1.0 Title Page

Statistical Analysis Plan

Study 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

Date: 13 Mar 2020

Version 1.0

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3.0 Abbreviation

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
CRAC	Central Radiographic Assessment Committee
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

4.0 Introduction

This draft statistical analysis plan (SAP) describes the detailed statistical methods, including analysis conventions, for primary and secondary objectives as outlined in the protocol for Study M16-289 Amendment 4 (which is currently also in draft stage).

Efficacy and safety analyses will be performed using SAS Version 9.3 or higher (SAS Institute, Inc., Cary, NC 27513) under the UNIX operating system. The SAP will be finalized prior to any comparative analysis of study data by treatment arm.

5.0 Study Objectives and Design

5.1 Objectives

5.1.1 Primary Objective

The primary objectives of the study are to assess if treatment with rovalpituzumab tesirine (Rova-T) improves overall survival (OS) compared to topotecan in subjects with advanced or metastatic Delta-like protein 3 high expression in tumor ($DLL3^{high}$), small-cell lung cancer (SCLC) who have first disease progression during or following front-line platinum based chemotherapy.

5.1.2 Secondary Objectives

The secondary objectives of the study are as follows:

- to demonstrate if the treatment with Rova-T improves progression free survival (PFS) assessed by Central Radiographic Assessment Committee (CRAC) compared to topotecan;
- to assess the effect on physical functioning scale in EORTC-QLQ-C15-PAL questionnaire at post-baseline Week 7 due to treatment with rovalpituzumab tesirine compared to topotecan;

- to assess if treatment with rovalpituzumab tesirine improves clinical benefit rate (CBR) assessed by CRAC 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.

5.1.3 Exploratory Objectives

The exploratory objectives are

- to determine if treatment with rovalpituzumab tesirine improves objective response rate (ORR);
- to compare the duration of objective response between two arms;
- to compare the safety and tolerability of rovalpituzumab tesirine to topotecan;

in subjects with advanced or metastatic DLL3^{high} SCLC who have first disease progression during or following front-line platinum based chemotherapy

5.2 Design Diagram

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. DLL3^{high} is defined as ≥ 75% tumor cells staining positive according to the VENTANA DLL3 (SP347) IHC Assay.

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

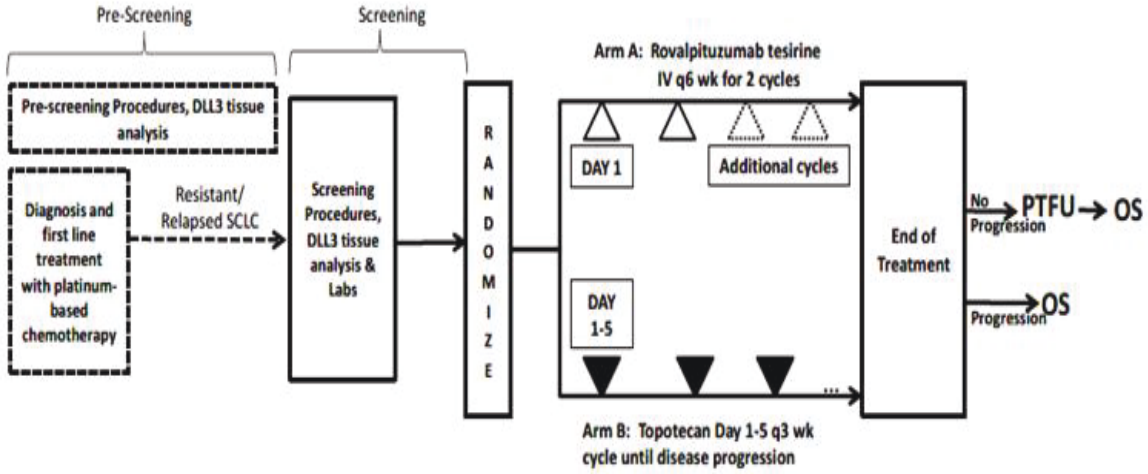
- Subjects assigned to Arm A will receive 0.3 mg/kg rovalpituzumab tesirine (IV) on Day 1 of a 42-Day cycle for 2 cycles, along with 8 mg orally (PO) of dexamethasone twice daily on Day –1, Day 1, and Day 2. Regimen of Arm A will be administered for the 2 cycles planned unless earlier discontinuation is warranted due to disease progression, unacceptable toxicity or any other

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

- 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.

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 Protocol Section 5.3.1.1.
3. Topotecan will be administered until disease progression, unacceptable toxicity or any other reason requiring treatment discontinuation.

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. 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 of the study protocol.

Disease assessments, for the purposes of efficacy assessments, will be performed by a CRAC blinded to study treatment information and independent of investigators and personnel who are involved in conducting the study.

The study procedures for each visit are outlined in Appendix A and Appendix B.

5.3 Randomization and Stratification

All subjects in the study will be randomized using an Interactive Response Technology (IRT) system. The site will contact the IRT to obtain a Screening (subject) number once the subject has signed the informed consent. 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.

Subjects who meet the eligibility criteria will be stratified according to the following 4 factors:

- prior history of brain metastases and Prophylactic cranial irradiation (PCI) (brain metastases, no brain metastases and PCI, no brain metastases nor PCI,),

- 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 versus ≤ ULN) at screening.

5.4 Sample Size

The sample size of the study is determined by 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 497 deaths are needed to detect a hazard ratio of 0.75 (i.e., a reduction in the hazard death of 25%) which corresponds to an increase in median OS to 8.67 months in rovalpituzumab tesirine arm (Arm A) assuming, an exponential survival time distribution. It is projected that an observed hazard ratio of 0.826 or less would result in statistically significance in the final analysis of OS.

