research Variables

Optional samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. The samples may be analyzed as part of a multi-study assessment of factors influencing the subjects' response to the investigational product (or drugs of the same or similar class) or the development and progression of the subjects' disease or related conditions. The samples may also be used to develop new diagnostic tests, therapies, research methods or technologies. The results from these analyses are exploratory in nature and may not be included with the study report.

5.4 Removal of Subjects from Therapy or Assessment

Each subject has the right to withdraw from study treatment at any time. In addition, the investigator may discontinue a subject from the study treatment at any time for any reason if the investigator considers it necessary, including the occurrence of an adverse event or noncompliance with the protocol. Each subject will be withdrawn from the study or study treatment (as applicable) per Section 5.4.1 if any of the following occur:

- The subject has radiographic progression according to RECIST version 1.1 (with the exception of CNS only progression, Arm A) and the subject is not eligible or does not provide consent to receive an additional two doses of rovalpituzumab tesirine (Arm A).
- The subject requires cancer-directed radiotherapy or surgery related to clinical disease progression (with the exception of CNS only progression, Arm A), or alternate anti-cancer agents during the study period.

- The subject experiences treatment toxicity which, in the investigator's opinion, prohibits further therapy or the investigator believes it is otherwise in the best interest of the subject.
- Subject is suspected to be pregnant; pregnancy is confirmed or begins breastfeeding during the treatment portion of the study.
- The subject decides to withdraw consent for any reason.
- Any other medical reason that AbbVie or the study investigator deems appropriate.
- Significant non-compliance to the protocol.

Discontinued subjects will not be replaced.

All subjects will receive a final dose of study drug no later than 04 December 2019. Follow up activities, including Overall Survival assessments, End of Treatment visits and AE/SAE collection should occur no later than 12 February 2020.

5.4.1 Discontinuation of Individual Subjects

Subjects who complete therapy or who discontinue study treatment prior to reaching an event of radiographic disease progression are to continue assessments until disease progression. Refer to Section 5.3.1 for more details.

When a subject discontinuation from the study (without reaching a protocol-defined endpoint) is planned, the investigator is to notify the AbbVie Therapeutic Area Medical Director (TA MD) or the clinical team representative (Section 7.0) as soon as possible (provided, in each case, subject care and safety are not compromised). If not notified prior to discontinuation, the AbbVie TA MD may contact the site to discuss the reason for withdrawal from the study.

The visit an investigator identifies radiographic disease progression or the subject is not eligible or does not consent for two additional doses of rovalpituzumab tesirine (Arm A only), or a subject meets other criteria for study treatment discontinuation will be considered the EOT Visit. The reason(s) for the discontinuation from study treatment will

be recorded and assessments will be performed per Appendix C and Appendix D, Study Activities Tables. It is preferable that EOT Visit procedures be conducted prior to the initiation of another anti-cancer therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition.

If a subject is discontinued with an ongoing adverse event or an unresolved clinically significant laboratory result, the site will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory results or adverse event is achieved.

Subjects no longer undergoing clinical assessments will have survival information collected at every 6 weeks (± 1 week) until the endpoint of death, the subject becomes lost to follow-up or termination of the study by AbbVie, whichever occurs first or until 12 February 2020.

In the event that a positive result is obtained on a pregnancy test for a subject during the study, the administration of investigational product to that subject must be discontinued immediately. The site must report the positive pregnancy test result within 24 hours to AbbVie by entering the information into the Pregnancy eCRF in the EDC system.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator and provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

5.5.2 Rovalpituzumab Tesirine (Arm A)

Rovalpituzumab tesirine, the investigational agent under study in this protocol, is an ADC. Rovalpituzumab tesirine will be given by IV infusion over approximately 30 minutes (window 20 – 45 minutes), adjusted to subject tolerability, at a dose of 0.3 mg/kg on Day 1 of a 42-Day cycle for 2 cycles. Dexamethasone will be co-administered orally (PO) twice daily at a dose of 8 mg to all subjects randomized to Arm A on Day –1, Day 1, and Day 2 of each 42-day cycle in which rovalpituzumab tesirine is administered. Dexamethasone dosing should occur such that there are approximately 12-hours (i.e., 10 – 14 hours) between AM and PM doses. The first dose of the dexamethasone on the day of dosing should be at least 30 minutes but no more than 4 hours prior to the rovalpituzumab tesirine infusion. If the dose of dexamethasone is vomited within 15 minutes of taking the medication, the subject should retake the medication.

In the event that a subject arrives for rovalpituzumab tesirine administration on Day 1, but has not taken any or all required dexamethasone doses on Day –1 and/or Day 1, rovalpituzumab tesirine administration may not proceed, and rovalpituzumab tesirine will be held until the required dexamethasone dosing has occurred.

Dosing is based on actual body weight of the subject to the nearest kilogram, assessed in the clinic on Day 1 of each cycle, and administered according to the calculated dose. In cases of weight gain due to fluid retention, dosing should be based on most recent pre-fluid retention actual weight.

Subjects must meet all of the following on infusion day before receiving study drug:

- Absolute neutrophil count $\geq$ 1,000/μL
- Platelet count $\geq$ 75,000/μL

- Resolution of study drug-related AEs, including findings indicative of pleural or pericardial effusions, and clinically-significant laboratory abnormalities to Grade 0 or 1 (excluding ANC and alopecia), or to baseline grade.

All subjects assigned to Arm A will be administered 2 cycles of rovalpituzumab tesirine no later than 04 December 2019 unless earlier discontinuation is warranted due to disease progression (see exception below), unacceptable toxicity or any other reason.

Subjects developing CNS-only disease progression during the initial cycle of rovalpituzumab tesirine may be allowed to remain on treatment after receiving local definitive treatment for CNS disease.

Up to two additional cycles of rovalpituzumab tesirine may be permitted, however the last dose on study must be administered no later than 04 December 2019 for subjects in Arm A who provide consent and who satisfy all of the appropriate criteria as described in Section 5.3.1.1.

5.5.3 Topotecan (Arm B)

Topotecan is a semi-synthetic derivative of camptothecin and is an anti-tumor drug with topoisomerase I-inhibitory activity. Topotecan will be given as an IV infusion over 30 minutes at a dose of 1.5 mg/m^2 on Days 1 – 5 of 21-Day cycle. Topotecan may be administered at a lower dose if required by the local label.

All subjects assigned to Arm B will continue to receive topotecan until disease progression or 04 December 2019 (whichever is later), unless earlier discontinuation is warranted due to unacceptable toxicity or any other reason.

5.5.4 Identity of Investigational Products

Rovalpituzumab tesirine is supplied as lyophilized drug packaged in a 10 mL, clear glass vial. Each vial provides 30 mg rovalpituzumab tesirine. When reconstituted with 3.2 mL of sterile water for injection, each vial provides 10 mg/mL rovalpituzumab tesirine (30 mg total). Vials of rovalpituzumab tesirine will be supplied to each participating site. A

complete description of the chemistry and formulation may be found in the Investigator's Brochure.[12]

Topotecan is the comparator chemotherapy, and will be administered at a starting dose of 1.5 mg/m^2 by IV infusion over 30 minutes, daily for 5 consecutive days, starting on Day 1 of a 21 day cycle. Topotecan may be administered at a lower dose if required by the local label. Instructions for use are available in the local approved product labeling. Topotecan will be supplied by AbbVie for all countries except for the United States of America.

Table 3. Identity of Investigational Products

Study Drug	Dosage Form	Strength	Route of Administration	Manufacturer
Rovalpituzumab tesirine	Powder for solution for infusion in vials	30 mg vial (10 mg/mL when reconstituted with 3.2 mL of sterile water for injection)	IV infusion after further dilution	AbbVie
Topotecan*	Powder or solution for infusion in vials**	1 mg, 2 mg and/or 4 mg vials***	IV infusion after further dilution	various****

* Topotecan will be supplied as an investigational medicinal product by AbbVie except in USA.

** Topotecan is commercially available as both a powder and solution for infusion. Availability will vary by region.

*** Where provided by AbbVie, Topotecan, will be supplied as 4 mg vials unless unavailable.

****Topotecan will be sourced from various commercial manufacturers depending on availability and region.

Table 4. Non-Investigational Medicinal Products

Drug Product	Dosage Form	Dose	Route of Administration	Supplier
Dexamethasone	Tablets	8 mg twice daily (BID) to all subjects randomized to Arm A	Oral	AbbVie/Clinical Sites

AbbVie will provide non-investigational medicinal products unless specified otherwise by AbbVie. AbbVie may provide non-investigational products depending on operational or regulatory requirements. For countries where dexamethasone is obtained locally from commercial sources (Australia, Japan and USA), AbbVie may reimburse for dexamethasone to participating sites as required. Instructions for use are available in the approved product labeling.

All non-investigational medicinal products (not provided by AbbVie) should be obtained from a licensed pharmacy or wholesaler. Each site will be responsible for maintaining drug accountability records, including product description, manufacturer, and lot numbers for all non-investigational products dispensed by the site.

5.5.4.1 Packaging and Labeling

Rovalpituzumab Tesirine

Vials of rovalpituzumab tesirine will be packaged in cartons. Each vial and carton will be labeled per country requirements. Labels must remain affixed to the vial and carton. Rova-T drug product is classified as a Dangerous Goods/Hazardous Material and is packaged and shipped by AbbVie according to US Department of Transportation (DOT) and International Air Transport Association (IATA) certified regulations.

Dexamethasone

Dexamethasone supplied by AbbVie will be provided in commercial primary packaging with a study label affixed to the primary container and/or secondary packaging. Each bottle, carton and/or blister will be labeled per country requirements.

Labels must remain affixed to the bottle, carton and/or blister.

Topotecan

Topotecan supplied by AbbVie will be provided in commercial primary packaging with a study label affixed to the primary container and/or secondary packaging. Each vial and carton will be labeled per country requirements.

Labels must remain affixed to the vial and carton.

5.5.4.2 Storage and Disposition of Study Drugs

For all storage areas and refrigerators, temperature logs will be maintained to document proper storage conditions. The temperature must be recorded on temperature logs to

verify proper function on each business day. Temperature excursions must be reported to AbbVie immediately.

Sites should use the AbbVie Temperature Excursion Management System (ATEMS) module via IRT, if available, or fax copies of the temperature log indicating the extent of the excursion (time, duration of the temperature excursion, min/max values and study drugs affected) to AbbVie Clinical Drug Supply Management (CDSM) including the Storage Temperature Excursion Reporting Form.

In case of a temperature excursion, study medication should be quarantined and not dispensed until AbbVie CDSM or ATEMS deems the medication as acceptable.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to the destruction facility.

Rovalpituzumab Tesirine

Lyophilized rovalpituzumab tesirine must be stored at refrigerated temperature (2° to 8°C/36° to 46°F), protected from light, and must not be frozen. Specific storage conditions for reconstituted and diluted IP will be provided in a separate document outside of this protocol.

Dexamethasone

Dexamethasone supplied by AbbVie should be stored at 15° to 25°C (59° to 77°F) and protected from light. If dexamethasone is obtained locally from commercial sources, the approved product labeling should be referenced for appropriate storage conditions.

Topotecan

Topotecan supplied by AbbVie must be stored refrigerated at 2° to 8°C (36° to 46°F). Keep the vial in the outer carton to protect from light. If topotecan is obtained locally

from commercial sources, the approved product labeling should be referenced for appropriate storage conditions.

5.5.4.3 Preparation/Reconstitution of Dosage Forms

Rovalpituzumab Tesirine

Rovalpituzumab tesirine is supplied as lyophilized drug in a 30 mg vial. When reconstituted with 3.2 mL of sterile water for injection, each vial provides 30 mg of rovalpituzumab tesirine at a solution concentration of 10 mg/mL. Rovalpituzumab tesirine is intended for intravenous infusion after further dilution in a suitable diluent such as 0.9% sodium chloride for injection.

Since rovalpituzumab tesirine dosing is based on body weight, multiple vials of reconstituted drug product may be required to achieve the desired dose. Specific dose preparation and documentation details will be provided to the site pharmacy in a separate document.

Topotecan

The preparation of topotecan for dosing and administration should be done in accordance with the locally approved product label or Summary of Product Characteristics (SmPC).

5.5.5 Method of Assigning Subjects to Treatment Arms

All subjects in the study will be randomized using an Interactive Response Technology (IRT) system. Before the study is initiated, directions for the IRT will be provided to each site. The site will contact the IRT to obtain a Screening (subject) number once the subject has signed the informed consent and a study-specific procedure has been performed (i.e., central laboratory samples drawn). Once the screening number is assigned, if the subject is not randomized into the study, the reason for screen failure will be documented in the source document and in the eCRF.

The IRT will randomize subjects in a 2:1 ratio, with two-thirds of the subjects randomized to the rovalpituzumab tesirine treatment arm and the other one-third to the topotecan arm. The stratification data used for randomization should be the last values obtained for the stratification factor prior to randomizing the subject in IRT.

A bottle number randomization schedule and a subject randomization schedule will be generated by the Clinical Statistics Department at AbbVie prior to the start of the study.

5.5.6 Selection and Timing of Dose for Each Subject

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

Subjects in Arm A will receive 2 cycles of rovalpituzumab tesirine, 0.3 mg/kg via IV on Day 1 of the 42-Day cycle. Two additional cycles of rovalpituzumab tesirine may be permitted for subjects in Arm A as described in Section 5.3.1.1. Prior to dosing rovalpituzumab tesirine, subjects will receive 8 mg twice daily oral dexamethasone (PO) as premedication on Day –1, Day 1 (the day of dosing) and Day 2.

Subjects in Arm B will receive topotecan at 1.5 mg/m^2 via IV on Days 1 - 5 of each 21-Day cycle. Topotecan may be administered at a lower dose if required per the local label.

5.5.6.1 Dose Modifications

5.5.6.1.1 Dose Treatment Delays Due to Toxicity or Progression (Arm A, Rovalpituzumab Tesirine)

Subjects who experience toxicity during a cycle must have recovered as specified above before the next cycle may proceed. Any dose modifications except those indicated as mandatory below (including dose delay, reduction, resumption, and discontinuation) are to be performed at the discretion of the investigator. Further guidelines suggesting dose

modifications based on prior studies of rovalpituzumab tesirine are provided in Section 5.5.6.1.2, Dose Reduction Guidelines.

In cases of treatment delays of > 28 days due to toxicity, the subject will be discontinued from treatment. In cases where treatment benefit is observed, longer dose delays due to toxicity, if required, can be discussed with the TAMD.

For subjects in Arm A, in the event of isolated CNS progression during Cycle 1 (see Section 5.3.2.3), Cycle 2 of the investigational product may be administered no sooner than 1 week after the completion of CNS disease-directed local therapy.

5.5.6.1.2 Dose Reduction Guidelines (Arm A, Rovalpituzumab Tesirine)

Investigational product dose reductions and discontinuation of investigational product for specific toxicities should occur as outlined in Table 5, Dose Reductions for rovalpituzumab tesirine Investigational Product (IP) and Table 6, Dose Reductions and Discontinuation for Unacceptable Toxicities. Dose reductions for unacceptable toxicities described in Table 6 are mandatory. Reduced dose levels are described in (Table 5). Generally, if an unacceptable toxicity recurs after two dose reductions, treatment will be discontinued (for further details, refer to Table 6). If the investigational product dose is reduced, no re-escalation will be allowed. If different unacceptable toxicities occur in sequential treatment cycles (e.g., Grade 3 LFT after the first dose and Grade 3 thrombocytopenia lasting more than 7 days after the second dose), dose reduction will proceed to the next lower dose level. If different unacceptable toxicities occur within one cycle, maximum specified dose reduction will be implemented. Dose reductions and discontinuation are not allowed for dexamethasone. If the full dose of dexamethasone cannot be administered due to an AE, the rovalpituzumab tesirine infusion should be delayed until the full dose of dexamethasone can be administered.

Exceptions to the dose modification guidelines should be discussed with the TA MD prior to implementation.

Table 5. Dose Reductions for Rovalpituzumab Tesirine Investigational Product (IP)

Starting Dose	First Dose Reduction (Reduce Dose)	Second Dose Reduction (Reduce Dose)
0.3 mg/kg	0.2 mg/kg	0.1 mg/kg

Table 6. Dose Reductions and Discontinuation for Unacceptable Toxicities

Toxicity[a]	First Occurrence	Second Occurrence
Grade 3 thrombocytopenia lasting more than 7 days	Reduce dose to 0.2 mg/kg	Reduce dose to 0.1 mg/kg
Grade 4 thrombocytopenia/Grade 3 thrombocytopenia with bleeding/Need for platelet transfusion	Reduce dose to 0.1 mg/kg	Discontinue Rova-T
Grade 4 neutropenia lasting more than 7 days	Reduce dose to 0.2 mg/kg	Reduce dose to 0.1 mg/kg
Grade 3 febrile neutropenia	Reduce dose to 0.2 mg/kg	Reduce dose to 0.1 mg/kg
Grade 4 febrile neutropenia	Reduce dose to 0.1 mg/kg	Discontinue Rova-T
Grade 3 Liver Function Tests (LFTs)[b]	Reduce dose to 0.2 mg/kg	Reduce dose to 0.1 mg/kg
Grade 4 LFTs or Grade 3 LFTs with concomitant Bilirubin Grade 2 or higher[b]	Reduce dose to 0.1 mg/kg	Discontinue Rova-T
Grade 3 or 4 hypoalbuminemia	Reduce dose to 0.1 mg/kg	Discontinue Rova-T
Any other Grade 3 or 4 laboratory abnormality considered clinically significant and treatment-related	Reduce dose to 0.2 mg/kg	Reduce dose to 0.1 mg/kg
Grade 3 serosal effusions or edema or Grade 2 capillary leak syndrome	Reduce dose to 0.1 mg/kg	Discontinue Rova-T
Grade 4 serosal effusions or edema or Grade ≥ 3 capillary leak syndrome	Discontinue Rova-T	N/A
Grade 2 serosal effusions or edema	Reduce dose to 0.2 mg/kg	Reduce dose to 0.1 mg/kg
Grade 3 photosensitivity reaction	Reduce dose to 0.2 mg/kg See Section 6.1.8.2	Reduce dose to 0.1 mg/kg See Section 6.1.8.2
Grade 4 photosensitivity reaction	Discontinue Rova-T	N/A
Potential DILI (Drug-induced liver injury)	See Section 6.1.8.3	See Section 6.1.8.3
Grade 2 pneumonitis	Reduce dose to 0.1 mg/kg	Discontinue Rova-T
Grade ≥ 3 pneumonitis	Discontinue Rova-T	N/A
Any other Grade 3 or Grade 4 non-laboratory treatment-related toxicity with the exception of fatigue, asthenia, nausea, or other manageable constitutional symptom	Reduce dose to 0.2 mg/kg	Reduce dose to 0.1 mg/kg

a. Refer to Appendix I, for Serosal effusions and edema AE group definition and CTCAE v 4.0 Grading of Relevant AEs for definitions of NCI-CTCAE severity grades.

b. If potential DILI is suspected please follow guidelines of Section 6.1.8.3.

5.5.6.1.3 Dose Reductions, Delays and Discontinuation Due to Toxicity or Progression (Arm B, Topotecan)

Dose reductions, delays and discontinuation for topotecan should occur as outlined in the local label.

In cases of treatment delays of > 28 days due to toxicity, the subject will be discontinued from treatment. In cases where treatment benefit is observed, longer dose delays due to toxicity, if required, can be discussed with the TAMD.

5.5.7 Blinding

This is an open-label study.

5.5.8 Data for Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be formed and constituted according to appropriate regulatory guidelines. Detailed information regarding the composition of the committee and detailed procedures will be documented in a separate charter. The IDMC will review the efficacy and safety data periodically and provide recommendations according to the charter. The IDMC may recommend stopping the trial for efficacy or futility, or recommend adjusting the size of the study.

5.5.9 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

5.5.10 Drug Accountability

The site will record the dose of rovalpituzumab tesirine and topotecan given to each subject in the source documents and on the eCRF. If the investigator will obtain topotecan commercially, site inventory and accountability will not be performed in IRT

and drug accountability forms will not be provided by AbbVie. It will be the responsibility of the investigator/site to maintain local accountability of topotecan sourced commercially. If the investigative site has received topotecan centrally sourced by AbbVie, site inventory and accountability of these drugs will be performed in the IRT system and drug accountability forms will be provided.

Upon receipt of a shipment of rovalpituzumab tesirine and, if applicable, topotecan, the representative at each site will; 1) open and inspect the shipment; 2) verify that the study drug has been received intact, in the correct amounts and at the correct address; 3) sign and date the Proof of Receipt (POR) or similar documentation accompanying the shipment; 4) register the shipment as received via the IRT; 5) if applicable, transfer the Temptale files (shipment temperature record) to AbbVie CDSM. Note: some regions may receive drug in shipment containers without the use of Temptales. In these instances, a special validated shipping container will be used. All study drugs must be retained in the designated secure area under proper storage conditions. This will be documented by signing and dating the POR or similar document or via direct recording in the IRT.

An overall accountability of the study drug supplied by AbbVie will be performed and verified by the site monitor throughout the study and at the study site closeout visit. An accurate running inventory of rovalpituzumab tesirine and if applicable topotecan and/or dexamethasone will be maintained utilizing the IRT drug accountability module and, if required, according to the policy of the investigative site and will include the lot number, POR number(s), the bottle/kit numbers, and the date study drug was dispensed for each subject.

Upon completion or termination of the study, all original vials containing rovalpituzumab tesirine and, if applicable, topotecan and/or dexamethasone (empty containers will be defaced and discarded on site) will be returned to AbbVie according to AbbVie's instructions, or if pre-arranged between the sponsor and site, destruction of used and unused study drug will be performed at the site. Rova-T is classified as a Dangerous Good/Hazardous Material according to US Department of Transportation (DOT) and

International Air Transport Association (IATA). Dangerous Goods/Hazardous Materials must be packaged and shipped according to applicable regulations.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This is an open-label study where subjects will be randomized in a 2:1 ratio to rovalpituzumab tesirine or topotecan in the second line treatment of advanced or metastatic SCLC. Rovalpituzumab tesirine has previously demonstrated promising preliminarily efficacy and tolerability in Phase 1 and 2 trials in second and later lines SCLC. Topotecan has been chosen as the comparator chemotherapy since it is currently the only approved treatment for second line SCLC.

5.6.2 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. Adverse events and, when applicable, clinical laboratory data will be graded using NCI CTCAE, version 4.0.[9]

Response will be assessed according to RECIST v1.1[10] 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 investigational product. Pharmacokinetic assessments for drug activity are also common in clinical studies.

5.6.3 Suitability of Subject Population

Subjects with advanced or metastatic DLL3^{high} SCLC experiencing first disease progression during or following front-line platinum-based chemotherapy and meeting inclusion and exclusion selection criteria as outlined in the Section 5.2.1 and Section 5.2.2 are appropriate for this study. Such subjects are appropriate to define efficacy and safety

of rovalpituzumab tesirine since it is an intended indication for this investigational agent. This population is also suitable for topotecan treatment since it is the second line standard of care in this tumor type.

5.6.4 Selection of Doses in the Study

In a recent Phase 1 study (Study SCRX16-001) with rovalpituzumab tesirine, the maximum tolerated dose (MTD) was established at 0.4 mg/kg every 3 weeks based on the incidence of Cycle 1 toxicities, while the recommended Phase 2 dose (RPTD) in SCLC was chosen as 0.3 mg/kg every 6 weeks for a total of two doses with the allowance to retreat at the same dose level and schedule upon progression. The RPTD is based on the toxicity and efficacy profile during multiple cycles of dosing (AbbVie Stemcentrx data on file).

The chosen dose regimen, two doses of 0.3 mg/kg rovalpituzumab tesirine administered 6 weeks apart, is based on the safety and efficacy observed in Study SCRX16-001, where delayed and/or cumulative toxicities were observed with both q3wk and q6wk schedules and appeared to be related to total dose administered. The dosing regimens of 0.2 mg/kg q3wk for a total of 3 doses (q3wk × 3) and 0.3 mg/kg q6wk for a total of 2 doses (q6wk × 2) were evaluated in expansion cohorts.

Both regimens were tolerated, but the 0.3 mg/kg q 6wk regimen demonstrated a trend towards lower rates of treatment-emergent adverse events (TEAE), related TEAEs, Grade 3/4 TEAEs and related Grade 3/4 TEAEs. In addition, although the 0.3 mg/kg regimen appeared to have a higher incidence of Grade 3/4 thrombocytopenia, this AE was generally clinically manageable. On the other hand, objective responses appear to be more durable in subjects treated with the 0.3 mg/kg q6wk regimen based on preliminary data. Therefore, 0.3 mg/kg q6wk × 2 is the chosen dose regimen for this study. The maximum dose of rovalpituzumab tesirine in this study will not exceed 0.3 mg/kg at each dose.

The starting dose of topotecan is 1.5 mg/m^2 administered intravenously daily for 5 consecutive days starting on Day 1 of a 21-day cycle. Topotecan may be administered at a lower dose if required by the local label. Subjects may continue receiving topotecan until disease progression, unacceptable toxicity, or other reason for study discontinuations.

6.0 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 or topotecan, depending on country specific requirements. Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For AEs, please refer to Sections 6.1.1 through 6.1.6. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event 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 drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide another cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (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 adverse event 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 adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. 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, [meets protocol specific criteria (see Section 6.1.8 regarding toxicity management)] and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event 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 adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (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 or admission to an outpatient facility.
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 serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.1.3 Adverse Events Expected Due to SCLC or Progression of SCLC

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

These adverse events may occur alone or in various combinations and are considered expected adverse events for regulatory reporting in SCLC subjects for this protocol.

The term "disease progression" should not be used when reporting AEs or SAEs, instead associated symptoms should be reported. However, in cases of fatal events clearly related to the progression of disease under study the terms "malignant neoplasm progression" or "disease progression" are acceptable when the immediate cause of death is not known.

6.1.2 Adverse Event Severity

The investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.0).[9] If a reported adverse event increases in severity, the initial adverse event should be given an outcome date and a new adverse event reported on a different date from the end date of the previous adverse event to reflect the change in severity. For all reported serious adverse events that increase in severity, the supplemental eCRFs also need to be updated to reflect the change in severity.

When CTCAE criteria cannot be used, the event should be graded as defined below:

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

6.1.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

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, an "Other" cause of event must be provided by the investigator for the serious adverse event.

6.1.4 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 (Section 6.1.6) that are more likely related to disease progression will therefore be considered as an expected SAE and will not be subject to expedited reporting. These events should be recorded on the AE eCRF as described in Section 6.1.1.3. After the AE reporting period, deaths

attributed to progression of disease under study should be not be recorded on the AE eCRF.

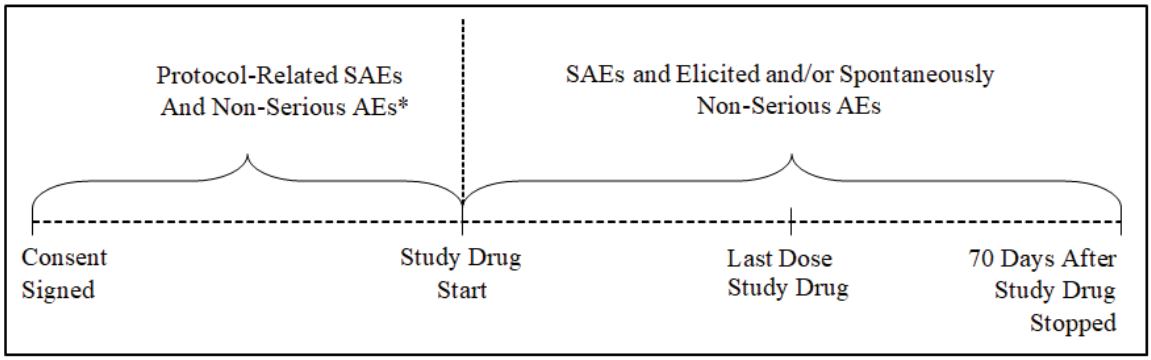
Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE eCRF. Generally, only one such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient 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 patient 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.

6.1.5 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 70 days, following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, protocol-related serious adverse events and protocol-related non-serious adverse events will be collected from the time the subject signed the study-specific informed consent, only if considered by the investigator to be casually related to study-required procedures.

Adverse event 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.

6.1.6 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events 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 serious adverse event.

Email: [redacted]

FAX to: [redacted]

For safety concerns, contact the Oncology Safety Management Team at:

Oncology Safety Team
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Email:

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director:

[redacted]
Therapeutic Area Medical Director
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Telephone Contact Information:
Office:
Mobile: [redacted]
Email:

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]

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with

global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

In Japan, the principal investigator will provide documentation of all serious adverse events to the Director of the investigative site and the Sponsor.

6.1.7 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 24 hours of the investigative site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1).

All subjects should be informed that contraceptive measures (refer to Section 5.2.4, Contraception Recommendations and Pregnancy Testing for the details on contraception) should be taken throughout the study and for at least 6 months after 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 adverse event. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.8 Toxicity Management

Subjects will be monitored continuously for toxicity while on study treatment. Toxicity will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0.[9] If a subject has an AE possibly related to investigational product administration, then dose interruptions/holds with possible modifications as described below may be implemented. Adjustments to these guidelines may occur based on the clinical judgment of the investigator with notification to the TA MD.

6.1.8.1 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., cardiac 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, or disease progression, should be ruled out. When appropriate, a unifying diagnosis should be reported, e.g., "heart failure," not the signs and symptoms "pleural effusion" and "edema limbs."

When considered clinically significant (e.g., Grade 2 or higher and considered related to investigational product):

- Systemic corticosteroids, when initiated promptly, have been reported to be beneficial in some prior cases. The investigator should consider a tapering regimen, such as dexamethasone up to 8 mg orally twice a day for 5 days, followed by 4 mg orally twice a day for 5 days, then 2 mg orally twice a day for 5 days. Alternatively, nonsteroidal therapies for serositis may be considered, such as non-steroidal anti-inflammatory drugs (NSAIDs, e.g., ibuprofen 400 – 600 mg orally three to four times daily) or colchicine (e.g., 0.6 mg orally two to three times daily) given for 1 – 2 weeks.
- Until clinical experience suggests otherwise, guidance for dose delay and/or reduction, as well as criteria for ongoing dosing, should follow Section 5.5.6.1

6.1.8.2 Management of Skin Reactions

All cutaneous reactions which develop during treatment warrant prompt evaluation. Skin toxicity with rovalpituzumab tesirine may consist of photosensitivity but possibly other reactions such as palmar-plantar erythrodysesthesia or erythema multiforme. As such, development of a cutaneous reaction during treatment warrants prompt evaluation by the investigator or designee.

Photosensitivity reactions may occur hours to days after sun exposure. Patients should be advised to avoid direct and indirect sun exposure as much as possible from Cycle 1 Day 1 until 30 days after the final dose. When sun exposure is unavoidable, patients should wear protective clothing and sunglasses, and use a broad-spectrum sunscreen and lip balm (SPF 30 or greater). 31 – 90 days after last dose, the patient may resume outdoor activities with appropriate sun protection including broad brimmed hat, protective clothing and sunscreen SPF 30 or higher

If clinically consistent with photosensitivity, the AE should be reported as such (using medically accurate and descriptive AE terminology), and managed as described in Table 7. Photodocumentation of skin toxicity should be available upon request by the TA MD. The investigative site will take measures to protect the identity of the patient. These measures include taking the photograph very close to the affected skin region to exclude facial features, or if facial features cannot be excluded due to the location of the skin reaction, covering identifying features (such as the eyes) with a black rectangle.

Formal evaluation by a dermatologist, including possible skin biopsy, to rule out alternative etiologies such as erythema multiforme (which may warrant discontinuation of investigational product) and to facilitate the most appropriate terminology for AE reporting, is recommended.

All events of cutaneous toxicity should be monitored until resolution or return to baseline. Recommendations for management of photosensitivity reactions are outlined in Table 7.

Table 7. Recommended Management of Photosensitivity

CTCAE v4.0		Treatment Recommendations	Rova-T Dose Modifications
Grade 1	Painless erythema and erythema covering < 10% BSA	Low-potency topical steroid (face) High-potency topical steroid (body)	–
Grade 2	Tender erythema covering 10 – 30% BSA	Low-potency topical steroid (face) High-potency topical steroid (body) 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) High-potency topical steroid (body) Prednisone 0.5 mg/kg × 7 days	Reduce dose
Grade 4	Life-threatening consequences; urgent intervention indicated	Low-potency topical steroid (face) High-potency topical steroid (body) Prednisone 0.5 mg/kg × 7 days Hospitalization	Discontinue

In order to simplify the collection of detailed Safety Data associated with dermatological issues, prior to the verification of a specific diagnosis the general term of "Skin Toxicity" should be recorded on the Adverse Event eCRF and the corresponding details should be captured on the Skin Toxicity Supplemental eCRF (as outlined in the form). Once a final dermatological diagnosis is verified, the AE eCRF should be updated to reflect the specific diagnosis.

6.1.8.3 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.

A potential DILI is defined as:

- ALT or AST elevation > 3 times (3×) upper limit of normal (ULN) ***and***
- Total bilirubin > 2 × 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 × ULN should be followed by repeat testing within 48 – 72 hours of all four of the usual measures (ALT, AST, alkaline phosphatase, and total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing. An 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 available to the investigator immediately. All data must be recorded in the CRF. If symptoms persist or repeat testing shows AT > 3 × 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, investigational product 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

The investigational product will be discontinued if potential DILI is suspected and:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and (TBL > 2 × ULN or INR > 1.5)
- ALT or AST > 3 × 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.

6.1.8.4 Monitoring and Management of Edema

The majority of the edema events with rovalpituzumab tesirine have been reported as low grade 1 or 2 (mild or moderate); however, a small number of fatal events of generalized edema have been reported with rovalpituzumab tesirine. Physical exams and monitoring of weight gain and signs or symptoms of fluid retention should be conducted during treatment.

Consistent with institutional guidelines or standard practice, the use of diuretics with or without albumin may be considered in subjects with clinically significant edema and hypoalbuminemia. The selection and use of diuretics in subjects should be based on individual clinical characteristics and include monitoring of electrolyte status and signs or symptoms of intravascular volume depletion such as hypotension and impaired renal function.