5.5 Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be formed and constituted according to appropriate regulatory guidelines. The IDMC will be scheduled to review safety data approximately every 3 months after the first IDMC meeting, or at any time requested by the IDMC. Detailed information regarding the composition of the committee and detailed procedures will be documented in a separate charter.

Data will be analyzed by the Statistical and Data Analysis Center (SDAC), an external vendor outside of the Sponsor, and the results from analyses will be reviewed by the IDMC. Details will be provided in the IDMC charter.

5.6 Planned Analyses

5.6.1 Final Analysis

Final analysis will be performed when at least 497 deaths have occurred, which is projected to be approximately 38 months the first subject randomized.

5.6.2 Supportive Analysis

A supportive analysis is planned to support activities in Rova-T program that are not related to TAHOE study, specifically potential regulatory submission of data from Phase I/II for consideration of early registration. The supportive analysis will be conducted during 2Q 2019 and will include approximately the first 190 enrolled subjects. The result of the analysis will not impact the study conduct in any way unless it is warranted based on a review of safety data. There is no intent to stop the trial early to claim efficacy based on this supportive analysis. Nevertheless, one sided alpha of 10^{-6} will be spent at the supportive analysis per regulatory agency feedback since efficacy data will be analyzed. The supportive analysis will be conducted by SDAC which is an independent group external to the Sponsor. The study team that is involved in the conduct of this trial will not have access to, or any knowledge of, the results that would be generated during the supportive analysis. The details of the conduct of the supportive analysis are documented in the Trial integrity plan (TIP).

5.6.3 Interim Analysis for Early Efficacy

An interim efficacy analyses of OS will be performed after observing about 373 deaths (i.e., 75% of the 497 deaths required at final analysis). At the interim analysis, OS will be tested at the significance level determined based on the actual number of deaths using the Lan-DeMets alpha spending function with O'Brien and Fleming boundary so that the overall 1-sided significance level is maintained at 0.025. When 373 deaths are observed, an alpha spending of 0.0097 for the interim OS analysis will be allocated to test for superiority. The final OS analysis will be performed at a one-sided nominal alpha level of 0.0221, adjusting for the interim look at OS data. If the interim analysis is performed at

373 deaths, the HR boundary for demonstrating superiority in OS at the interim will be 0.773. The HR boundary for demonstrating superiority at the final analysis with 497 deaths will be 0.826.

The trial will be considered for early stopping for efficacy if the Independent Data Monitoring Committee (IDMC) makes such a recommendation after consideration of the OS results and all supportive evidence including other efficacy endpoints and safety.

5.7 Type I Error Adjustment Procedures

5.7.1 Type I Error Control for Supportive analysis

The one-sided alpha of 10^{-6} will be spent for the early look at the efficacy data for supportive analysis. However, there is no provision to stop the trial early to claim efficacy based on this interim analysis.

5.7.2 Type I Error Control for Interim Analysis

O'Brien-Fleming method will be used to adjust for multiple testing to maintain one-sided type I error level at 2.5% for the whole study. As described in Section 11.2, stratified log-rank test would be used for primary efficacy analyses. With interim analysis planned at 373 events and final analysis planned at 497 events, the simulation results suggest that the information fraction (IF) at interim analysis is estimated to be approximately 75%. With this IF at interim analyses, a one-sided type I error of 0.0097 will be used for interim analysis with 373 events for early efficacy, and final analysis will be carried out at one-sided type I error of 0.0221 to preserve type I error at one-sided 2.5% for the whole study.

5.7.3 Type I Error Adjustment Procedures for Multiple Testing

As mentioned above, the overall one-sided type I error for testing the primary and all secondary endpoints will be preserved at 2.5%. The primary and secondary endpoints will be tested using a fixed-sequence hierarchical testing strategy. At each analysis

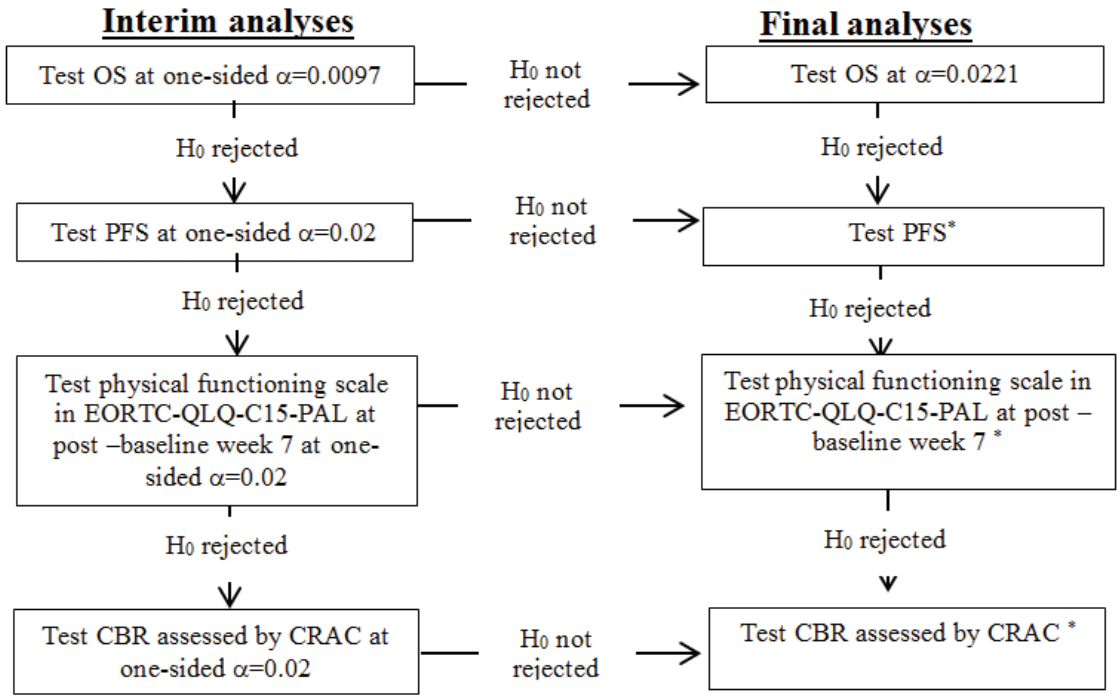
timepoints (i.e., interim and final analyses), the treatment effects on primary and secondary endpoints will be tested in the following order

Testing Order	Endpoint
1	OS
2	PFS, assessed by CRAC
3	Change from baseline in physical functioning scale on EORTC-QLQ C15-PAL questionnaire at post-baseline Week 7
4	clinical benefit rate assessed by CRAC

To protect overall Type I error across primary and all the secondary endpoints, we will follow "overall hierarchical" testing strategy.[10] The O'Brien Fleming alpha spending function will be used for the OS endpoint. For all the secondary endpoints one-sided alpha of 0.02 will be allocated for the interim analysis; the alpha spend in the final analysis will be calculated using the group sequential design methodology and estimated information fraction at interim analysis. For example, the one-sided alpha for the PFS endpoint in the final analysis would be 0.014 and 0.018 if the information fraction at the interim analysis is 0.8 and 0.9, respectively. The interim analysis will be driven by the timing of observing 373 OS events.

The testing procedure is displayed in Figure 2.

Figure 2. Testing Procedure



* The alpha for the final analysis will be calculated using the group sequential design methodology and estimated information fraction at interim analysis.

6.0 Analysis Sets

The following analysis sets will be used for analysis of safety and efficacy endpoints of the study.

Randomized Set will comprise all randomized subjects regardless of whether they received study treatment. Subjects will be classified in the treatment groups, "rovalpituzumab tesirine" or "Topotecan," according to the treatment they were assigned at the time of randomization. Unless otherwise specified (and except for subgroup and sensitivity analyses), the Randomized Set will be the default dataset for analysis of efficacy data.

Per-protocol Set (PPS) will be comprised of a subset of patients in the Randomized Set excluding those with deviation(s) from study inclusion and exclusion criteria. Subjects meeting any of the following criteria will be excluded from PPS:

- Those entered into the study even though did not satisfy the entry criteria
- Those who developed withdrawal criteria during the study but were not withdrawn
- Those who received the wrong treatment
- Those who received an excluded concomitant treatment
- Those who were randomized but did not receive any dose of study medication

Subjects will be classified according to treatment assigned.

Safety Set will be comprised of a subset of subjects who receive at least one dose of study treatment (either rovalpituzumab tesirine or topotecan). Subjects will be classified according to the treatment they had received (as-treated).

7.0 Analysis Conventions

This section provides general considerations for data handling, summary, and analysis. This also includes general definitions of certain kinds of endpoints.

Continuous variables will be summarized by sample size (N), mean, standard deviation (St. Dev.), median, minimum, and maximum. Frequency and percentage will be provided for categorical variables and 95% confidence intervals (CIs) will be generated for parameter estimates of interest, unless specified otherwise.

For the analysis of efficacy endpoints, the Randomized Set will be the primary analysis set whereas the Per Protocol Set (PPS) will be used for supportive analysis only. Analysis for the sub-groups will be carried out in the subset of Randomized Set meeting the sub-group selection criteria at the enrollment.

The change from baseline analysis for the QOL measures, patients with missing baseline values will be excluded. Descriptive summaries for the efficacy endpoints will be reported by treatment groups. These summaries will also be reported at the individual levels of each stratification factors.

The statistical comparisons for the primary and secondary endpoints will be made according to the multiplicity adjustment plan described in Section 5.7.2 to preserve the familywise one-sided type 1 error rate at 0.025. The statistical comparisons for all the other exploratory efficacy endpoints will be performed at a nominal one-sided 2.5% significance level. Confidence intervals for parameters (e.g., median survival times, HR) will be constructed with 2-sided 95% confidence level, whenever applicable. No type I error adjustment for multiple comparisons will be carried out for these exploratory endpoints.

Dealing with Multiple Values on the Same Day

In case multiple values are collected on the same day at a baseline or post-baseline visit, the arithmetic average (for continuous summary) will be used for analyses unless otherwise specified.

Definition of Baseline Observation

Unless otherwise specified, the baseline observation is defined as the last non-missing measurement collected prior to the first dose date of any study drug (rovalpituzumab tesirine or dexamethasone) for Arm A; topotecan for Arm B).

Definition of Final Observation for Laboratory and Vital Sign Parameters

For lab and vital sign parameters, the final observation is defined as the last non-missing post-baseline measurement collected not more than 70 days after the last dose of investigational product.

Missing Data

No missing data imputation will be implemented, unless specified otherwise.

Definition of Study Day (Day Relative to the day of Randomization) and Rx Day (Day Relative to the First Dose of Study Drug)

Study Day of any observation is defined for post-randomization observations as:

Study Day = Date of observation – Date of randomization + 1,

and for observations pre-dating randomization as:

Study Day = Date of observation – Date of randomization.

Thus, the day of randomization is defined as Study Day 1, while the day prior to the randomization is defined as Study Day –1 (there is no Study Day 0).

Study Rx Day of any post-baseline observation is defined as the number of days from the day of the first dose of any study drug (rovalpituzumab tesirine or topotecan) to the date of observation. It is calculated for each observation as follows:

- Study Rx Day = Date of observation – Date of first dose of any study drug + 1

Definition of Analysis Windows

All time points and corresponding time windows are based on Study Rx Days, unless specified otherwise. For analysis at visit, especially for the laboratory data (hematology, chemistry, and urinalysis), nominal days and visit windows for the 2 treatment arms (Arm A and Arm B) are given in the table below. If more than one observation is included in a time window, the observation closest to the nominal day should be used. If there are two observations equally distant to the nominal day, the later one will be used in analyses.