Systemic corticosteroids, when initiated promptly, have been reported to be beneficial in some prior cases.

Reported Term	Grade 1	Grade 2	Grade 3	Grade 4
Generalized edema (Anasarca)	Noted on exam; 1+ pitting edema	Interfering with instrumental ADLs; oral therapy initiated	Interferes with self care ADL; intravenous therapy indicated; skin breakdown	Life-threatening consequences
Definition: A disorder characterized by fluid accumulation in the tissues of the body including the skin.				
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.				
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				

6.1.8.5 Pneumonitis

Pneumonitis has been infrequently reported with rovalpituzumab tesirine but has resulted in fatal outcomes. Although the causal role of rovalpituzumab tesirine could not be ruled out, the reports of pneumonitis had one or more confounders including underlying pulmonary disease/cancer, prior thoracic radiation, prior cytotoxic chemotherapy or clinical evidence suggestive of an alternative diagnosis including pneumonia.

Heavily pretreated SCLC patients and patients with a history of pneumonitis may be at increased risk, and careful monitoring for signs and symptoms of pneumonitis is important. The risk of pneumonitis is increased with prior radiation to lung.

In general, signs and symptoms coinciding with or preceding pneumonitis may include new or worsening cough, chest pain and/or shortness of breath, fever, and radiographic changes (reticular markings, ground glass opacities). Protocol defined disease assessments providethe opportunity for on study pulmonary monitoring with "gold standard" diagnostic method for detection of pneumonitis. The protocol allows for additional imaging per physician discretion for signs and symptoms of pulmonary toxicity.

The diagnosis of drug induced pneumonitis is one of exclusion. Other etiologies including infection, which is a common cause of pulmonary infiltrates with clinical and radiographic appearance similar to drug-induced pneumonitis, need to be carefully considered and excluded before the diagnosis of drug induced pneumonitis can be established.

If pneumonitis is suspected, close monitoring including additional laboratory and imaging investigation per institutional guidelines may be necessary. Systemic corticosteroids may be beneficial for rapidly progressive or more severe pneumonitis. For events of Grade 1 pneumonitis close monitoring is recommended; while dose modifications for Grade 2 or discontinuation of Rova-T for Grades 3 and 4 are required, please see Section 5.5.6.1 of the protocol.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product.

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.

6.2.2 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 adverse events 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.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitor(s):

Primary Contact:	Alternate Contact:
[redacted] Study Management Associate III AbbVie [redacted] 1 North Waukegan Road North Chicago, IL 60064	[redacted] Therapeutic Area Medical Director AbbVie [redacted] 1 North Waukegan Road North Chicago, IL 60064
Office: Email: [redacted]	Office: Fax: Email: [redacted]

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

In Japan, the investigator will record all protocol deviations in the appropriate medical records at site.

8.0 Statistical Methods and Determination of Sample Size

Following the fourth safety review by the IDMC, on 04 December 2018 the IDMC recommended that enrollment in the study is discontinued due to overall survival concerns associated with the study drug. For patients currently on treatment in Arm A, the IDMC

recommends that sites and patients make individual decisions as to whether or not to continue treatment based on patient level response. The data collection plan has been minimized given the status change of this study. With all these changes, no statistical testing will be performed for the efficacy endpoints. The efficacy endpoints will be analyzed using the original statistical methodologies as appropriate. The efficacy endpoints for which there is not enough data to implement the statistical models will be summarized by treatment arms. The statistical section remains unchanged to reflect the original analysis plan.

8.1 Statistical and Analytical Plans

This section describes the planned statistical analyses to be performed using data captured according to this protocol. A complete statistical analysis plan (SAP) describing in more detail all planned analyses will be finalized prior to database lock.

The final analysis will be performed when at least 489 deaths have occurred, which is projected to be approximately 35 months after study initiation.

The following analysis populations are considered:

- **Randomized Set:** It includes all randomized subjects, with subjects grouped according the treatment arm to which they are randomized regardless the actual treatment received, following intent-to-treat principle. The randomized set will be the analysis set for the efficacy endpoints.
- **Per Protocol Set:** It includes all subjects in the randomized set without any major protocol violations which may affect the evaluation of the primary efficacy endpoint. Major protocol violations will be defined in the SAP prior to the database lock. Subjects will be classified according to treatment assigned at the time of randomization. This set will be used for supportive analysis of efficacy endpoints.
- **Safety Set:** It includes all subjects who received at least one dose of study drug and subjects will be classified according to treatment received.

- **Pharmacokinetic-Evaluable Set:** It consists of all subjects who receive at least one dose of study drug, with subjects classified according to the actual treatment received. A baseline measurement and at least one blood sample following a dose of study treatment is required for inclusion in this analysis.

8.1.1 Disposition of Study Subjects

The disposition of subjects will be summarized by treatment arm for the randomized set. The subject disposition includes the number of subjects for whom study drug was permanently discontinued (including the reasons for discontinuation), and the number of subjects who discontinued early from the study.

8.1.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized in the randomized set.

8.1.3 Efficacy Endpoints

Efficacy endpoints will be analyzed in the randomized set, including all randomized subjects, with subjects grouped according to the treatment assigned at randomization, following intent-to-treat principle, unless otherwise specified. Assessment of response and progression will be determined by the CRAC according to RECIST v1.1.

8.1.4 Primary Efficacy Endpoint and Analysis

Overall survival (OS) is the primary efficacy endpoint. OS is defined as the time from the date of randomization to the date of death from any cause (i.e., date of subject's death – date of randomization + 1). For subjects who are alive at the time of analysis, the data will be censored at the last date they were documented to be alive. Subjects with no post-baseline information will be censored at the date of randomization plus 1 day.

Comparison between the two treatment arms at the final analysis will be performed via a one-sided log-rank test, stratified by the randomization stratification factors, testing the null hypothesis (rovalpituzumab tesirine arm (Arm A) is not superior to topotecan arm

(Arm B) in OS). The hazard ratio (HR) of Arm A over Arm B will be estimated using a stratified Cox proportional hazards model. The OS curves for each arm will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% confidence interval for median OS will be computed. Landmark survival rate, defined as the survival rate estimated using the Kaplan-Meier approach at pre-defined timepoints from randomization (e.g., 6, 12 and 18 months), will be summarized, presenting two-sided 95% CIs.

8.1.5 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Progression-free survival (PFS) based on the CRAC per RECIST v1.1
- Patient reported outcomes (PROs) – physical functioning domain at C2D1 for Rovalpituzumab tesirine arm and C3D1 for topotecan arm
- Objective response rate (ORR: CR + PR) based on the CRAC per RECIST v1.1
- Clinical benefit rate (CBR: CR + PR + SD) based on the CRAC per RECIST v1.1
- Duration of objective response (DOR) based on the CRAC per RECIST v1.1

PFS is defined as the time from randomization to documented CRAC-assessed disease progression based on RECIST v1.1 or death from any cause (whichever occurs earlier). For the analysis of PFS, data for subjects without disease progression or death will be censored at the time of the last radiographic assessment (or, if no radiographic assessment was performed after the baseline visit, subject's data will be censored at the time of randomization plus 1 day). Data from subjects who are lost to follow-up will be included in the analysis as censored observations on the last date of radiographic assessment that the subject was documented to be progression free. The PFS rates at 6 and 12 months and corresponding 95% CIs will also be estimated using KM estimates on the PFS curve for each arm. Methods for PFS analysis are similar to those described for the OS endpoint.

A sensitivity analysis of PFS will be performed based on investigator-assessed disease progression or death from any cause. Accounting for subjects who initiated a new anti-cancer therapy prior to progressive disease or death, an additional sensitivity analysis of PFS will be performed, considering the date of last radiographic assessment by CRAC prior to or on the start date of new anti-cancer therapy/procedure, as a censoring date.

Analyses of ORR and CBR will be performed for the randomized subjects with at least one measureable disease at baseline. For subjects whose tumors meet the criteria of partial or complete response (PR or CR), tumor measurements must be confirmed by repeat assessments performed no less than 4 and no more than 6 weeks after the criteria for response are first met.

Objective response rate includes confirmed complete response (CR) and confirmed partial response (PR) assessed by the CRAC based on RECIST v1.1 from the date of randomization until disease progression or death, whichever comes first. A subject who did not meet CR or PR, including those who did not have post-baseline radiological assessments will be considered as non-responder.

Comparison of ORR will be carried out using a one-sided Cochran-Mantel-Haenszel (CMH) test, stratified by the randomization stratification factors. Odds ratio will be presented with two-sided 95% CI. The difference in ORR will be provided with two-sided 95% CI. Rates and corresponding 95% exact CI will be calculated by Clopper-Pearson method for each arm. Sensitivity analysis based on investigator-determined ORR will also be performed.

Clinical benefit includes complete response (CR), partial response (PR), and stable disease (SD) assessed by the CRAC based on RECIST v1.1 from the date of randomization until disease progression or death, whichever comes first. A subject who did not meet CR, PR, or SD, including those who did not have post-baseline radiological assessments, will be considered as non-responder. The same statistical methodology will be used as that for ORR endpoint.

A sensitivity analysis of ORR and CBR will be performed, accounting for subjects who initiated a new anti-cancer therapy. Modified endpoints of ORR and CBR, defined as rates of response from the date of randomization until initiation of new anti-cancer therapy/procedure, disease progression, or death, whichever comes first, will be analyzed using the same methodology as that for the endpoints of ORR and CBR.

Only subjects with an objective response will be included in the analysis of duration of response (DOR). DOR is defined as the time between the date of first response (CR or PR by CRAC, whichever is recorded first) to the date of the first documented tumor progression (assessed by CRAC per RECIST 1.1) or death due to any cause, whichever comes first. If a subject is still responding (i.e., has not progressed nor died after CR or PR), then the subject's data will be censored at date of the last radiographic assessment by CRAC. Methods for DOR analysis are similar to those described for the OS endpoint.

8.1.6 Patient Reported Outcomes (PROs)

The EORTC QLQ-C15-PAL/LC13 scoring manual will be used to transform the raw scores into the domain scores (global heath, functional scales, symptom scales/items). Physical functioning domain of the QLQ-C15-PAL PRO questionnaire is a secondary endpoint in the hypothesis testing hierarchy (see Section 8.3). The other scales will be analyzed on an exploratory basis. Change from baseline of the items and domains of the QLQ-C15-PAL/LC13 will be summarized by treatment arm. The EQ-5D-5L manual and the published weights will be used to convert the individual items to the utility scores. Change from baseline of the EQ-5D-5L utility score and VAS will be summarized by treatment arm.

Treatment group differences will be evaluated by analyzing the change from baseline using a one-way analysis of variance (ANOVA) model. Proportion of subjects with clinically meaningful worsening in physical functioning will be compared between the treatment arms.

8.1.7 Pharmacokinetic and Exposure-Response Analyses

Serum concentrations of rovalpituzumab tesirine ADC as well as the incidence and timing of ATA formation will be tabulated and summary statistics will be computed. Serum concentration and ATA data from this study may be combined with data from other studies and analyzed using population pharmacokinetic methodologies.

The relationship between pharmacokinetics (e.g., exposure) and clinical trial findings including, but not limited to demographics, efficacy, and/or safety measures may also be explored. Additional analyses will be performed if useful. Results of the population pharmacokinetic and exposure-response analyses will be provided in a separate report.

8.1.8 Planned Sensitivity and Subgroup Analyses

Analysis of OS will be performed in the per protocol set. The same methodology as for analyses specified in Section 8.1.4 will be applied.

For randomized subjects, analysis for OS will be performed in the following subgroups:

- Prior history of brain metastases (yes versus no)
  - PCI (yes vs no) in subjects with no prior history of brain metastases
- Sensitivity to first line platinum-based regimen (sensitive [OR/SD after first line therapy and progression/recurrence-free interval ≥ 90 days] versus refractory/resistant [PD as best response to or < 90 days progression/recurrence-free interval after first line therapy])
- LDH (> ULN vs. ≤ ULN) at Screening
- Overall VALG stage (Limited Disease vs Extensive Disease) at initial diagnosis
- Gender
- Race

Difference in OS between rovalpituzumab tesirine and topotecan arms will be assessed by an unstratified log-rank test for each subgroup. Hazard ratios will be calculated by a Cox's model.

8.2 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 treatment-emergent adverse events (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 used. NCI CTCAE version 4.0 will be used in the grading of adverse events and laboratory abnormalities that are reported as adverse events.

8.2.1 Treatment-Emergent Adverse Events (TEAEs)

TEAEs reported during the study will be coded using a MedDRA[12] dictionary. Incidence of TEAEs will be summarized by treatment arm and the following:

- System organ class and preferred term
- System organ class, preferred term, and severity

These summaries will be presented for the following subsets:

- Serious TEAEs
- All TEAEs
- Drug-related TEAEs

For tables reporting AEs by severity, if a subject has multiple occurrences of an AE with the same organ class and preferred term, the most severe event will be presented.

8.2.2 Clinical Laboratory Evaluation

Laboratory parameters will be summarized by treatment arm at each visit. Each summary will include the values of the laboratory parameters and changes from baseline. Shift

tables from baseline will be presented for laboratory values in the chemistry and hematology panels. Parameters will be classified according to the laboratory reference normal ranges. A listing will be provided for out-of-normal range as well as clinically significant abnormal lab values.

8.2.3 Vital Signs

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

8.2.4 ECOG Performance Status

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

8.2.5 Electrocardiogram

ECG status will be summarized for each scheduled visit by treatment arm. Shifts from baseline may be tabulated.

8.2.6 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 treatment arm. The table will be sorted by the incidence use of the entire sample.

8.3 Type I Error Adjustment Procedure for Multiple Testing

To meet global regulatory requirements, a multiple testing strategy will be implemented to control the family-wise type I error (alpha) for comparisons of rovalpituzumab tesirine arm versus topotecan arm with respect to the primary and secondary endpoints in the order specified below.

The following null hypotheses are considered:

H1: Rovalpituzumab tesirine arm is not superior to topotecan arm in OS.

H2: Rovalpituzumab tesirine arm is not superior to topotecan arm in PFS.

H3: Rovalpituzumab tesirine arm is not superior to topotecan arm in PRO physical functioning scale at C2D1 for rovalpituzumab tesirine arm and C3D1 for topotecan arm.

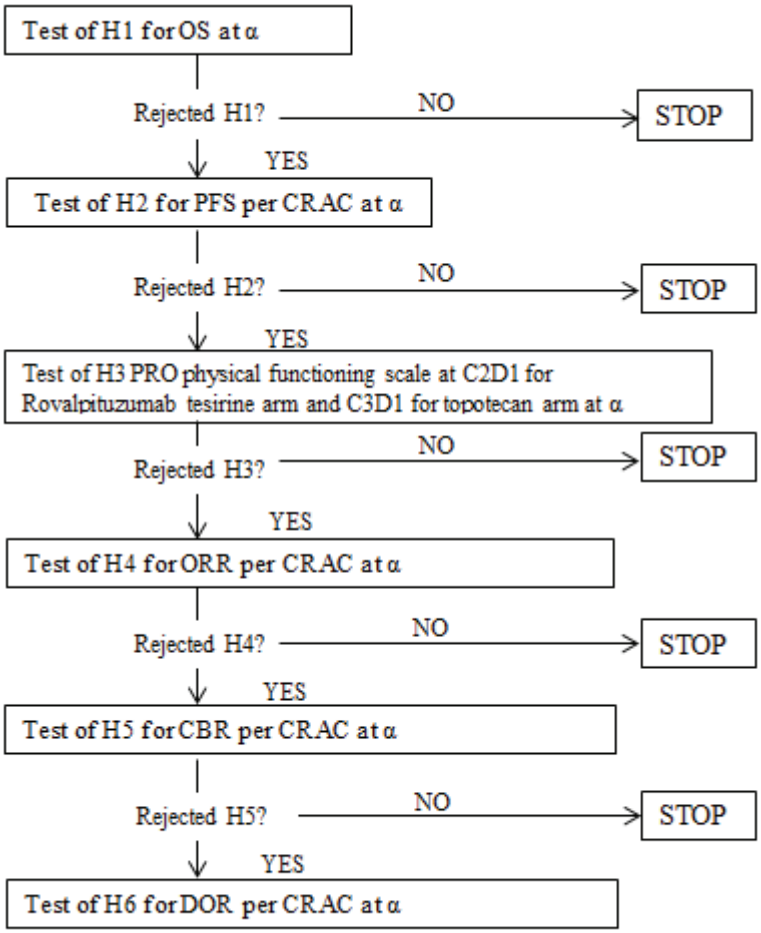
H4: Rovalpituzumab tesirine arm is not superior to topotecan arm in ORR.

H5: Rovalpituzumab tesirine arm is not superior to topotecan arm in CBR.

H6: Rovalpituzumab tesirine arm is not superior to topotecan arm in DOR.

The family of null hypotheses will be tested using a hierarchical procedure, ie, in a fixed sequence of {H1, H2, H3, H4, H5, H6}. Hypothesis H1 will be tested first, and no further tests will be performed if H1 is not rejected. Thereafter, each hypothesis will be tested in the order specified if and only if H1 and all preceding null hypotheses are rejected. Otherwise testing in the hierarchical sequence will stop. All the testing at final analysis will be carried out at one-sided 0.025 level of significance.