Table 1. Visit Window laboratory and vital sign analysis

Study Visit (Week)	Nominal Study Rx Day	Time Window (Study Rx Days Range)
Baseline		Baseline definition
3	22	2 to ≤ 32
6	43	33 to ≤ 53
…	…	…
3•X	7•3•X + 1	7•3•X - 9 to ≤ 7•3•X + 11

The endpoints based on subject self-reported health related quality of life (QoL) and symptom assessments will be analyzed for post-treatment Week 3, Week 7 and subsequently with the increment of 6 weeks (i.e., Week 13, Week 19, and Week 24). The visit windows for the PRO endpoints are defined in Table 2 below.

Table 2. Visit Window for PRO analysis

Study Visit (Week)	Nominal Study Rx Day	Time Window (Study Rx Days Range)
Baseline		Baseline definition
3	22	2 to ≤ 28
7	50	29 to ≤ 70
13	92	71 to ≤ 112
…	…	…
7 + 6•X	(7+6•X) 7 + 1	(7+6•X) 7 - 20 to ≤ (7 + 6•X) 7 + 21

7.1 Data Handling Convention at Database Level

There is no applicable data handling convention at database level.

8.0 Demographics, Baseline Characteristics, Medical History, Previous/Concomitant Medications, and Prior Oncology Therapies

Data for demographic, baseline characteristics, medical history, prior/concomitant medications, prior systemic therapies, and prior procedures will be summarized by treatment groups using the Randomized Set population.

8.1 Demographic and Baseline Characteristics

Continuous demographic data (e.g., age, height, and weight) will be summarized with N, mean, standard deviation (St. Dev.), median, minimum, and maximum. Frequencies and percentages will be computed for the following categorical parameters (but not limited to): sex, race, ethnicity, age group (< 55, 55 to < 65, 65 to < 75, 75 to < 85, and ≥ 85 years old), tobacco and alcohol use (unknown, never, current, former), and ECOG performance status (0, 1, ≥ 2).

Subject's baseline characteristics will be summarized, including (but not limited to) stratification factors, small cell lung cancer history (overall VALG stage at study entry/initial diagnosis, overall TNM at study entry/initial diagnosis, TNM staging (T, N, M) at study entry, weeks from initial diagnosis to randomization, DLL3 status, DLL3 expression in percentage), prior systemic therapies (sensitivity to first line platinum-based regimen, number of subjects who progressed prior to completion of platinum-based regimen, days from completion of prior regimen to progression for those who completed it, treatment received, reason for discontinuation of prior treatment), prior radiation therapy (number of subjects with any prior radiation, type of radiation, treatment intent, best outcome), prior procedures, electrocardiogram, and echocardiogram.

There will be no statistical comparison of demographic and baseline measurements between treatment arms.

8.2 Medical History

Medical history data will be summarized and presented using conditions/diagnoses as captured on the eCRF. The conditions/diagnoses will be presented in alphabetical order. The number and percentage of subjects with a particular condition/diagnosis will be summarized for each treatment arm. Subjects reporting more than one condition/diagnosis will be counted only once for that condition/diagnosis. There will be no statistical comparison of the medical history between treatment arms.

8.3 Prior and Concomitant Medications

A prior medication is defined as any medication with an end date prior to the date of randomization and collected on the electronic case report forms (eCRFs). A concomitant medication is defined as any drug that started on the day of or after randomization, but not more than 70 days after the last study drug administration. Medications with a start date prior to the date of randomization and continuing after randomization are also classified as concomitant medications. A medication will also be considered a concomitant medication if one of the following three cases occur: (1) the start date is missing and the end date is either after or on the day of randomization; (2) the start date is not missing but not more than 70 days after the last study drug administration and the end date is missing; (3) both the start date and the end date are missing.

Prior and concomitant medications will be summarized separately by the anatomical therapeutic chemical (ATC) codes in the World Health Organization (WHO) dictionary. Subjects reporting the same medication generic name two or more times will be counted only once for that generic name. Subjects reporting more than one medication will be counted only once in the total number of subjects taking a concomitant medication. In addition, the number of prior and concomitant medications will also be presented for each treatment arm.

There will be no statistical comparison of prior and concomitant medications between treatment arms.

9.0 Subject Disposition

Subject disposition summary will be presented on all the screened subjects by investigator site and overall. The following information will be presented:

- Subjects who were screened
- Subjects who screen failed
- Subjects who were randomized
- Subjects who were randomized without any major protocol violations

- Subjects who took at least one dose of study drug (rovalpituzumab tesirine; topotecan)
- Subjects who completed/discontinued the study drug

In addition, a subject disposition summary will be presented for the Randomized Set by treatment arm assigned at randomization – the numbers and percentages of subjects who were randomized, and discontinued the study.

In addition, treatment disposition summary will be presented for the safety set, classifying subjects according to actual treatment received. The numbers and percentages of subjects who discontinued the study drug and primary reason for study drug discontinuation will be provided. No statistical tests will be performed.

10.0 Study Drug

10.1 Study Drug Exposure

Summary of study drug exposure will be presented on the safety set.

The following summaries will be presented by treatment group:

- The number and percentage of subjects with total number of cycles of rovalpituzumab tesirine and topotecan received,
- Descriptive summary of average dose level per cycle (mg/kg for rovalpituzumab tesirine; mg for dexamethasone; mg/m^2 for topotecan),

An overview of interruption and dose reduction will be presented for each of rovalpituzumab tesirine, dexamethasone, and topotecan treatments as following:

- The number and percentage of subjects who had at least one interruption of study drug (rovalpituzumab tesirine/dexamethasone/topotecan) administration, and further breakdowns by the number of interruptions and by reason,
- The number and percentage of subjects who had at least one dose reduction, and further breakdowns by the number of dose reductions and by reason.