See flowchart below for illustration.



8.4 Determination of Sample Size

Following the fourth safety review by the IDMC, on 04 December 2018 the IDMC recommended that enrollment in the study is discontinued due to overall survival concerns associated with the study drug. 444 subjects were enrolled in the study. The following paragraph describes how the sample size was determined for the study.

The sample size of the study is primarily determined by the analysis of OS. Approximately 600 subjects in total will be randomized to rovalpituzumab tesirine

(Arm A) or topotecan (Arm B) in a 2:1 ratio. It is assumed that median overall survival in the topotecan arm (Arm B) will be around 6.5 months. Based on a log-rank test, at a one-sided significance level of 0.025 and a power of 85%, a total of 489 deaths are needed to detect an increase in median OS to 8.67 months in rovalpituzumab tesirine arm (Arm A), corresponding to a hazard ratio of 0.75 (i.e., a reduction in the hazard death of 25%). It is projected that an observed hazard ratio of 0.829 or less, corresponding to 1.34 months or greater improvement in median OS, would result in statistically significance in the final analysis of OS.

8.5 Interim Analysis

No interim efficacy analysis is planned.

8.6 Accrual/Study Duration Considerations

The total study duration and accrual duration are approximately projected to be 35 months and 24 months, respectively. A total of 600 subjects are expected to enroll during the accrual period.

8.7 Randomization Methods

The randomization numbers of the study will assign to subjects in a 2:1 ratio to either receive 0.3 mg/kg rovalpituzumab tesirine or topotecam. Randomization will be stratified as follows:

- prior history of brain metastases (yes versus no),
- prior PCI (yes vs. no) for subjects with no prior history of brain metastases
- sensitivity to first line platinum-based regimen [sensitive (OR/SD after first line therapy and progression/recurrence-free interval ≥ 90 days) versus refractory/resistant (PD as best response to or < 90 days progression/recurrence-free interval after first line therapy)],
- LDH level (> ULN vs. ≤ ULN) at screening.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent 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, informed consent 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 and all other applicable regulatory requirements.

Any serious adverse events 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 AbbVie.

9.2 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. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 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 informed consent form.

Informed consent will be obtained for treatment post radiologic disease progression, and consent form should be signed at the time of progressive disease if treatment is to be continued (Arm A).

The tumor biopsy at the time of disease progression is an optional research sample and will only be performed if the subject has voluntarily signed and dated an informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. If the subject does not consent to the optional tumor biopsy at the time of disease progression, it will not impact the subject's participation in the study. In the event a subject withdraws consent to participate from the study, stored biomarker and tumor material for exploratory research 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 and tumor material for exploratory research 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.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the principal investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the principal investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents. The Investigator Awareness Date (SAE CRF) may serve

as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

Patient reported data must be completed for each subject screened/enrolled in this study. Some of these data are being collected with an Electronic Patient Reported Outcome (ePRO) system called Trialmax, provided by the technology vendor CRF Health of Plymouth Meeting, PA, USA. The ePRO system is in compliance with Title 21 CFR Part 11. The documentation related to the system validation of the ePRO system is available through the vendor, CRF Health, while the user acceptance testing of the study specific PRO design will be conducted and maintained at AbbVie.

The subject will be entering the data on an electronic device; these data will be uploaded to a server. The data on the server will be considered source, and maintained and managed by CRF Health.

Internet access to the ePRO data will be provided by CRF Health for the duration of the study. This access will be available for the duration of the study to the site investigator, as well as delegated personnel. Such access will be removed from investigator sites following the receipt of the study archive. Data from the ePRO system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's ePRO data. It will be possible for the investigator to make paper print-outs from that media. The (instrument/scale) will be collected electronically via a Tablet/Laptop device into which the subject will directly enter the required pieces of information. The electronic device will be programmed to allow data entry for only the visits specified in the protocol and will not allow for subjects to complete more than one of the same assessment at any one visit. All data entered on the device will be immediately stored to the device itself and (manually/automatically) uploaded to a central server administrated by (ePRO Vendor). The Investigator and delegated staff will be able

to access all uploaded subject entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

Any research that may be done using optional exploratory research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from optional exploratory research may be provided to investigators and used in scientific publications or presented at medical conventions. Optional exploratory research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator (Director of the Site in Japan) and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator (Director of the Site in Japan) and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator (Director of the Site in Japan) must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory

requirements. If the investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit, or the date of the last subject's last survival follow-up contact, whichever is later.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for rovalpituzumab tesirine and the product labeling for topotecan and dexamethasone, as appropriate.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	A Randomized, Open-Label, Multicenter, Phase 3 Study of Rovalpituzumab Tesirine Compared with Topotecan for Subjects with Advanced or Metastatic DLL3^{high} Small Cell Lung Cancer (SCLC) who have First Disease Progression During or Following Front-Line Platinum-Based Chemotherapy (TAHOE)
Protocol Date:	08 January 2019

Signature of Principal Investigator — Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Pharmacokinetics
		Clinical Drug Supply Management
		Statistics
		Bioanalysis

Appendix C. Study Activities for Arm A (Rovalpituzumab Tesirine)

Category	Description	Screening	Treatment (Cycle 1 and Cycle 2)[a]									End of Treatment (EOT)[b]	PTFU[c]		Survival FU (OS)[d]
		Day –28 to Day –1	Day –1	Day 1[e] (–3 d)	Day 2	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 22 (±3 d)	Day 29 (± 3 d)	Day 36 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue Treatment	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
Location	Clinic Visit[cc]	X		X				X				X	X		
	Phone Contact[cc]					X	X		X	X					X
Safety Assessments	Informed Consent[f]	X													
	Inclusion/Exclusion Criteria	X													
	Medical and Surgical History Including Malignancy History[g]	X													
	Physical examination[h]	X		X				X				X			
	Vital Signs[i]	X		X				X				X			
	Hematology and Serum Chemistry[j]	X		X[k]				X				X			
	Coagulation Tests[j]	X		X[k]								X			
	Urinalysis[j]	X		X[k]				X				X			
	Pregnancy Test	X		X								X	X[l]		
	Electrocardiogram (ECG)[m]	X										X			
	Echocardiogram[n]	X		X								X			

Category	Description	Screening	Treatment (Cycle 1 and Cycle 2)[a]									End of Treatment (EOT)[b]	PTFU[c]		Survival FU (OS)[d]
		Day –28 to Day –1	Day –1	Day 1[e] (–3 d)	Day 2	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 22 (±3 d)	Day 29 (± 3 d)	Day 36 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue Treatment	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
	Performance Status (ECOG)	X		X								X			
	Fluid Retention Questionnaire[o]			X		X	X	X	X	X		X			
	SAE/Adverse Events	SAE/Procedure-related only	X	X		X	X	X	X	X		X[p]	X[p]		X[p]
	Concomitant Medications			X		X	X	X	X	X		X	X[p]		X[p]
Treatment	Rovalpituzumab Tesirine			X											
	Dexamethasone		X	X	X										
Response Assessment	Disease/Response Assessment (Radiographic Imaging)[q]	X									X[s]	X[r]	X[s]	X[s]	
	MRI/CT of the Brain[t]	X													
	Patient Reported Outcome (PRO)[u]	X		X [u]											
	Survival Status														X

Category	Description	Screening	Treatment (Cycle 1 and Cycle 2)[a]									End of Treatment (EOT)[b]	PTFU[c]		Survival FU (OS)[d]
		Day –28 to Day –1	Day –1	Day 1[e] (–3 d)	Day 2	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 22 (±3 d)	Day 29 (± 3 d)	Day 36 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue Treatment	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
PK and PD/ Biomarker	Pharmacokinetics, Anti-therapeutic Antibody (ATA) and Neutralizing Antibodies (nAb)[v]			X								X			
	Archived or Fresh Tumor Material[w]	X													
	Tumor Material at Time of Disease Progression[x]											X	X		
	Blood for Inflammatory Markers and ctDNA (10 mL)[y]			X [y]											
	Blood for Tumor & Soluble Markers (5 mL)[y]			X [y]											
	Circulating Tumor Cells (10 mL)[z]	X		X [z]											
	Pharmacogenetics (DNA/RNA)[aa]			X[aa]											
	Serosal Fluid[bb]				Day 1 through 70 days after last study treatment										

a. Up to two additional cycles of rovalpituzumab tesirine may be permitted for subjects in Arm A meeting criteria as described in Section 5.3.1.1. Subjects receiving additional doses of rovalpituzumab tesirine will follow the same study schedule as in Cycles 1 and 2.

b. EOT Visit occurs within 7 days of documentation of the decision to discontinue treatment and prior to subjects beginning any new anti-cancer therapy if possible. Subjects in Arm A should be evaluated for eligibility of two additional doses of rovalpituzumab tesirine prior to proceeding with EOT procedures.

c. For subjects who discontinue investigational product for reasons other than disease progression, the first PTFU visit will occur at 6 weeks (± 1 week) after the last Disease/Response Assessment, then every 6 weeks (± 1 week) until disease progression or initiation of new anti-cancer therapy, whichever occurs first.

d. Subjects will be followed for subsequent anti-cancer therapies (dates and responses), as well as survival status, every 6 weeks* (± 1 week) until the endpoint of death, the subject becomes lost to follow-up or withdraws consent, or termination of the study by AbbVie, whichever occurs first (*or as requested by AbbVie to support data analysis).

e. Procedures performed at Screening (with the exception of vital signs) do not need to be repeated if performed within 28 days of randomization unless clinically indicated. Randomization may occur within 3 calendar days prior to C1D1. Starting at C2D1, study assessments for Day 1 visits may be performed within 3 business days prior to the visit. Disease/Response Assessment may be performed within 7 days prior to the Day 1 visit unless otherwise indicated.

f. Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken or before any prohibited medications are withheld from the subject in order to participate in this study. Informed consent may be obtained before the 28-day screening window for DLL3 testing.

g. Medical and Surgical History includes demographics and documentation of clinically significant medical condition, surgical history, and malignancy history.

h. Height will be collected at the Screening visit only. For height assessments, the subject should not wear shoes. The physical examination performed at screening does not need to be repeated on CID1 if performed within 7 days of C1D1.

i. Vital signs include weight, sitting blood pressure, heart rate and body temperature. Weight will be collected in the clinic prior to dosing at each cycle and the recorded actual weight will be utilized for dosing calculations. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections. Vital signs should be collected prior to the infusion (including C1D1).

j. All laboratory samples will be assessed using a certified central laboratory. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions as per standard of care. Refer to Table 2, Clinical Laboratory Tests for details.

k. The clinical laboratory tests performed at Screening do not need to be repeated on C1D1 if performed within 7 days of C1D1 and meet eligibility criteria, unless clinically indicated. Starting at Cycle 2, lab assessment may be performed 3 business days prior to Day 1 visits.

l. For female subjects of childbearing potential, 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. Urine pregnancy tests will be performed at Day 1 of each cycle, at the EOT Visit, and during the PTFU period until 6 months after the last dose of study drug. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing. Post-menopausal female subjects ≤ 55 years of age must have a FSH level > 40 IU/L and will have FSH performed at Screening and assessed by the investigator.

m. A resting 12-lead ECG will consist of a single 12-lead study performed within a 5-minute window after at least 5 minutes of quiet rest in a supine position. Additional ECG monitoring may occur as clinically indicated during the study.

n. Echocardiograms are required at Screening, Day 1 of each cycle starting C2D1, and EOT. Screening echocardiogram will be performed within 3 business days of randomization to assess for the presence of any pericardial effusion as well as cardiac function (left ventricular ejection fraction, LVEF). Subsequent echocardiograms should be performed within –3 business days of dosing visit to assess for the presence of any pericardial effusion. Additional echocardiogram monitoring may occur as clinically indicated during the study.

o. Subjects will be asked about the development of any new or worsening peripheral edema or dyspnea (Appendix J, Fluid Retention Questionnaire). The assessments on Days 8, 15, 29, and 36 may take place by phone, with the site contacting the subject and reviewing the questionnaire. Starting Day 1 (during the treatment period for Arm A) and through the EOT visit, subjects will maintain a diary of daily weights (captured on the Fluid Retention Questionnaire).

p. Collection of SAE/AE and Concomitant Medications may be required at this visit in order to meet the collection window requirement of Day 1 of study treatment through 70 days after last treatment. Any ongoing SAE/AE that require appropriate standard of care should also be conducted.

q. Diagnostic quality, spiral CT scans are recommended; other CT methods or MRI may be used if performed consistently throughout the study for each individual subject. Scans of the chest and abdomen must be obtained; scans of the neck and pelvis must also be obtained if there is documented or suspected involvement in these regions. Screening scans may be performed within 28 days prior to randomization. Disease response will be determined by the Investigator at each assessment according to RECIST v1.1. Effusion (pleural, pericardial, and etc.) assessments will be performed by a radiologist at each radiographical assessment and any new findings communicated to the Investigator prior to the next dose of investigational product. Effusions should contribute to disease status only if confirmed malignant by cytology. Scheduled tumor assessments will not be affected by delays in therapy and/or drug holidays. Subjects will continue to be monitored by the same diagnostic method throughout the study.

r. May be omitted if assessment was performed within the preceding 6 weeks.

s. Radiographic assessments will occur every 6 weeks (± 1 week) for the first 30 weeks then every 9 weeks (± 1 week) until progression or death. If the subject qualifies to receive 2 additional cycles of Rova-T, radiographic assessments will continue to occur every 6 weeks for the first 30 weeks and then every 9 weeks until second progression or death.

t. MRI/CT of the brain is required at screening. Subsequent MRI/CT of the brain post screening is required only when clinically indicated (e.g., CNS metastasis history and if CNS progression is suspected).

u. PRO assessments are required at Screening and before infusion on C1D1.

v. At each cycle, approximately 6 mL of blood will be collected by venipuncture for pharmacokinetic (PK), Anti-therapeutic antibody (ATA), and neutralizing antibodies (nAb) testing. The pre-infusion sample will be collected prior to dosing on Day 1 (–3 business days window is permitted) and the second sample will be collected 30 minutes (± 10 minutes) post-infusion. Only one collection will be required at the EOT visit. The date and time of each sample collected will be recorded to the nearest minute.

w. Tumor material must be collected to confirm DLL3 expression. Subjects that provide consent for DLL3 testing at any time after initial diagnosis must be registered in IRT.

x. An optional tumor biopsy may be obtained at the time of disease progression, from subjects who consent to undergo biopsy procedure. Informed consent is required for the optional tumor biopsy at time of disease progression. The sample can be collected at the EOT or at the time of disease progression

y. On Cycle 1 Day 1 (–3 business days window is permitted), the collection of blood for inflammatory markers, ctDNA, tumor and soluble markers will be pre-infusion.

z. Whole blood sample will be collected for CTC analysis during screening and pre-dose on Cycle 1 Day 1. –3 business days window is permitted. CTCs implemented only at specific sites based on feasibility.

aa. Pharmacogenetic collection should occur unless precluded by local or national regulations or policies. Pharmacogentic sample to be collected on Day 1 of Cycle 1 only and is collected pre-infusion (–3 business days window is permitted).

bb. Any pericardial, pleural, and/or ascitic fluid collected as part of routine care (e.g., as part of a therapeutic thoracentesis, pericardiocentesis, or paracentesis) must be procured for testing, for any AE starting from C1D1 through 70 days after the last study treatment. Collected fluid must also be tested centrally and/or locally for cytology if disease progression due to appearance/worsening of effusion is suspected.

cc. Procedures for visits where no treatment is administered and phone contacts from Day 8 to Day 36 of each cycle may be performed within ± 3 day window relative to the due date. Procedures will include symptom review for presence of neurotoxicity, neutropenic colitis, fever, interstitial lung disease, serosal effusions (including pleural and pericardial), peripheral edema, cutaneous reactions (e.g., photosensitivity).

Appendix D. Study Activities for Arm B (Topotecan)

Category	Description	Screening	Treatment (Each Cycle)								End of Treatment (EOT)[a]	PTFU[b]		Survival FU (OS)[c]
		Day –28 to Day –1	Day 1[d] (–3 d)	Day 2	Day 3	Day 4	Day 5	Day 8 (± 3 d)	Day 15 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue tx	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
Location	Clinic Visit	X	X	X	X	X	X				X	X		
	Phone Contact[x]							X	X					X
Screening, Baseline, and Safety Assessments	Informed Consent[e]	X												
	Inclusion/Exclusion Criteria	X												
	Medical and Surgical History Including Malignancy History[f]	X												
	Physical examination[g]	X	X								X			
	Vital Signs[h]	X	X								X			
	Hematology and Serum Chemistry[i]	X	X[j]								X			
	Coagulation Tests[i]	X	X[j]											
	Urinalysis[i]	X	X[j]											
	Pregnancy Test[k]	X	X								X	X		
	Electrocardiogram (ECG)[-l]	X												
	Echocardiogram	X												

Category	Description	Screening	Treatment (Each Cycle)								End of Treatment (EOT)[a]	PTFU[b]		Survival FU (OS)[c]
		Day –28 to Day –1	Day 1[d] (–3 d)	Day 2	Day 3	Day 4	Day 5	Day 8 (± 3 d)	Day 15 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue tx	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
	Performance Status (ECOG)	X	X								X			
	Fluid Retention Questionnaire[n]		X[n]											
	SAE/Adverse Events	SAE/Procedure-related only	X	X	X	X	X	X	X		X[o]	X[o]		X[o]
	Concomitant Medications		X	X	X	X	X	X	X		X[o]	X[o]		X[o]
Treatment	Topotecan		X	X	X	X	X							
Response Assessment	Disease/Response Assessment (Radiographic Imaging)[p]	X								X[r]	X[q]	X[r]	X[r]	
	MRI/CT of the Brain	X[s]												
	Patient Reported Outcome (PRO)[t]	X	X[t]											
	Survival Status													X

Category	Description	Screening	Treatment (Each Cycle)								End of Treatment (EOT)[a]	PTFU[b]		Survival FU (OS)[c]
		Day –28 to Day –1	Day 1[d] (–3 d)	Day 2	Day 3	Day 4	Day 5	Day 8 (± 3 d)	Day 15 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue tx	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
PD/ Biomarker	Archived or Fresh Tumor Material[u]	X												
	Circulating Tumor Cells (10 mL)[v]	X	X [v]											
	Pharmacogenetics (DNA/RNA)[w]		X[w]											

a. EOT Visit occurs within 7 days of documentation of the decision to discontinue treatment and prior to subjects beginning any new anti-cancer therapy if possible.

b. For subjects who discontinue investigational product for reasons other than disease progression, the first PTFU visit will occur at 6 weeks (± 1 week) after the last Disease/Response Assessment, then every 6 weeks (± 1 week) until disease progression or initiation of new anti-cancer therapy, whichever occurs first.

c. Subjects will be followed for subsequent anti-cancer therapies (dates and responses), as well as survival status, every 6 weeks* (± 1 week) until the endpoint of death, the subject becomes lost to follow-up or withdraws consent, or termination of the study by AbbVie, whichever occurs first (*or as requested by AbbVie to support data analysis).

d. Procedures performed at Screening (with the exception of vital signs) do not need to be repeated if performed within 28 days of randomization unless clinically indicated. Randomization may occur within 3 calendar days prior to C1D1. Starting at C2D1, study assessments for Day 1 visits may be performed within 3 days prior to the visit. Disease/Response Assessment may be performed within 7 days prior to the Day 1 visit unless otherwise indicated.

e. Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken or before any prohibited medications are withheld from the subject in order to participate in this study. Informed consent may be obtained before the 28-day screening window. Informed consent is also required for the optional tumor biopsy at time of disease progression.

f. Medical and Surgical History includes demographics and documentation of clinically significant medical condition, surgical history, and malignancy history.

g. Height will be collected at the Screening visit only. For height assessments, the subject should not wear shoes. The physical examination performed at screening does not need to be repeated on CID1 if performed within 7 days of C1D1.

h. Vital sign determinations include weight, sitting blood pressure, heart rate and body temperature. Weight will be collect prior to dosing at each cycle and recorded actual weight will be utilized for dosing calculations. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections. Vital signs should be collected prior to the infusion (including C1D1).

i. All laboratory samples will be assessed using a certified central laboratory. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions as per standard of care. Refer to Table 2, Clinical Laboratory Tests for details.

j. The clinical laboratory tests performed at screening do not need to be repeated on C1D1 if performed within 7 days of C1D1 and meet eligibility criteria, unless clinically indicated. Starting at Cycle 2, lab assessment may be performed 3 business days prior to Day 1 visits.

k. For female subjects of childbearing potential, 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. Urine pregnancy tests will be performed at Day 1, at the EOT visit, and during the PTFU period until 1 month after the last dose of study drug. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing. Post-menopausal female subjects ≤ 55 years of age must have a FSH level > 40 IU/L and will have FSH performed at Screening and assessed by the investigator.

l. A resting 12-lead ECG will consist of a single 12-lead study performed within a 5-minute window after at least 5 minutes of quiet rest in a supine position. Additional ECG monitoring may occur as clinically indicated during the study.

m. Screening echocardiogram will be performed within 3 business days of randomization and results should be available prior to randomization to assess for the presence of any pericardial effusion as swell as cardiac function (left ventricular ejection fraction, LVEF). Additional Echocardiogram monitoring may occur as clinically indicated during the study.

n. Subjects will be asked about the development of any new or worsening peripheral edema or dyspnea (Appendix J, Fluid Retention Questionnaire). Assessments will occur only in Cycle 1.

o. Collection of SAE/AE and Concomitant Medications may be required at this visit in order to meet the collection window requirement of Day 1 of study treatment through 70 days after last treatment. Any ongoing SAE/AE that require appropriate standard of care should also be conducted.

p. Diagnostic quality, spiral CT scans are recommended; other CT methods or MRI may be used if performed consistently throughout the study for each individual subject. Scans of the chest and abdomen must be obtained; scans of the neck and pelvis must also be obtained if there is documented or suspected involvement in these regions. Screening scans may be performed within 28 days prior to randomization. Disease response will be determined by the Investigator at each assessment according to RECIST v1.1. Effusion (pleural, pericardial, and etc.) assessments will be performed by a radiologist at each radiographical assessment and any new findings communicated to the Investigator prior to the next dose of investigational product. Effusions should contribute to disease status only if confirmed malignant by cytology. Scheduled tumor assessments will not be affected by delays in therapy and/or drug holidays. Subjects will continue to be monitored by the same diagnostic method throughout the study.

q. May be omitted if previous assessment was performed within the preceding 6 weeks.

r. Radiographic assessments will occur every 6 weeks (± 1 week) for the first 30 weeks then every 9 weeks (± 1 week) until progression or death.

s. MRI/CT of the brain is required at screening. Subsequent MRI/CT of the brain post screening is required only when clinically indicated (e.g., CNS metastasis history and if CNS progression is suspected).

t. PRO assessments are required at Screening and before infusion on C1D1.

u. Tumor material must be collected to confirm DLL3 expression. Subjects that provide consent for DLL3 testing at any time after initial diagnosis must be registered in IRT.

v. Whole blood sample will be collected for CTC analysis during screening and pre-dose on Cycle 1 Day 1. –3 business day window is permitted. CTCs implemented only at specific sites based on feasibility.

w. Pharmacogenetic collection should occur unless precluded by local or national regulations or policies. Pharmacogenetic sample to be collected on Day 1 of Cycle 1 only and is collected pre-infusion (–3 business days window is permitted).

x. Procedures for visits where no treatment is administered phone contacts for Day 8 and Day 15 of each cycle may be performed within ± 3 day window relative to the due date. Procedures will include symptom review for presence of neurotoxicity, neutropenic colitis, fever, interstitial lung disease, serosal effusions (including pleural and pericardial), peripheral edema, cutaneous reactions (e.g., photosensitivity).

Appendix E. 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.

Appendix F. New York Heart Association 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.

Appendix G. Calculated Creatinine Clearance Using Modified Cockcroft-Gault Equation

MODIFIED COCKCROFT AND GAULT FORMULA

For the calculation of estimated creatinine clearance rate (eCCR) using Ideal Body Mass [IBM] instead of Mass.

$$eCCr = \frac{(140 - Age) \bullet IBM\ (kg) \bullet [0.85\ if\ Female]}{72 \bullet Serum\ Creatinine\ (mg/dL)}$$

Or, if serum creatinine is in μmol/L:

$$eCCr = \frac{(140 - Age) \bullet IBM\ (kg) \bullet [1.23\ if\ Male,\ 1.04\ if\ Female]}{Serum\ Creatinine\ (\mu mol/L)}$$

Ideal Body Mass should be used:

$$IBM\ (kg) = [(height\ cm - 154) \bullet 0.9] + (50\ if\ Male,\ 45.5\ if\ Female)$$

Appendix H. Response Evaluation Criteria for Solid Tumors (RECIST) v 1.1 for Tumor Response

Response criteria will be assessed using RECIST (version 1.1).[10] Changes in the measurable lesions over the course of therapy must be evaluated using the criteria listed below.

Eligibility

Subjects with measurable disease at baseline can have objective tumor response evaluated by RECIST (version 1.1). Measurable disease is defined by the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology if possible.

Measurability

Measurable Lesions	Lesions accurately measured in at least one dimension with a minimum size of: • Longest diameter ≥ 10 mm (CT scan slice thickness no greater than 5 mm) • 10 mm caliper measurement by clinical exam
Non-Measurable Lesions	All other lesions, including small lesions (longest diameter < 10 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung and also abdominal masses that are not confirmed and followed by imaging techniques.
Measurable Malignant Lymph Nodes	To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Malignant Lymph Nodes	Pathological lymph nodes with ≥ 10 to < 15 mm short axis.

Special Considerations Regarding Lesion Measurability	Bone lesions Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as MRI/CT can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable. Cystic lesions Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions. Lesions with prior local treatment Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

All measurements should be taken and recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 28 days before randomization.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Methods of Measurement

Conventional CT should be performed with cuts of 5 mm or less in slice thickness contiguously. This applies to tumors of the chest and abdomen. A scale should be incorporated into all radiographic measurements. MRI can be performed if required by local law, but should have sponsor approval.

If prior to enrollment, it is known a subject is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI should be used to evaluate the subject at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease. For subjects who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI should be made based upon discussion with the AbbVie medical monitor.

For accurate objective response evaluation, ultrasound (US) should not be used to measure tumor lesions.

The utilization of endoscopy and laparoscopy for objective tumor evaluation is not advised. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases.

Baseline Documentation of "Target" and "Non-Target" Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Tumor lesions situated in a previously irradiated area, or in an area subjected to other

loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence (stable, increasing or decreasing) or absence of each should be noted throughout follow-up.

Evaluation of Target Lesions

Complete Response (CR):

The disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR):

At least 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 the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started (baseline or after) or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD):

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started (baseline or after).

Assessment of Target Lesions:

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (< 5 mm). However, sometimes target lesions or lymph nodes become too small to measure. If it is in the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present, but too small to measure, a default value of 5 mm should be assigned (as derived from the 5 mm CT slice thickness). The measurement of these lesions is potentially non-reproducible; therefore

providing this default value will prevent false responses or progression based upon measurement error.

Evaluation of Non-Target Lesions

Complete Response (CR):

The disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD:

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD):

Unequivocal progression of existing non-target lesions.

In this setting, to achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

New Lesions

The appearance of new malignant lesions denotes disease progression. While there are no specific criteria for the identification of new radiographic lesions, the findings of a new lesion should be unequivocal; i.e., not attributable to differences in scanning technique, timing of scanning, phase of contrast administration, change in imaging modality or finding thought to represent something other than tumor (e.g., some 'new' bone lesions may be simply healing or flare of pre-existing lesions). A lesion identified on a follow-up

study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the subject who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The subject's brain metastases are considered evidence of progressive disease even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal (e.g., too small to measure), continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is a new lesion, then progression should be declared using the date of the initial scan.

Appendix I. CTCAE v 4.0 Grading of Relevant AEs

Group	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Serosal 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.				
	Capillary leak syndrome	–	Symptomatic; medical intervention indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated
	Definition: A disorder characterized by leakage of intravascular fluids into the extravascular space. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. It can lead to generalized edema and multiple organ failure.				
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.				

Group	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Edema (cont.)	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.				
	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.				

Group	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
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 × 10^9/L	< 1500 – 1000/mm^3; < 1.5 – 1.0 × 10^9/L	< 1000 – 500/mm^3; < 1.0 – 0.5 × 10^9/L	< 500/mm^3; < 0.5 × 10^9/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 × 10^9/L	< 75,000 – 50,000/mm^3; < 75.0 – 50.0 × 10^9/L	< 50,000 – 25,000/mm^3; < 50.0 – 25.0 × 10^9/L	< 25,000/mm^3; < 25.0 × 10^9/L
	Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.				
Respiratory, thoracic and mediastinal disorders	Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)
	Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma				
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).				
	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.				

Group	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Skin (cont.)	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.				

Appendix J. Fluid Retention Questionnaire

Fluid Retention Questionnaire for Study M16-289

Subject ID: _____

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

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. Weight should be taken without outer garments such as hats, coats or shoes. Measurements while in light indoor clothing only, or undergarments only, are acceptable; however, please try to use the same or similar clothing (including any accessories or jewelry) from day to day when measuring weight.
   - 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 or ☐No

3. Have you noticed any new or worsening shortness of breath during the days above?

   ☐Yes or ☐No

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

_____ Date: _____

Appendix K. Adverse Events Expected Due to SCLC or Progression of SCLC

Preferred Term (MedDRA Version 19.1)
Malignant pleural effusion
Metastases to pleura
Oesophageal obstruction
Pneumonia bacterial
Vocal cord paralysis
Dysphonia
Dysphagia
Superior vena cava syndrome
Horner's syndrome
Myasthenic 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
Cancer pain
Inappropriate Anti-Diuretic Hormone (SIADH) secretion
Tumour pain
Pulmonary embolism*
Deep vein thrombosis*
Lower respiratory tract infection*
Respiratory tract infection*
Upper respiratory tract infection*
Opportunistic infection*
Viral infection*
Fungal infection*
Bacterial infection*
Lung abscess*

Empyema*
Lymphadenopathy
Decreased appetite
Malaise
Weight decreased
Pain

* Includes life threatening or fatal events.

Appendix L. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes

Section 1.0 Title Page
"Sponsor/Emergency Contact:"
Title previously read:

Medical Director

Has been changed to read:

Therapeutic Area Medical Director

Section 1.2 Synopsis
Subsection Methodology
Last paragraph previously read:

Survival Follow-up will continue until the endpoint of death, the subject becomes lost to follow-up or withdraws consent or termination of the study by AbbVie, whichever occurs first.

Has been changed to read:

Survival Follow-up will continue until the endpoint of death, the subject becomes lost to follow-up or withdraws consent, termination of the study by AbbVie, or until 12 February 2020 whichever occurs first.

Section 1.2 Synopsis
Subsection Duration of Treatment:
Previously read:

Regimen of Arm A will be administered for 2 cycles unless earlier discontinuation is warranted due to disease progression, unacceptable toxicity or any other reason; up to two additional cycles of rovalpituzumab tesirine may be permitted for subjects in Arm A who consent and satisfy all of the protocol defined criteria.

Regimen of Arm B will be administered until disease progression, unacceptable toxicity or any other reason requiring treatment discontinuation.

Has been changed to read:

Regimen of Arm A will be administered for 2 cycles unless earlier discontinuation is warranted due to disease progression, unacceptable toxicity or any other reason; up to two additional cycles of rovalpituzumab tesirine may be permitted however the last dose on study must be administered no later than 04 December 2019 for subjects in Arm A who consent and satisfy all of the protocol defined criteria.

Regimen of Arm B will be administered until disease progression, unacceptable toxicity, any other reason requiring treatment discontinuation, or no later than 04 December 2019, whichever comes first.

Follow up activities, including overall survival assessments, End of Treatment visits and AE/SAE reporting must occur no later than 12 February 2020.

Section 1.2 Synopsis
Subsection Criteria for Evaluation:
Heading "Efficacy:"
First paragraph previously read:

Overall Survival (OS): After the End of treatment, survival information will be collected at approximately 6-week intervals (or as requested by sponsor to support data analysis) continuing until the endpoint of death, the subject becomes lost to follow-up, or AbbVie terminates the study.

Has been changed to read:

Overall Survival (OS): After the End of treatment, survival information will be collected at approximately 6-week intervals (or as requested by sponsor to support data analysis) continuing until the endpoint of death, the subject becomes lost to follow-up, AbbVie terminates the study, or until 12 February 2020.

Section 1.2 Synopsis
Subsection Statistical Methods:
Heading "Efficacy:"
Add: new first paragraph

Following the fourth safety review by the IDMC, on 04 December 2018, the IDMC recommended that enrollment in the study is discontinued due to overall survival concerns associated with the study drug. For patients currently on treatment in Arm A, the IDMC recommends that sites and patients make individual decisions as to whether or not to continue treatment based on patient level response. The data collection plan has been minimized given the status change of this study. With all these changes, no statistical testing will be performed for the efficacy endpoints. The efficacy endpoints will be analyzed using the original statistical methodologies as appropriate. The efficacy endpoints for which there is not enough data to implement the statistical models will be summarized by treatment arms. The statistical section remains unchanged to reflect the original analysis plan.

Section 1.2 Synopsis
Subsection Statistical Methods:
Heading "Sample Size:"
Add: new first paragraph

Following the fourth safety review by the IDMC, on 04 December 2018 the IDMC recommended that enrollment in the study is discontinued due to overall survival concerns associated with the study drug. 444 subjects were enrolled in the study. The following paragraph describes how the sample size was determined for the study.

Section 1.3 List of Abbreviations and Definition of Terms
Delete:

CRAC	Central Radiographic Assessment Committee

Section 5.1 Overall Study Design and Plan: Description
First bullet, last sentence previously read:

Up to two additional cycles of rovalpituzumab tesirine may be permitted for subjects in Arm A meeting certain criteria, as described in Section 5.3.1.1.

Has been changed to read:

Up to two additional cycles of rovalpituzumab tesirine may be permitted, however the last dose on study must be administered no later than 04 December 2019 for subjects in Arm A meeting certain criteria, as described in Section 5.3.1.1 .

Section 5.1 Overall Study Design and Plan: Description
Last bullet, last sentence previously read:

The Arm B regimen will be administered until disease progression, unacceptable toxicity or any other reason requiring treatment discontinuation.