For each cycle, the number and percentages of subjects with interruption and reason will be presented (42-day cycle for rovalpituzumab tesirine; 21-day cycle for topotecan). Similarly, the number and percentages of subjects with dose reduction and reason will be presented at each cycle.

10.2 Relative Dose Intensity (RDI) of Rovalpituzumab Tesirine

Dose intensity of rovalpituzumab tesirine will be summarized for the safety set (Arm A only).

For a subject, the total dose is defined as the sum of rovalpituzumab tesirine doses (mg/kg) administered during the study. Treatment duration of rovalpituzumab tesirine is defined as total number of weeks rovalpituzumab tesirine treated, i.e., (date of last injection – date of first injection + 42)/7, by adding the appropriate number of days to complete the last cycle.

The observed dose intensity ($DI_{observed}$), expressed in units of dose level divided by unit of treatment duration, i.e., mg/kg/week, is the ratio of the total dose (mg/kg) received to the total duration of treatment (weeks);

$$DI_{observed} = \frac{Total\ dose\ (mg/kg)}{Actual\ total\ treatment\ duration\ (weeks)}$$

The theoretical dose intensity ($DI_{protocol}$) will be expressed in the same unit as those used for the observed dose intensity;

$$DI_{protocol} = \frac{Dose\ per\ cycle\ (mg/kg)}{Theoretical\ duration\ of\ one\ cycle\ (weeks)}$$

The relative dose intensity (*RDI*), expressed in percentage (%), is calculated as the ratio of the observed dose intensity to the dose intensity indicated in the protocol;

$$RDI = \frac{DI_{observed}}{DI_{protocol}} \times 100 \cdot$$

Simple continuous summary statistics for the observed dose intensity will be presented. The number and percentages of subjects will be presented for the following categories of RDI < 70%, 70% to < 90%, 90% to < 110%, 110% to < 120%, and 120% or higher.

11.0 Efficacy Analysis

11.1 General Considerations

Unless otherwise specified, all efficacy analyses described below will be performed on the Randomized Set. Efficacy endpoints of response and progression used in analyses will be based on Central Radiographic Assessment Committee (CRAC). Disease progression will be defined as progression of disease according to RECIST v1.1. For subjects whose tumors meet the criteria of partial or complete response (PR or CR), tumor response must be confirmed by repeat measurements performed no less than 4 and no more than 8 weeks after the criteria for response are first met.

For change from baseline analysis of QOL measures, patients with missing baseline value will be excluded. Descriptive summaries for the efficacy endpoints will be reported by treatment groups. These summaries will also be reported at the individual levels of each stratification factors.

The statistical comparisons for the primary and secondary endpoints will be done according to the multiplicity adjustment plan described in Section 5.7.2 to preserve the familywise one-sided type 1 error rate to 0.025. The statistical comparisons for all the other exploratory efficacy endpoints will be performed at a nominal one-sided 2.5% significance level. Confidence intervals for parameters (e.g., median survival times, HR) will be constructed with 2-sided 95% confidence level, whenever applicable. No type I error adjustment for multiple comparisons will be carried out for these exploratory endpoints.

11.1.1 Analysis of Efficacy Endpoints by Variable Type

Time to events (TTE) variables

All TTE endpoints defined in this study are concerned with only the first incidence of an event of interest, and recurrence of the same event is not considered for endpoint derivation. An event however may be defined in a composite manner, i.e., as the occurrence of one among several different outcomes. The composite event is observed when at least one of the component events occurs, and the time to the earliest among the occurring component events is considered to be the TTE for the composite event.

Time to events (TTE) endpoints will be derived as follows:

TTE = Date of first occurrence of an event or censoring – date of randomization + 1.

TTE endpoints will be computed in days and converted into months (1 month = 30.4375 days) for analysis. Thus, for subjects who experience the event of interest, time to event will be defined as the time from randomization to the first occurrence of the event. When multiple assessments are needed to ascertain the occurrence of an event, the earliest date among all of these assessments is taken to be date of the event or censoring. For a subject who does not experience an event on the study, time will be right censored at the time of his/her last available adequate post-baseline assessment that rules out the occurrence of the event. If a subject had no post-baseline assessment and did not experience the event of interest, then TTE will be censored at the date of randomization and we will set TTE = 1 day, by convention.

TTE endpoints will be summarized by number of events observed, number of subjects censored, and times corresponding to 25% (1st quartile), 50% (median) and 75% (3rd quartile) event probabilities. Kaplan-Meier (KM) estimates will be calculated and plotted. Comparison between treatment arms will be based on stratified log-rank tests as specified.

A Cox proportional-hazards regression model[4] with the treatment and stratification factors as covariates will be used to estimate the HR of rovalpituzumab tesirine to topotecan and its two-sided 95% CI. Only the main effects of the stratification variables will be fitted. Measure of treatment effects will be provided in term of HR (rovalpituzumab tesirine to Topotecan) from the above model with HR value less than 1 representing treatment benefit. For all of the above time-to-deterioration endpoints, death will be considered as event.

Continuous variables

Summary of continuous endpoints at baseline, post-baseline and change from baseline (as available) will be provided. Change from baseline values will be analyzed using an analysis of covariance (ANCOVA) model including stratification factors and baseline as covariates and 95% CI for treatment group difference will be provided.

11.2 Efficacy Analyses

Overall Survival (OS)

All events of death available at the time of analysis will be included, regardless of whether the event occurred while the subject was still taking study drug or after the subject discontinued study drug.

The primary endpoint OS will be compared between treatment Arms rovalpituzumab tesirine and topotecan at both interim and final analysis. Superiority of rovalpituzumab tesirine (Arm A) to topotecan (Arm B) in terms of OS will be evaluated using stratified log-rank test, adjusting for the study stratification factors.

This stratified log rank test will be implemented in SAS using LIFETEST procedure as follows:

```
proc lifetest method=km;
   time <follow-up time>*<Censoring status>(<censoring codes>);
   strata <stratification factors> / group=<treatment>
                           test = logrank;
run;
```

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, using the Brookmeyer and Crowley method. Landmark survival rate, defined as the survival rate estimated using the Kaplan-Meier approach at pre-defined time points from randomization (e.g., 6, 12, 18, and 24 months), will be presented with two-sided 95% CIs, using Greenwood's method for calculating standard errors.

Estimation of HR

A Cox proportional-hazards regression model[4] with the treatment and stratification factors as covariates will be used to estimate the HR of rovalpituzumab tesirine to topotecan and its two-sided 95% CI. Only the main effects of the stratification variables will be fitted.

Where, treatment takes value 1, if treated with rovalpituzumab tesirine, otherwise 0, for topotecan. Effron's approximate method (1977) will be used for handling ties. In SAS, estimate of HR will be estimated using PHREG procedure and Effron's method[5] will be employed by using TIES = EFFRON option in MODEL statement.[19] Following SAS code will be used

```
PROC PHREG;
  CLASS <treatment>;
  MODEL <follow-up time>*<Censoring status>(<censoring codes>)=
<strata variables> <treatment> /TIES=EFFRON RL;
RUN;
```

Progression-free Survival (PFS)

All disease progression assessed by CRAC per RECIST v1.1 will be included, regardless of whether the event occurred while subject was taking the study drug or had previously

discontinued the study drug. 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.

Analysis methods for PFS endpoint are similar to those described for the OS endpoint. The PFS rates at 6, 9 and 12 months and corresponding 95% CIs will also be estimated using KM estimates on the PFS curve for each arm.

Clinical Benefit Rate (CBR)

Subjects with clinical benefit includes those who achieve confirmed complete or partial response (CR or PR), or stable disease (SD) for at least 12 weeks (2 tumor assessments) as adjudged by the CRAC based on RECIST v1.1.

The clinical benefit rate (CR, PR, and SD) rate will be reported with exact (binomial) two-sided 95% CI for each treatment arm.

CBR will be compared between treatment arms using a Cochran-Mantel-Haenszel (CMH) test, stratified by the randomization stratification factors. The difference in CBR will be summarized with two-sided 95% CI. Rates and corresponding 95% exact CIs will be calculated by Clopper-Pearson method for each arm. Sensitivity analysis based on investigator-determined CBR will also be performed.

Objective Response Rate (ORR)

Analysis of ORR will be performed for the randomized subjects with measureable disease at baseline.

Objective response includes complete response (CR) and partial response (PR) assessed by the CRAC based on RECIST v1.1 Subjects who do not achieve CR or PR, including those who do not have post-baseline radiological assessments will be considered as non-responders.

The same statistical methodology will be used as that for CBR endpoint.

Duration of Response (DOR)

Only subjects with a confirmed 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) 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. For subjects who never experienced CR or PR, these subjects' data will not be included in the duration of response analysis.

Distribution of the duration of response will be estimated for each treatment arm using Kaplan-Meier methodology. Median duration of overall response with corresponding 95% CI for each treatment arm will be provided. Due to the non-randomization nature of the analysis set for DOR, the analysis of DOR will be considered descriptive and will not be compared between treatment arms.

Patients Reported Outcomes (PRO)

The endpoints based on subject self-reported health related quality of life (QoL) and symptom assessments will be analyzed for post-treatment Week 3, Week 7 and subsequently with the increment of 6 weeks (i.e., Week 13, Week 19, and Week 24). The EORTC QLQ-C15-PAL/LC13 and the European Quality of Life-5 Dimensions (EQ-5D-5L) are used to measure the QoL and symptom assessments.

QLQ-C15-PAL & QLQ-LC13

The QLQ-C15-PAL is an abbreviated 15-item version of the EORTC QLQ-C30 for palliative care. The QLQ-C15-PAL questionnaire has four abbreviated scales measuring physical functioning, emotional functioning, nausea and vomiting, and fatigue. These

scales are estimated using the algorithm specified in *Addendum to the EORTC QLQ-C30 Scoring Manual: Scoring of the EORTC QLQ-C15-PAL* (July, 2006).

For each scale in QLQ-C15-PAL questionnaire, the raw score (RS) is computed as the mean of component items over the number of items answered for that scale if at least 50% of the items are answered, and set as missing otherwise. Then the scale score (SS) will be computed as:

$$SS = \{(RS - 1)/range\} \cdot 100.$$

The lung cancer module (QLQ-LC13) is composed of one multi-item scale to assess dyspnea, and a series of single items assessing coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, hemoptysis, and pain.

All scales and single items are reported on categorical responses, and will be linearly converted to 0 through 100 numeric values. Given a scale, the raw score (RS) is computed as the mean of component items over the number of items answered for that scale if at least 50% of the items are answered. It will be set as missing otherwise. Then the scale score, $SS = \{(RS - 1)/range\} \cdot 100$, will be computed.

For single-item measures (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties), none of the single-item measures can be computed if not answered. If a scale score cannot be computed, the outcome for that score is left blank.

The analysis of continuous endpoint of EORTC QLQ-C15-PAL PF scale score will be performed by analyzing the change in scale score from baseline to the given time point, using an analysis of covariance (ANCOVA) model including stratification factors and baseline as covariates, and 95% CI for treatment group difference will be provided.

Change from baseline at post-baseline Week 7 in the physical function scale is one of the secondary efficacy endpoints, and other scales and items are considered exploratory.