Has been changed to read:

The Arm B regimen will be administered until disease progression, unacceptable toxicity or any other reason requiring treatment discontinuation, or no later than 04 December 2019, whichever comes first.

Section 5.1 Overall Study Design and Plan: Description
Delete: seventh paragraph

Disease assessments, for the purposes of efficacy assessments, will be performed by a Central Radiographic Assessment Committee (CRAC) blinded to study treatment information and independent of investigators and personnel who are involved in conducting the study (Section 5.3.1.1).

Section 5.3.1.1 Study Procedures
Subsection Echocardiogram
Previously read:

Subjects will have echocardiograms performed per Appendix C and Appendix D, Study Activities Tables to assess any pericardial effusion during Screening, and prior to dosing at every cycle for subjects on Arm A, and prior to dosing at every other cycle for subjects on Arm B, if present, as well as cardiac function (left ventricular ejection fraction, LVEF). Additional echocardiograms may occur as clinically indicated during the study.

Has been changed to read:

Subjects will have echocardiograms performed per Appendix C and 0, Study Activities Tables to assess any pericardial effusion during Screening, and prior to dosing at every cycle for subjects on Arm A, if present, as well as cardiac function (left ventricular ejection fraction, LVEF). Additional echocardiograms may occur as clinically indicated during the study.

Section 5.3.1.1 Study Procedures
Subsection Disease/Response Assessment (Radiographic Imaging)
First paragraph, sixth sentence previously read:

Disease response will be determined by the investigator at each assessment according to RECIST v1.1 (Appendix H, Response Evaluation Criteria for Solid Tumors (RECIST) v 1.1)[10] and independently reviewed by CRAC (described below).

Has been changed to read:

Disease response will be determined by the investigator at each assessment according to RECIST v1.1 (Appendix H, Response Evaluation Criteria for Solid Tumors (RECIST) v 1.1).[10]

Section 5.3.1.1 Study Procedures
Subsection Disease/Response Assessment (Radiographic Imaging)
Last paragraph
Delete: last sentence

If so, all imaging should be submitted to the CRAC to be reviewed. PET or PET/CT or X-rays, if performed with the purpose of disease status evaluation should be submitted for CRAC review.

Section 5.3.1.1 Study Procedures
Subsection Central Radiographic Assessment Committee (CRAC)
Delete: Subsection title and text

Central Radiographic Assessment Committee (CRAC)

In addition to being reviewed by the investigator and/or site staff, radiographic assessment scans will be assessed by a Central Radiographic Assessment Committee (CRAC), as outlined in the Appendix C and Appendix D, Study Activities Tables. Sites will collect the appropriate scans and submit to the central facility at each subject's disease assessment. In addition to baseline scans, on-study scans will be sent to the CRAC for review throughout the treatment period. Scans will continue to occur as specified and be reviewed by the CRAC as long as the subject is receiving study treatment, including additional cycles post-progression in Arm A with rovalpituzumab tesirine.

Subject treatment management will be based on review by the local investigator and/or qualified medical staff. The investigator should treat according to clinical judgment and the CRAC will make the definitive decision on tumor response or progression in regards to the PFS endpoint.

The CRAC will be blinded to subject treatment arm assignments.

Section 5.3.1.1 Study Procedures
Subsection Health Resource Utilization
Delete: Subsection title and text

Health Resource Utilization

Health Resource Utilization will be documented at each clinic visit per Appendix C and Appendix D, Study Activities. Information regarding hospitalizations, emergency room visits, and physician office visits will be collected since the last study visit.

Section 5.3.1.1 Study Procedures
Subsection Fluid Retention Questionnaire (Including Subject Daily Weight)
First paragraph
Delete: last sentence

The Arm B assessments will take place on Cycles 1 – 4 and Days 8 and 15 may take place by phone.

Section 5.3.1.1 Study Procedures
Subsection Fluid Retention Questionnaire (Including Subject Daily Weight)
Last paragraph, first sentence previously read:

Starting on Day 1 through the EOT visit, subjects will maintain a diary of daily weight (captured on the Fluid Retention Questionnaire).

Has been changed to read:

Starting on Day 1 through the EOT visit, subjects in Arm A will maintain a diary of daily weight (captured on the Fluid Retention Questionnaire).

Section 5.3.1.1 Study Procedures
Subsection Additional Two Cycles of Rovalpituzumab Tesirine (Arm A only)
First paragraph previously read:

Two additional cycles of rovalpituzumab tesirine may be permitted for subjects in Arm A who provide consent and who satisfy all of the following criteria:

Has been changed to read:

Up to two additional cycles of rovalpituzumab tesirine may be permitted, however the last dose on study must be administered no later than 04 December 2019 for subjects in Arm A who provide consent and who satisfy all of the following criteria:

Section 5.3.1.1 Study Procedures
Subsection <u>End of Treatment (EOT) Visit</u>
Last paragraph previously read:

Disease/Response assessment, including MRI/CT if clinically indicated, submission of scans to the CRAC, PRO assessments, blood for inflammatory markers, blood for tumor and soluble markers, and CTC may be omitted if performed within the last 6 weeks.

Has been changed to read:

Disease/Response assessment, including MRI/CT if clinically indicated, may be omitted if performed within the last 6 weeks.

Section 5.3.1.1 Study Procedures
Subsection <u>Survival Follow Up (OS)</u>
Last paragraph, second sentence previously read:

During this period, the subject will be followed every 6 weeks (± 1 week) for subsequent anti-cancer therapies (dates and responses), and survival status until the endpoint of death, the subject becomes lost to follow-up, termination of the study by AbbVie, whichever occurs first.

Has been changed to read:

During this period, the subject will be followed every 6 weeks (± 1 week) for subsequent anti-cancer therapies (dates and responses), and survival status until the endpoint of death, the subject becomes lost to follow-up, termination of the study by AbbVie, or until 12 February 2020 whichever occurs first.

Section 5.3.1.2 Collection and Handling of Biomarker and/or Optional Exploratory Research Samples
Subsection Blood (Plasma) for Inflammatory Markers and Circulating Tumor DNA (ctDNA)
Previously read:

At the indicated times noted in Appendix C, Study Activities, blood will be collected, processed to plasma for testing of inflammatory markers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibodies (ANA), rheumatoid factor (RF) and ctDNA. Samples will be collected on Day 1 of each cycle (pre-infusion) and at the EOT or at the time of disease progression.

Has been changed to read:

At the indicated times noted in Appendix C, Study Activities, blood will be collected, processed to plasma for testing of inflammatory markers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibodies (ANA), rheumatoid factor (RF) and ctDNA. Samples will be collected on Cycle 1 Day 1 (pre-infusion).

Section 5.3.1.2 Collection and Handling of Biomarker and/or Optional Exploratory Research Samples
Subsection Blood (Serum) for Tumor and Soluble Markers
Last sentence previously read:

Samples will be collected on Day 1 of each cycle (pre-infusion) and at the EOT or at the time of disease progression.

Has been changed to read:

Samples will be collected on Cycle 1 Day 1 (pre-infusion).

Section 5.3.1.2 Collection and Handling of Biomarker and/or Optional Exploratory Research Samples
Subsection Blood for Circulating Tumor Cells
Last sentence previously read:

Whole blood sample will be collected for CTC analysis during screening, pre-dose on Cycle 1 Day 1, Cycle 3 Day 1 (–3 business days window is permitted) and at the End of Treatment only at specific sites based on feasibility.

Has been changed to read:

Whole blood sample will be collected for CTC analysis during screening, and pre-dose on Cycle 1 Day 1.

Section 5.3.1.2 Collection and Handling of Biomarker and/or Optional Exploratory Research Samples
Subsection Pharmacogenetic Samples
First sentence previously read:

Whole blood samples for DNA and RNA isolation will be collected on Cycle 1 Day 1 (pre-infusion) (–3 business days window is permitted) and EOT Visit from each subject.

Has been changed to read:

Whole blood samples for DNA and RNA isolation will be collected on Cycle 1 Day 1 (pre-infusion) (–3 business days window is permitted) from each subject.

Section 5.4 Removal of Subjects from Therapy or Assessment
Add: new last paragraph

All subjects will receive a final dose of study drug no later than 04 December 2019. Follow up activities, including Overall Survival assessments, End of Treatment visits and AE/SAE collection should occur no later than 12 February 2020.

Section 5.4.1 Discontinuation of Individual Subjects
Fifth paragraph previously read:

Subjects no longer undergoing clinical assessments will have survival information collected at every 6 weeks (± 1 week) until the endpoint of death, the subject becomes lost to follow-up or termination of the study by AbbVie, whichever occurs first.

Has been changed to read:

Subjects no longer undergoing clinical assessments will have survival information collected at every 6 weeks (± 1 week) until the endpoint of death, the subject becomes lost to follow-up or termination of the study by AbbVie, whichever occurs first or until 12 February 2020.

Section 5.5.2 Rovalpituzumab Tesirine (Arm A)
Fifth paragraph previously read:

All subjects assigned to Arm A will be administered 2 cycles of rovalpituzumab tesirine unless earlier discontinuation is warranted due to disease progression (see exception below), unacceptable toxicity or any other reason.

Has been changed to read:

All subjects assigned to Arm A will be administered 2 cycles of rovalpituzumab tesirine no later than 04 December 2019 unless earlier discontinuation is warranted due to disease progression (see exception below), unacceptable toxicity or any other reason.

Section 5.5.2 Rovalpituzumab Tesirine (Arm A)
Last paragraph previously read:

Two additional cycles of rovalpituzumab tesirine may be permitted for subjects in Arm A who provide consent and who satisfy all of the appropriate criteria as described in Section 5.3.1.1.

Has been changed to read:

Up to two additional cycles of rovalpituzumab tesirine may be permitted, however the last dose on study must be administered no later than 04 December 2019 for subjects in Arm A who provide consent and who satisfy all of the appropriate criteria as described in Section 5.3.1.1.

Section 5.5.3 Topotecan (Arm B)
Last paragraph previously read:

All subjects assigned to Arm B will continue to receive topotecan until disease progression, unless earlier discontinuation is warranted due to unacceptable toxicity or any other reason.

Has been changed to read:

All subjects assigned to Arm B will continue to receive topotecan until disease progression or 04 December 2019 (whichever is later), unless earlier discontinuation is warranted due to unacceptable toxicity or any other reason.

Section 8.0 Statistical Methods and Determination of Sample Size
Add: new text

Following the fourth safety review by the IDMC, on 04 December 2018 the IDMC recommended that enrollment in the study is discontinued due to overall survival concerns associated with the study drug. For patients currently on treatment in Arm A, the IDMC recommends that sites and patients make individual decisions as to whether or not to continue treatment based on patient level response. The data collection plan has been minimized given the status change of this study. With all these changes, no statistical testing will be performed for the efficacy endpoints. The efficacy endpoints will be analyzed using the original statistical methodologies as appropriate. The efficacy endpoints for which there is not enough data to implement the statistical models will be summarized by treatment arms. The statistical section remains unchanged to reflect the original analysis plan.

Section 8.3 Type I Error Adjustment Procedure for Multiple Testing
Item H2, H4, H5, and H6 previously read:

H2: Rovalpituzumab tesirine arm is not superior to topotecan arm in PFS per CRAC.

H4: Rovalpituzumab tesirine arm is not superior to topotecan arm in ORR per CRAC.

H5: Rovalpituzumab tesirine arm is not superior to topotecan arm in CBR per CRAC.

H6: Rovalpituzumab tesirine arm is not superior to topotecan arm in DOR per CRAC.

Has been changed to read:

H2: Rovalpituzumab tesirine arm is not superior to topotecan arm in PFS.

H4: Rovalpituzumab tesirine arm is not superior to topotecan arm in ORR.

H5: Rovalpituzumab tesirine arm is not superior to topotecan arm in CBR.

H6: Rovalpituzumab tesirine arm is not superior to topotecan arm in DOR.

Section 8.4 Determination of Sample Size
Add: new first paragraph

Following the fourth safety review by the IDMC, on 04 December 2018 the IDMC recommended that enrollment in the study is discontinued due to overall survival concerns associated with the study drug. 444 subjects were enrolled in the study. The following paragraph describes how the sample size was determined for the study.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Clinical
		Pharmacokinetics
		Clinical Drug Supply Management
		Statistics
		Bioanalysis

Has been changed to read:

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Pharmacokinetics
		Clinical Drug Supply Management
		Statistics
		Bioanalysis

Appendix C. Study Activities for Arm A (Rovalpituzumab Tesirine)
Previously read:

Category	Description	Screening	Treatment (Cycle 1 and Cycle 2)[a]									End of Treatment (EOT)[b]	PTFU[c]		Survival FU (OS)[d]
		Day –28 to Day –1	Day –1	Day 1[e] (–3 d)	Day 2	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 22 (±3 d)	Day 29 (± 3 d)	Day 36 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue Treatment	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
Location	Clinic Visit[dd]	X		X				X				X	X		
	Phone Contact[dd]					X	X		X	X					X
Safety Assessments	Informed Consent[f]	X													
	Inclusion/Exclusion Criteria	X													
	Medical and Surgical History Including Malignancy History[g]	X													
	Physical examination[h]	X		X				X				X			
	Vital Signs[i]	X		X				X				X			
	Hematology and Serum Chemistry[j]	X		X[k]				X				X			
	Coagulation Tests[j]	X		X[k]								X			
	Urinalysis[j]	X		X[k]				X				X			
	Pregnancy Test	X		X								X	X[l]		
	Electrocardiogram (ECG)[m]	X										X			

Category	Description	Screening	Treatment (Cycle 1 and Cycle 2)[a]									End of Treatment (EOT)[b]	PTFU[c]		Survival FU (OS)[d]
		Day –28 to Day –1	Day –1	Day 1[e] (–3 d)	Day 2	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 22 (±3 d)	Day 29 (± 3 d)	Day 36 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue Treatment	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
	Echocardiogram[n]	X		X								X			
	Performance Status (ECOG)	X		X								X			
	Fluid Retention Questionnaire[o]			X		X	X	X	X	X		X			
	SAE/Adverse Events	SAE/Procedure-related only	X	X		X	X	X	X	X		X[p]	X[p]		X[p]
	Concomitant Medications			X		X	X	X	X	X		X	X[p]		X[p]
Treatment	Rovalpituzumab Tesirine			X											
	Dexamethasone		X	X	X										
Response Assessment	Disease/Response Assessment (Radiographic Imaging)[q]	X									X[s]	X[r]	X[s]	X[s]	
	Central Radiographic Assessment Committee (CRAC) Review[t]	X									X	X[r]	X	X	
	MRI/CT of the Brain[u]	X													
	Heath Resource Utilization			X				X				X	X		
	Patient Reported Outcome (PRO)[v]	X		X				X				X	X		
	Survival Status														X

Category	Description	Screening	Treatment (Cycle 1 and Cycle 2)[a]									End of Treatment (EOT)[b]	PTFU[c]		Survival FU (OS)[d]
		Day –28 to Day –1	Day –1	Day 1[e] (–3 d)	Day 2	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 22 (±3 d)	Day 29 (± 3 d)	Day 36 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue Treatment	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
PK and PD/ Biomarker	Pharmacokinetics, Anti-therapeutic Antibody (ATA) and Neutralizing Antibodies (nAb)[w]			X								X			
	Archived or Fresh Tumor Material[x]	X													
	Tumor Material at Time of Disease Progression[y]											X	X		
	Blood for Inflammatory Markers and ctDNA (10 mL)[z]			X								X[z]	X[z]		
	Blood for Tumor & Soluble Markers (5 mL)[z]			X								X[z]	X[z]		
	Circulating Tumor Cells (10 mL)[aa]	X		X								X			
	Pharmacogenetics (DNA/RNA)[bb]			X[bb]								X			
	Serosal Fluid[cc]				Day 1 through 70 days after last study treatment										

a. Up to two additional cycles of rovalpituzumab tesirine may be permitted for subjects in Arm A meeting criteria as described in Section 5.3.1.1. Subjects receiving additional doses of rovalpituzumab tesirine will follow the same study schedule as in Cycles 1 and 2.

b. EOT Visit occurs within 7 days of documentation of the decision to discontinue treatment and prior to subjects beginning any new anti-cancer therapy if possible. Subjects in Arm A should be evaluated for eligibility of two additional doses of rovalpituzumab tesirine prior to proceeding with EOT procedures.

c. For subjects who discontinue investigational product for reasons other than disease progression, the first PTFU visit will occur at 6 weeks (± 1 week) after the last Disease/Response Assessment, then every 6 weeks (± 1 week) until disease progression or initiation of new anti-cancer therapy, whichever occurs first.

d. Subjects will be followed for subsequent anti-cancer therapies (dates and responses), as well as survival status, every 6 weeks* (± 1 week) until the endpoint of death, the subject becomes lost to follow-up or withdraws consent, or termination of the study by AbbVie, whichever occurs first (*or as requested by AbbVie to support data analysis).

e. Procedures performed at Screening (with the exception of vital signs) do not need to be repeated if performed within 28 days of randomization unless clinically indicated. Randomization may occur within 3 calendar days prior to C1D1. Starting at C2D1, study assessments for Day 1 visits may be performed within 3 business days prior to the visit. Disease/Response Assessment and CRAC Review may be performed within 7 days prior to the Day 1 visit unless otherwise indicated.

f. Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken or before any prohibited medications are withheld from the subject in order to participate in this study. Informed consent may be obtained before the 28-day screening window for DLL3 testing.

g. Medical and Surgical History includes demographics and documentation of clinically significant medical condition, surgical history, and malignancy history.

h. Height will be collected at the Screening visit only. For height assessments, the subject should not wear shoes. The physical examination performed at screening does not need to be repeated on CID1 if performed within 7 days of C1D1.

i. Vital signs include weight, sitting blood pressure, heart rate and body temperature. Weight will be collected in the clinic prior to dosing at each cycle and the recorded actual weight will be utilized for dosing calculations. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections. Vital signs should be collected prior to the infusion (including C1D1).

j. All laboratory samples will be assessed using a certified central laboratory. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions as per standard of care. Refer to Table 2, Clinical Laboratory Tests for details.

k. The clinical laboratory tests performed at Screening do not need to be repeated on C1D1 if performed within 7 days of C1D1 and meet eligibility criteria, unless clinically indicated. Starting at Cycle 2, lab assessment may be performed 3 business days prior to Day 1 visits.

l. For female subjects of childbearing potential, 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. Urine pregnancy tests will be performed at Day 1 of each cycle, at the EOT Visit, and during the PTFU period until 6 months after the last dose of study drug. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing. Post-menopausal female subjects ≤ 55 years of age must have a FSH level > 40 IU/L and will have FSH performed at Screening and assessed by the investigator.

m. A resting 12-lead ECG will consist of a single 12-lead study performed within a 5-minute window after at least 5 minutes of quiet rest in a supine position. Additional ECG monitoring may occur as clinically indicated during the study.

n. Echocardiograms are required at Screening, Day 1 of each cycle starting C2D1, and EOT. Screening echocardiogram will be performed within 3 business days of randomization to assess for the presence of any pericardial effusion as well as cardiac function (left ventricular ejection fraction, LVEF). Subsequent echocardiograms should be performed within –3 business days of dosing visit to assess for the presence of any pericardial effusion. Additional echocardiogram monitoring may occur as clinically indicated during the study.

o. Subjects will be asked about the development of any new or worsening peripheral edema or dyspnea (Appendix J, Fluid Retention Questionnaire). The assessments on Days 8, 15, 29, and 36 may take place by phone, with the site contacting the subject and reviewing the questionnaire. Starting Day 1 (during the treatment period for Arm A) and through the EOT visit, subjects will maintain a diary of daily weights (captured on the Fluid Retention Questionnaire).

p. Collection of SAE/AE and Concomitant Medications may be required at this visit in order to meet the collection window requirement of Day 1 of study treatment through 70 days after last treatment. Any ongoing SAE/AE that require appropriate standard of care should also be conducted.

q. Diagnostic quality, spiral CT scans are recommended; other CT methods or MRI may be used if performed consistently throughout the study for each individual subject. Scans of the chest and abdomen must be obtained; scans of the neck and pelvis must also be obtained if there is documented or suspected involvement in these regions. Screening scans may be performed within 28 days prior to randomization. Disease response will be determined by the Investigator at each assessment according to RECIST v1.1. Effusion (pleural, pericardial, and etc.) assessments will be performed by a radiologist at each radiographical assessment and any new findings communicated to the Investigator prior to the next dose of investigational product. Effusions should contribute to disease status only if confirmed malignant by cytology. Scheduled tumor assessments will not be affected by delays in therapy and/or drug holidays. Subjects will continue to be monitored by the same diagnostic method throughout the study.

r. May be omitted if assessment was performed within the preceding 6 weeks.

s. Radiographic assessments will occur every 6 weeks (± 1 week) for the first 30 weeks then every 9 weeks (± 1 week) until progression or death. If the subject qualifies to receive 2 additional cycles of Rova-T, radiographic assessments will continue to occur every 6 weeks for the first 30 weeks and then every 9 weeks until second progression or death.

t Site will collect the appropriate scans and submit to the central facility at each subject's disease assessment.

u. MRI/CT of the brain is required at screening. Subsequent MRI/CT of the brain post screening is required only when clinically indicated (e.g., CNS metastasis history and if CNS progression is suspected).

v. PRO assessments are required at Screening, before infusion on Day 1 of each cycle starting C2D1, Day 22 of each cycle, EOT, and PTFU (if applicable).

w. At each cycle, approximately 6 mL of blood will be collected by venipuncture for pharmacokinetic (PK), Anti-therapeutic antibody (ATA), and neutralizing antibodies (nAb) testing. The pre-infusion sample will be collected prior to dosing on Day 1 (–3 business days window is permitted) and the second sample will be collected 30 minutes (± 10 minutes) post-infusion. Only one collection will be required at the EOT visit. The date and time of each sample collected will be recorded to the nearest minute.

x. Tumor material must be collected to confirm DLL3 expression. Subjects that provide consent for DLL3 testing at any time after initial diagnosis must be registered in IRT.

y. An optional tumor biopsy may be obtained at the time of disease progression, from subjects who consent to undergo biopsy procedure. Informed consent is required for the optional tumor biopsy at time of disease progression. The sample can be collected at the EOT or at the time of disease progression

z. On Day 1 (–3 business days window is permitted) of each cycle, the collection of blood for inflammatory markers, ctDNA, tumor and soluble markers will be pre-infusion. A sample will also be collected once at the EOT or at the time of disease progression.

aa. Whole blood sample will be collected for CTC analysis during screening and pre-dose on Cycle 1 Day 1 and Cycle 3 Day 1 (if applicable). –3 business days window is permitted. Sample will also be collected at the EOT. CTCs implemented only at specific sites based on feasibility.

bb. Pharmacogenetic collection should occur unless precluded by local or national regulations or policies. Pharmacogentic sample to be collected on Day 1 of Cycle 1 only and is collected pre-infusion (–3 business days window is permitted).

cc. Any pericardial, pleural, and/or ascitic fluid collected as part of routine care (e.g., as part of a therapeutic thoracentesis, pericardiocentesis, or paracentesis) must be procured for testing, for any AE starting from C1D1 through 70 days after the last study treatment. Collected fluid must also be tested centrally and/or locally for cytology if disease progression due to appearance/worsening of effusion is suspected.

dd. Procedures for visits where no treatment is administered and phone contacts from Day 8 to Day 36 of each cycle may be performed within ± 3 day window relative to the due date. Procedures will include symptom review for presence of neurotoxicity, neutropenic colitis, fever, interstitial lung disease, serosal effusions (including pleural and pericardial), peripheral edema, cutaneous reactions (e.g., photosensitivity).

Has been changed to read:

Category	Description	Screening	Treatment (Cycle 1 and Cycle 2)[a]									End of Treatment (EOT)[b]	PTFU[c]		Survival FU (OS)[d]
		Day –28 to Day –1	Day –1	Day 1[e] (–3 d)	Day 2	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 22 (±3 d)	Day 29 (± 3 d)	Day 36 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue Treatment	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
Location	Clinic Visit[cc]	X		X				X				X	X		
	Phone Contact[cc]					X	X		X	X					X
Safety Assessments	Informed Consent[f]	X													
	Inclusion/Exclusion Criteria	X													
	Medical and Surgical History Including Malignancy History[g]	X													
	Physical examination[h]	X		X				X				X			
	Vital Signs[i]	X		X				X				X			
	Hematology and Serum Chemistry[j]	X		X[k]				X				X			
	Coagulation Tests[j]	X		X[k]								X			
	Urinalysis[j]	X		X[k]				X				X			
	Pregnancy Test	X		X								X	X[l]		
	Electrocardiogram (ECG)[m]	X										X			
	Echocardiogram[n]	X		X								X			

Category	Description	Screening	Treatment (Cycle 1 and Cycle 2)[a]									End of Treatment (EOT)[b]	PTFU[c]		Survival FU (OS)[d]
		Day –28 to Day –1	Day –1	Day 1[e] (–3 d)	Day 2	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 22 (±3 d)	Day 29 (± 3 d)	Day 36 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue Treatment	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
	Performance Status (ECOG)	X		X								X			
	Fluid Retention Questionnaire[o]			X		X	X	X	X	X		X			
	SAE/Adverse Events	SAE/Procedure-related only	X	X		X	X	X	X	X		X[p]	X[p]		X[p]
	Concomitant Medications			X		X	X	X	X	X		X	X[p]		X[p]
Treatment	Rovalpituzumab Tesirine			X											
	Dexamethasone		X	X	X										
Response Assessment	Disease/Response Assessment (Radiographic Imaging)[q]	X									X[s]	X[r]	X[s]	X[s]	
	MRI/CT of the Brain[t]	X													
	Patient Reported Outcome (PRO)[u]	X		X [u]											
	Survival Status														X

Category	Description	Screening	Treatment (Cycle 1 and Cycle 2)[a]									End of Treatment (EOT)[b]	PTFU[c]		Survival FU (OS)[d]
		Day –28 to Day –1	Day –1	Day 1[e] (–3 d)	Day 2	Day 8 (± 3 d)	Day 15 (± 3 d)	Day 22 (±3 d)	Day 29 (± 3 d)	Day 36 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue Treatment	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
PK and PD/ Biomarker	Pharmacokinetics, Anti-therapeutic Antibody (ATA) and Neutralizing Antibodies (nAb)[v]			X								X			
	Archived or Fresh Tumor Material[w]	X													
	Tumor Material at Time of Disease Progression[x]											X	X		
	Blood for Inflammatory Markers and ctDNA (10 mL)[y]			X [y]											
	Blood for Tumor & Soluble Markers (5 mL)[y]			X [y]											
	Circulating Tumor Cells (10 mL)[z]	X		X [z]											
	Pharmacogenetics (DNA/RNA)[aa]			X[aa]											
	Serosal Fluid[bb]				Day 1 through 70 days after last study treatment										

a. Up to two additional cycles of rovalpituzumab tesirine may be permitted for subjects in Arm A meeting criteria as described in Section 5.3.1.1. Subjects receiving additional doses of rovalpituzumab tesirine will follow the same study schedule as in Cycles 1 and 2.

b. EOT Visit occurs within 7 days of documentation of the decision to discontinue treatment and prior to subjects beginning any new anti-cancer therapy if possible. Subjects in Arm A should be evaluated for eligibility of two additional doses of rovalpituzumab tesirine prior to proceeding with EOT procedures.

c. For subjects who discontinue investigational product for reasons other than disease progression, the first PTFU visit will occur at 6 weeks (± 1 week) after the last Disease/Response Assessment, then every 6 weeks (± 1 week) until disease progression or initiation of new anti-cancer therapy, whichever occurs first.

d. Subjects will be followed for subsequent anti-cancer therapies (dates and responses), as well as survival status, every 6 weeks* (± 1 week) until the endpoint of death, the subject becomes lost to follow-up or withdraws consent, or termination of the study by AbbVie, whichever occurs first (*or as requested by AbbVie to support data analysis).

e. Procedures performed at Screening (with the exception of vital signs) do not need to be repeated if performed within 28 days of randomization unless clinically indicated. Randomization may occur within 3 calendar days prior to C1D1. Starting at C2D1, study assessments for Day 1 visits may be performed within 3 business days prior to the visit. Disease/Response Assessment may be performed within 7 days prior to the Day 1 visit unless otherwise indicated.

f. Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken or before any prohibited medications are withheld from the subject in order to participate in this study. Informed consent may be obtained before the 28-day screening window for DLL3 testing.

g. Medical and Surgical History includes demographics and documentation of clinically significant medical condition, surgical history, and malignancy history.

h. Height will be collected at the Screening visit only. For height assessments, the subject should not wear shoes. The physical examination performed at screening does not need to be repeated on CID1 if performed within 7 days of C1D1.

i. Vital signs include weight, sitting blood pressure, heart rate and body temperature. Weight will be collected in the clinic prior to dosing at each cycle and the recorded actual weight will be utilized for dosing calculations. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections. Vital signs should be collected prior to the infusion (including C1D1).

j. All laboratory samples will be assessed using a certified central laboratory. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions as per standard of care. Refer to Table 2, Clinical Laboratory Tests for details.

k. The clinical laboratory tests performed at Screening do not need to be repeated on C1D1 if performed within 7 days of C1D1 and meet eligibility criteria, unless clinically indicated. Starting at Cycle 2, lab assessment may be performed 3 business days prior to Day 1 visits.

l. For female subjects of childbearing potential, 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. Urine pregnancy tests will be performed at Day 1 of each cycle, at the EOT Visit, and during the PTFU period until 6 months after the last dose of study drug. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing. Post-menopausal female subjects ≤ 55 years of age must have a FSH level > 40 IU/L and will have FSH performed at Screening and assessed by the investigator.

m. A resting 12-lead ECG will consist of a single 12-lead study performed within a 5-minute window after at least 5 minutes of quiet rest in a supine position. Additional ECG monitoring may occur as clinically indicated during the study.

n. Echocardiograms are required at Screening, Day 1 of each cycle starting C2D1, and EOT. Screening echocardiogram will be performed within 3 business days of randomization to assess for the presence of any pericardial effusion as well as cardiac function (left ventricular ejection fraction, LVEF). Subsequent echocardiograms should be performed within –3 business days of dosing visit to assess for the presence of any pericardial effusion. Additional echocardiogram monitoring may occur as clinically indicated during the study.

o. Subjects will be asked about the development of any new or worsening peripheral edema or dyspnea (Appendix J, Fluid Retention Questionnaire). The assessments on Days 8, 15, 29, and 36 may take place by phone, with the site contacting the subject and reviewing the questionnaire. Starting Day 1 (during the treatment period for Arm A) and through the EOT visit, subjects will maintain a diary of daily weights (captured on the Fluid Retention Questionnaire).

p. Collection of SAE/AE and Concomitant Medications may be required at this visit in order to meet the collection window requirement of Day 1 of study treatment through 70 days after last treatment. Any ongoing SAE/AE that require appropriate standard of care should also be conducted.

q. Diagnostic quality, spiral CT scans are recommended; other CT methods or MRI may be used if performed consistently throughout the study for each individual subject. Scans of the chest and abdomen must be obtained; scans of the neck and pelvis must also be obtained if there is documented or suspected involvement in these regions. Screening scans may be performed within 28 days prior to randomization. Disease response will be determined by the Investigator at each assessment according to RECIST v1.1. Effusion (pleural, pericardial, and etc.) assessments will be performed by a radiologist at each radiographical assessment and any new findings communicated to the Investigator prior to the next dose of investigational product. Effusions should contribute to disease status only if confirmed malignant by cytology. Scheduled tumor assessments will not be affected by delays in therapy and/or drug holidays. Subjects will continue to be monitored by the same diagnostic method throughout the study.

r. May be omitted if assessment was performed within the preceding 6 weeks.

s. Radiographic assessments will occur every 6 weeks (± 1 week) for the first 30 weeks then every 9 weeks (± 1 week) until progression or death. If the subject qualifies to receive 2 additional cycles of Rova-T, radiographic assessments will continue to occur every 6 weeks for the first 30 weeks and then every 9 weeks until second progression or death.

t. MRI/CT of the brain is required at screening. Subsequent MRI/CT of the brain post screening is required only when clinically indicated (e.g., CNS metastasis history and if CNS progression is suspected).

u. PRO assessments are required at Screening and before infusion on C1D1.

v. At each cycle, approximately 6 mL of blood will be collected by venipuncture for pharmacokinetic (PK), Anti-therapeutic antibody (ATA), and neutralizing antibodies (nAb) testing. The pre-infusion sample will be collected prior to dosing on Day 1 (–3 business days window is permitted) and the second sample will be collected 30 minutes (± 10 minutes) post-infusion. Only one collection will be required at the EOT visit. The date and time of each sample collected will be recorded to the nearest minute.

w. Tumor material must be collected to confirm DLL3 expression. Subjects that provide consent for DLL3 testing at any time after initial diagnosis must be registered in IRT.

x. An optional tumor biopsy may be obtained at the time of disease progression, from subjects who consent to undergo biopsy procedure. Informed consent is required for the optional tumor biopsy at time of disease progression. The sample can be collected at the EOT or at the time of disease progression

y. On Cycle 1 Day 1 (–3 business days window is permitted), the collection of blood for inflammatory markers, ctDNA, tumor and soluble markers will be pre-infusion.

z. Whole blood sample will be collected for CTC analysis during screening and pre-dose on Cycle 1 Day 1. –3 business days window is permitted. CTCs implemented only at specific sites based on feasibility.

aa. Pharmacogenetic collection should occur unless precluded by local or national regulations or policies. Pharmacogentic sample to be collected on Day 1 of Cycle 1 only and is collected pre-infusion (–3 business days window is permitted).

bb. Any pericardial, pleural, and/or ascitic fluid collected as part of routine care (e.g., as part of a therapeutic thoracentesis, pericardiocentesis, or paracentesis) must be procured for testing, for any AE starting from C1D1 through 70 days after the last study treatment. Collected fluid must also be tested centrally and/or locally for cytology if disease progression due to appearance/worsening of effusion is suspected.

cc. Procedures for visits where no treatment is administered and phone contacts from Day 8 to Day 36 of each cycle may be performed within ± 3 day window relative to the due date. Procedures will include symptom review for presence of neurotoxicity, neutropenic colitis, fever, interstitial lung disease, serosal effusions (including pleural and pericardial), peripheral edema, cutaneous reactions (e.g., photosensitivity).