For each scale, the treatment group differences will be evaluated by analyzing the change from baseline to each of the post-baseline time-points and to the final measurement (last QoL assessment per subject) using a one-way analysis of variance (ANOVA) model including stratification factors and baseline as covariates. Simple summary statistics for QoL assessments at each timepoint will also be presented.

EQ-5D-5L

The EuroQol 5 Dimensions 5 Level (EQ-5D-5L) is a preference based measure of health status that consists of EQ-5D descriptive system and EQ visual analogue scale (VAS).

The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of the dimensions is divided into 5 levels of perceived problems: Level 1 (indicating no problem), Level 2 (indicating slight problems), Level 3 (indicating moderate problems), Level 4 (indicating severe problems), and Level 5 (indicating extreme problems). EQ-5D-5L health status, defined by the EQ-5D-5L descriptive system, will be converted into a single preference –weighted health status or "utility" index score by applying country-specific weights (if available) or U.S. weights (if not available).

The EQ VAS records the respondent's self-rated health on a visual analogue scale (0 to 100). The VAS score will be measured separately.

Mean change from baseline in EQ-5D-5L "utility" index score to each applicable post-baseline time point, and to the final measurement will be presented by treatment arm. The treatment group difference will be evaluated by analyzing the change from baseline using a one-way analysis of variance (ANOVA) model including stratification factors and baseline as covariates. The same methodology will apply to the mean change from baseline in VAS score.

11.3 Sensitivity Analyses

Sensitivity analyses will be conducted to evaluate the robustness of efficacy results. OS and PFS (by CRAC) will be analyzed in the PPS.

A sensitivity analysis of PFS will be performed based on investigator-assessed disease progression or death from any cause using the Randomized Set. The statistical methodology described in Section 11.1.1 for TTE endpoints will be used.

Sensitivity analyses of investigator-determined ORR will also be performed based on the Randomized Set (ORR analysis will only include the randomized subjects with measureable disease at baseline).

11.4 Subgroup Analyses

For randomized subjects, analysis of OS will be performed in the following subgroups on an as-stratified basis according to stratification data collected at randomization:

- Prior history of brain metastases and PCI (brain metastases, no brain metastases and PCI, no brain metastases nor PCI)
- 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])
- Lactate dehydrogenase (LDH) (> Upper Limit of Normal (ULN) vs. ≤ ULN) at Screening
- Overall Veterans Administration Lung Study Group (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.

12.0 Safety Analysis

12.1 General Considerations

Unless otherwise specified, safety analyses will be performed on the safety set.

Unless specified, all summaries/analyses involving AEs will only include treatment-emergent adverse events (TEAEs). TEAEs are defined as any adverse event with onset or increase in severity after the first dose of study drug (rovalpituzumab tesirine or topotecan) but no more than 70 days after the last dose of study drug administration.

A summary of continuous safety endpoints (e.g., change from baseline values in laboratory values, vital signs parameters) will include the mean, standard deviation, median and range. In the context of change from baseline analyses, summary of baseline and post-baseline data will also be provided. Categorical safety endpoints (e.g., incidence of AEs or clinically significant ECG values) will be summarized using frequencies and percentages. All the analyses will be carried out by treatment group.

Unscheduled assessment will not be included in the summary of change from baseline, but will be included in producing shift tables and summary of lab abnormalities.

12.2 Analysis of Adverse Events

Adverse Event Overview

The number and percentage of subjects experiencing TEAEs between the treatment groups will be summarized for the following adverse event categories.

- TEAEs
- NCI toxicity (maximum) grade 3 or 4 TEAEs
- Drug-related TEAEs
- NCI toxicity (maximum) grade 3 or 4 drug-related TEAEs
- Serious TEAEs
- NCI toxicity (maximum) grade 3 or 4 serious TEAEs

- Drug-related serious TEAEs
- TEAEs leading to discontinuation/reduction/interruption of study drug,
- Drug-related TEAEs leading to discontinuation/reduction/interruption of study drug
- TEAEs leading to death
- Drug-related TEAEs leading to death

Adverse Events by System Organ Class and Preferred Term

The number and percentage of subjects experiencing TEAEs will be tabulated according to the primary MedDRA system organ class (SOC) and MedDRA preferred term (PT) for each treatment group. Subjects reporting more than one adverse event for a given MedDRA PT will be counted only once for that term. Subjects reporting more than one type of adverse event within a MedDRA SOC will be counted only once for that SOC. Subjects reporting more than one type of adverse event will be counted only once in the overall total.

AEs by Preferred Term

The number and percentage of subjects experiencing adverse events will be tabulated according to the MedDRA PT for each treatment group. Subjects reporting more than one AE for a given MedDRA PT will be counted only once for that term.

AEs by Maximum Severity

Adverse events will be summarized by SOC, PT and maximum severity per NCI CTCAE v.4 grading in each treatment arm. If a subject has an AE with unknown severity, then the subject will be counted in the severity category of "unknown," unless the subject does not have another occurrence of the same AE with a severity present. In addition, Grade 3 or higher AE will also be summarized by SOC and PT.

AEs by Relationship

Adverse events possibly related to rovalpituzumab tesirine, dexamethasone, topotecan, as assessed by the investigator, will be summarized separately in each treatment arm. Following summaries will be presented for the AEs possibly related to rovalpituzumab tesirine, dexamethasone, topotecan, separately:

- Summary of AE by PT
- Summary of AE by SOC and PT
- Summary of Grade 3 or higher AE by SOC and PT
- Summary of SAE by SOC and PT
- Summary of rovalpituzumab tesirine discontinuation by SOC and PT (possibly related to rovalpituzumab tesirine only)
- Summary of topotecan discontinuation by SOC and PT (possibly related to topotecan only)

If a subject has an AE with unknown relationship, then the subject will be counted in the relationship category of "unknown," unless the subject does not have another occurrence of the same AE with a relationship present.