Appendix D. Study Activities for Arm B (Topotecan)
Previously read:

Category	Description	Screening	Treatment (Each Cycle)								End of Treatment (EOT)[a]	PTFU[b]		Survival FU (OS)[c]
		Day –28 to Day –1	Day 1[d] (–3 d)	Day 2	Day 3	Day 4	Day 5	Day 8 (± 3 d)	Day 15 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue tx	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
Location	Clinic Visit	X	X	X	X	X	X				X	X		
	Phone Contact[y]							X	X					X
Screening, Baseline, and Safety Assessments	Informed Consent[e]	X												
	Inclusion/Exclusion Criteria	X												
	Medical and Surgical History Including Malignancy History[f]	X												
	Physical examination[g]	X	X								X			
	Vital Signs[h]	X	X								X			
	Hematology and Serum Chemistry[i]	X	X[j]								X			
	Coagulation Tests[i]	X	X[j]											
	Urinalysis[i]	X	X[j]											
	Pregnancy Test[k]	X	X								X	X		
	Electrocardiogram (ECG)[-l]	X									X			
	Echocardiogram	X	X[m]								X			

Category	Description	Screening	Treatment (Each Cycle)								End of Treatment (EOT)[a]	PTFU[b]		Survival FU (OS)[c]
		Day –28 to Day –1	Day 1[d] (–3 d)	Day 2	Day 3	Day 4	Day 5	Day 8 (± 3 d)	Day 15 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue tx	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
	Performance Status (ECOG)	X	X								X			
	Fluid Retention Questionnaire[n]		X					X	X		X			
	SAE/Adverse Events	SAE/Procedure-related only	X	X	X	X	X	X	X		X[o]	X[o]		X[o]
	Concomitant Medications		X	X	X	X	X	X	X		X[o]	X[o]		X[o]
Treatment	Topotecan		X	X	X	X	X							
Response Assessment	Disease/Response Assessment (Radiographic Imaging)[p]	X								X[r]	X[q]	X[r]	X[r]	
	Central Radiographic Assessment Committee (CRAC) Review[s]	X								X	X[q]	X	X	
	MRI/CT of the Brain	X[t]												
	Heath Resource Utilization		X								X	X		
	Patient Reported Outcome (PRO)[u]	X	X								X	X		
	Survival Status													X

Category	Description	Screening	Treatment (Each Cycle)								End of Treatment (EOT)[a]	PTFU[b]		Survival FU (OS)[c]
		Day –28 to Day –1	Day 1[d] (–3 d)	Day 2	Day 3	Day 4	Day 5	Day 8 (± 3 d)	Day 15 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue tx	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
PD/ Biomarker	Archived or Fresh Tumor Material[v]	X												
	Circulating Tumor Cells (10 mL)[w]	X	X								X			
	Pharmacogenetics (DNA/RNA)[x]		X[x]								X			

a. EOT Visit occurs within 7 days of documentation of the decision to discontinue treatment and prior to subjects beginning any new anti-cancer therapy if possible.

b. For subjects who discontinue investigational product for reasons other than disease progression, the first PTFU visit will occur at 6 weeks (± 1 week) after the last Disease/Response Assessment, then every 6 weeks (± 1 week) until disease progression or initiation of new anti-cancer therapy, whichever occurs first.

c. Subjects will be followed for subsequent anti-cancer therapies (dates and responses), as well as survival status, every 6 weeks* (± 1 week) until the endpoint of death, the subject becomes lost to follow-up or withdraws consent, or termination of the study by AbbVie, whichever occurs first (*or as requested by AbbVie to support data analysis).

d. Procedures performed at Screening (with the exception of vital signs) do not need to be repeated if performed within 28 days of randomization unless clinically indicated. Randomization may occur within 3 calendar days prior to C1D1. Starting at C2D1, study assessments for Day 1 visits may be performed within 3 days prior to the visit. Disease/Response Assessment and CRAC Review may be performed within 7 days prior to the Day 1 visit unless otherwise indicated.

e. Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken or before any prohibited medications are withheld from the subject in order to participate in this study. Informed consent may be obtained before the 28-day screening window. Informed consent is also required for the optional tumor biopsy at time of disease progression.

f. Medical and Surgical History includes demographics and documentation of clinically significant medical condition, surgical history, and malignancy history.

g. Height will be collected at the Screening visit only. For height assessments, the subject should not wear shoes. The physical examination performed at screening does not need to be repeated on CID1 if performed within 7 days of C1D1.

h. Vital sign determinations include weight, sitting blood pressure, heart rate and body temperature. Weight will be collect prior to dosing at each cycle and recorded actual weight will be utilized for dosing calculations. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections. Vital signs should be collected prior to the infusion (including C1D1).

i. All laboratory samples will be assessed using a certified central laboratory. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions as per standard of care. Refer to Table 2, Clinical Laboratory Tests for details.

j. The clinical laboratory tests performed at screening do not need to be repeated on C1D1 if performed within 7 days of C1D1 and meet eligibility criteria, unless clinically indicated. Starting at Cycle 2, lab assessment may be performed 3 business days prior to Day 1 visits.

k. For female subjects of childbearing potential, 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. Urine pregnancy tests will be performed at Day 1, at the EOT visit, and during the PTFU period until 1 month after the last dose of study drug. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing. Post-menopausal female subjects ≤ 55 years of age must have a FSH level > 40 IU/L and will have FSH performed at Screening and assessed by the investigator.

l. A resting 12-lead ECG will consist of a single 12-lead study performed within a 5-minute window after at least 5 minutes of quiet rest in a supine position. Additional ECG monitoring may occur as clinically indicated during the study.

m. Screening echocardiogram will be performed within 3 business days of randomization and results should be available prior to randomization to assess for the presence of any pericardial effusion as swell as cardiac function (left ventricular ejection fraction, LVEF). Echocardiogram will then be performed every 6 weeks at alternating cycles starting C2D1 (–3 business days window is permitted). Additional Echocardiogram monitoring may occur as clinically indicated during the study.

n. Subjects will be asked about the development of any new or worsening peripheral edema or dyspnea (Appendix J, Fluid Retention Questionnaire). Assessments will occur Cycles 1 – 4. On Days 8 and 15, assessments may take place by phone, with the site contacting the subject and reviewing the questionnaire. Starting Day 1 and through the EOT visit, subjects will maintain a diary of daily weights (captured on the Fluid Retention Questionnaire).

o. Collection of SAE/AE and Concomitant Medications may be required at this visit in order to meet the collection window requirement of Day 1 of study treatment through 70 days after last treatment. Any ongoing SAE/AE that require appropriate standard of care should also be conducted.

p. Diagnostic quality, spiral CT scans are recommended; other CT methods or MRI may be used if performed consistently throughout the study for each individual subject. Scans of the chest and abdomen must be obtained; scans of the neck and pelvis must also be obtained if there is documented or suspected involvement in these regions. Screening scans may be performed within 28 days prior to randomization. Disease response will be determined by the Investigator at each assessment according to RECIST v1.1. Effusion (pleural, pericardial, and etc.) assessments will be performed by a radiologist at each radiographical assessment and any new findings communicated to the Investigator prior to the next dose of investigational product. Effusions should contribute to disease status only if confirmed malignant by cytology. Scheduled tumor assessments will not be affected by delays in therapy and/or drug holidays. Subjects will continue to be monitored by the same diagnostic method throughout the study.

q. May be omitted if previous assessment was performed within the preceding 6 weeks.

r. Radiographic assessments will occur every 6 weeks (± 1 week) for the first 30 weeks then every 9 weeks (± 1 week) until progression or death.

s. Site will collect the appropriate scans and or submit to the central facility at each subject's disease assessment.

t. MRI/CT of the brain is required at screening. Subsequent MRI/CT of the brain post screening is required only when clinically indicated (e.g., CNS metastasis history and if CNS progression is suspected).

u. PRO assessments are required at Screening, before infusion on Day 1 of each cycle, EOT, and PTFU (if applicable).

v. Tumor material must be collected to confirm DLL3 expression. Subjects that provide consent for DLL3 testing at any time after initial diagnosis must be registered in IRT.

w. Whole blood sample will be collected for CTC analysis during screening and pre-dose on Cycle 1 Day 1 and Cycle 3 Day 1 (if applicable). –3 business day window is permitted. Sample will also be collected at the EOT. CTCs implemented only at specific sites based on feasibility.

x. Pharmacogenetic collection should occur unless precluded by local or national regulations or policies. Pharmacogenetic sample to be collected on Day 1 of Cycle 1 only and is collected pre-infusion (–3 business days window is permitted).

y. Procedures for visits where no treatment is administered phone contacts for Day 8 and Day 15 of each cycle may be performed within ± 3 day window relative to the due date. Procedures will include symptom review for presence of neurotoxicity, neutropenic colitis, fever, interstitial lung disease, serosal effusions (including pleural and pericardial), peripheral edema, cutaneous reactions (e.g., photosensitivity).

Has been changed to read:

Category	Description	Screening	Treatment (Each Cycle)								End of Treatment (EOT)[a]	PTFU[b]		Survival FU (OS)[c]
		Day –28 to Day –1	Day 1[d] (–3 d)	Day 2	Day 3	Day 4	Day 5	Day 8 (± 3 d)	Day 15 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue tx	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
Location	Clinic Visit	X	X	X	X	X	X				X	X		
	Phone Contact[x]							X	X					X
Screening, Baseline, and Safety Assessments	Informed Consent[e]	X												
	Inclusion/Exclusion Criteria	X												
	Medical and Surgical History Including Malignancy History[f]	X												
	Physical examination[g]	X	X								X			
	Vital Signs[h]	X	X								X			
	Hematology and Serum Chemistry[i]	X	X[j]								X			
	Coagulation Tests[i]	X	X[j]											
	Urinalysis[i]	X	X[j]											
	Pregnancy Test[k]	X	X								X	X		
	Electrocardiogram (ECG)[-l]	X												
	Echocardiogram	X												

Category	Description	Screening	Treatment (Each Cycle)								End of Treatment (EOT)[a]	PTFU[b]		Survival FU (OS)[c]
		Day –28 to Day –1	Day 1[d] (–3 d)	Day 2	Day 3	Day 4	Day 5	Day 8 (± 3 d)	Day 15 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue tx	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
	Performance Status (ECOG)	X	X								X			
	Fluid Retention Questionnaire[n]		X[n]											
	SAE/Adverse Events	SAE/Procedure-related only	X	X	X	X	X	X	X		X[o]	X[o]		X[o]
	Concomitant Medications		X	X	X	X	X	X	X		X[o]	X[o]		X[o]
Treatment	Topotecan		X	X	X	X	X							
Response Assessment	Disease/Response Assessment (Radiographic Imaging)[p]	X								X[r]	X[q]	X[r]	X[r]	
	MRI/CT of the Brain	X[s]												
	Patient Reported Outcome (PRO)[t]	X	X[t]											
	Survival Status													X

Category	Description	Screening	Treatment (Each Cycle)								End of Treatment (EOT)[a]	PTFU[b]		Survival FU (OS)[c]
		Day –28 to Day –1	Day 1[d] (–3 d)	Day 2	Day 3	Day 4	Day 5	Day 8 (± 3 d)	Day 15 (± 3 d)	q6/q9 Weeks (± 1 wk)	Within 7 Days of Decision to Discontinue tx	q6 Weeks (± 1 wk)	q9 Weeks (± 1 wk)	q6 Weeks (± 1 wk)
PD/ Biomarker	Archived or Fresh Tumor Material[u]	X												
	Circulating Tumor Cells (10 mL)[v]	X	X [v]											
	Pharmacogenetics (DNA/RNA)[w]		X[w]											

a. EOT Visit occurs within 7 days of documentation of the decision to discontinue treatment and prior to subjects beginning any new anti-cancer therapy if possible.

b. For subjects who discontinue investigational product for reasons other than disease progression, the first PTFU visit will occur at 6 weeks (± 1 week) after the last Disease/Response Assessment, then every 6 weeks (± 1 week) until disease progression or initiation of new anti-cancer therapy, whichever occurs first.

c. Subjects will be followed for subsequent anti-cancer therapies (dates and responses), as well as survival status, every 6 weeks* (± 1 week) until the endpoint of death, the subject becomes lost to follow-up or withdraws consent, or termination of the study by AbbVie, whichever occurs first (*or as requested by AbbVie to support data analysis).

d. Procedures performed at Screening (with the exception of vital signs) do not need to be repeated if performed within 28 days of randomization unless clinically indicated. Randomization may occur within 3 calendar days prior to C1D1. Starting at C2D1, study assessments for Day 1 visits may be performed within 3 days prior to the visit. Disease/Response Assessment may be performed within 7 days prior to the Day 1 visit unless otherwise indicated.

e. Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken or before any prohibited medications are withheld from the subject in order to participate in this study. Informed consent may be obtained before the 28-day screening window. Informed consent is also required for the optional tumor biopsy at time of disease progression.

f. Medical and Surgical History includes demographics and documentation of clinically significant medical condition, surgical history, and malignancy history.

g. Height will be collected at the Screening visit only. For height assessments, the subject should not wear shoes. The physical examination performed at screening does not need to be repeated on CID1 if performed within 7 days of C1D1.

h. Vital sign determinations include weight, sitting blood pressure, heart rate and body temperature. Weight will be collect prior to dosing at each cycle and recorded actual weight will be utilized for dosing calculations. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections. Vital signs should be collected prior to the infusion (including C1D1).

i. All laboratory samples will be assessed using a certified central laboratory. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions as per standard of care. Refer to Table 2, Clinical Laboratory Tests for details.

j. The clinical laboratory tests performed at screening do not need to be repeated on C1D1 if performed within 7 days of C1D1 and meet eligibility criteria, unless clinically indicated. Starting at Cycle 2, lab assessment may be performed 3 business days prior to Day 1 visits.

k. For female subjects of childbearing potential, 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. Urine pregnancy tests will be performed at Day 1, at the EOT visit, and during the PTFU period until 1 month after the last dose of study drug. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing. Post-menopausal female subjects ≤ 55 years of age must have a FSH level > 40 IU/L and will have FSH performed at Screening and assessed by the investigator.

l. A resting 12-lead ECG will consist of a single 12-lead study performed within a 5-minute window after at least 5 minutes of quiet rest in a supine position. Additional ECG monitoring may occur as clinically indicated during the study.

m. Screening echocardiogram will be performed within 3 business days of randomization and results should be available prior to randomization to assess for the presence of any pericardial effusion as swell as cardiac function (left ventricular ejection fraction, LVEF). Additional Echocardiogram monitoring may occur as clinically indicated during the study.

n. Subjects will be asked about the development of any new or worsening peripheral edema or dyspnea (Appendix J, Fluid Retention Questionnaire). Assessments will occur only in Cycle 1.

o. Collection of SAE/AE and Concomitant Medications may be required at this visit in order to meet the collection window requirement of Day 1 of study treatment through 70 days after last treatment. Any ongoing SAE/AE that require appropriate standard of care should also be conducted.

p. Diagnostic quality, spiral CT scans are recommended; other CT methods or MRI may be used if performed consistently throughout the study for each individual subject. Scans of the chest and abdomen must be obtained; scans of the neck and pelvis must also be obtained if there is documented or suspected involvement in these regions. Screening scans may be performed within 28 days prior to randomization. Disease response will be determined by the Investigator at each assessment according to RECIST v1.1. Effusion (pleural, pericardial, and etc.) assessments will be performed by a radiologist at each radiographical assessment and any new findings communicated to the Investigator prior to the next dose of investigational product. Effusions should contribute to disease status only if confirmed malignant by cytology. Scheduled tumor assessments will not be affected by delays in therapy and/or drug holidays. Subjects will continue to be monitored by the same diagnostic method throughout the study.

q. May be omitted if previous assessment was performed within the preceding 6 weeks.

r. Radiographic assessments will occur every 6 weeks (± 1 week) for the first 30 weeks then every 9 weeks (± 1 week) until progression or death.

s. MRI/CT of the brain is required at screening. Subsequent MRI/CT of the brain post screening is required only when clinically indicated (e.g., CNS metastasis history and if CNS progression is suspected).

t. PRO assessments are required at Screening and before infusion on C1D1.

u. Tumor material must be collected to confirm DLL3 expression. Subjects that provide consent for DLL3 testing at any time after initial diagnosis must be registered in IRT.

v. Whole blood sample will be collected for CTC analysis during screening and pre-dose on Cycle 1 Day 1. –3 business day window is permitted. CTCs implemented only at specific sites based on feasibility.

w. Pharmacogenetic collection should occur unless precluded by local or national regulations or policies. Pharmacogenetic sample to be collected on Day 1 of Cycle 1 only and is collected pre-infusion (–3 business days window is permitted).

x. Procedures for visits where no treatment is administered phone contacts for Day 8 and Day 15 of each cycle may be performed within ± 3 day window relative to the due date. Procedures will include symptom review for presence of neurotoxicity, neutropenic colitis, fever, interstitial lung disease, serosal effusions (including pleural and pericardial), peripheral edema, cutaneous reactions (e.g., photosensitivity).