12.3 Adverse Events of Special Interest (AESIs)

Specific treatment-emergent AESIs, including important identified risks, will be identified by the search criteria provided in Table 3.

Table 3. Adverse Events of Special Interest

Adverse Event of Special Interest	MedDRA Search Criteria/Codes
Important Identified Risks	
Pleural Effusion	PTs: 10035598 Pleural Effusion 10003522 Aspiration Pleural Cavity 10063045 Effusion
Pericardial Effusion	PTs: 10034474 Pericardial Effusion 10007610 Cardiac Tamponade 10034471 Pericardial Drainage 10063045 Effusion
Generalized Edema	PT 10018092 Generalised Oedema
Photosensitivity Reaction	PT 10034972 Photosensitivity Reaction
Important Potential Risks	
Pneumonitis	PTs: 10035742 Pneumonitis 10035745 Pneumonitis Chemical 10037765 Radiation Pneumonitis 10066728 Acute Interstitial Pneumonitis 10022611 Interstitial Lung Disease
Other AESIs	
Ascites	PT 10003445 Ascites

Table 3. Adverse Events of Special Interest (Continued)

Adverse Event of Special Interest	MedDRA Search Criteria/Codes
Cutaneous Reaction	SOC 10040785 Skin and Subcutaneous Tissue Disorders *The observed TEAEs under this SOC will be medically adjudicated to maintain a list of PTs that are not medically relevant and that will be excluded from the analysis.* *Current list of PTs to exclude:* *10001760 Alopecia* *10002424 Angioedema* *10011985 Decubitus Ulcer* *10014080 Ecchymosis* *10020642 Hyperhidrosis* *10051235 Madarosis* *10070533 Nail Bed Disorder* *10028694 Nail Disorder* *10062283 Nail Ridging* *10028692 Nail Discolouration* *10029410 Night Sweats* *10034754 Petechiae* *10037087 Pruritus* *10052576 Pruritus generalised* *10037549 Purpura* *10042682 Swelling Face*
Thrombocytopenia	SMQ 20000031 Haematopoietic Thrombocytopenia (broad)
Haemorrhages	SMQ 20000039 Haemorrhage Terms (Excluding Laboratory Terms; narrow)
Edema	PTs: 10030095 Oedema 10030124 Oedema Peripheral 10048961 Localised Oedema 10018092 Generalised Oedema 10042674 Swelling 10016807 Fluid Retention 10016803 Fluid Overload 10024770 Local Swelling 10048959 Peripheral Swelling 10007196 Capillary Leak Syndrome 10015993 Eyelid Oedema 10016029 Face Oedema 10052139 Eye Oedema 10034545 Periorbital Oedema

Table 3. Adverse Events of Special Interest (Continued)

Adverse Event of Special Interest	MedDRA Search Criteria/Codes
Hypoalbuminemia	PTs: 10020942 Hypoalbuminaemia 10005287 Blood Albumin Decreased 10005286 Blood Albumin Abnormal
Hepatotoxicity	SMQs: 20000007 Drug-Related Hepatic Disorders (severe events only; broad) 20000009 Cholestastis and Jaundice of Hepatic Origin (broad) 20000008 Liver Related Investigations, Signs and Symptoms (broad) *Exclude PT 10020942 Hypoalbuminaemia from this search since hypoalbuminemia is associated with chronic liver disease and therefore not included in AESI*
Anemia	SMQ 20000029: Haematopoietic Erythropenia (broad)
Neutropenia	SMQ 20000030: Haematopoietic Leukopenia (broad)
Infusion-Related Reaction	PT 10051792 Infusion related reaction
Nephrotoxicity	SMQ 20000003 Acute Renal Failure (broad)
Teratogenicity/Embryotoxicity	SMQ 20000185: Pregnancy and Neonatal Topics (broad)
Abuse Liability*	CMQ: 80000120 Abuse Liability
Febrile Neutropenia (Symptomatic Neutropenia)**	PTs: 10016288 Febrile Neutropenia 10049151 Neutropenic Sepsis 10059482 Neutropenic Infection

* Search performed as needed for the Drug Abuse Liability Assessment (DALA) report.

** Search performed for only patient narratives for specific safety assessments.

Time to onset

Time to onset is the Rx Day of the start date of the first occurrence of AESI. If a subject has not experienced an AESI, the subject will be censored on the day of the subject's last assessment (i.e., the day of the subject's last known laboratory assessment, last known vital sign assessment, last known physical exam, last known tumor assessment, or last known follow-up visit, whichever is the latest) or 70 days from the last study drug administered, whichever is earliest; if the subject has not experienced an AESI and had no

post-baseline assessment (i.e., none of laboratory assessment, vital sign assessment, physical exam, or tumor assessment), the subject will be censored on the day of the subject's first study drug.

Median onset time will be estimated using a Kaplan-Meier method with corresponding 95% CI for the median for each treatment arm.

12.3.1 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

SAEs and AEs leading to rovalpituzumab tesirine, dexamethasone, topotecan, dose reduction and dose interruption will be summarized separately by SOC and PT in each treatment arm. Separate listings for SAEs, AEs leading to death and AEs leading to treatment discontinuation will also be provided.

12.3.2 Listing of Adverse Events

The following additional summaries of adverse events will be prepared.

- Listing of treatment-emergent serious adverse events
- Listing of treatment-emergent adverse events that lead to discontinuation of study drug
- Listing of treatment-emergent fatal adverse events
- Listing of Grade 3 or higher adverse events

12.3.3 Deaths

The number and percentage of subject deaths will be summarized by treatment Arm 1) for deaths occurring while the subject was still receiving study drug (rovalpituzumab tesirine, dexamethasone, topotecan); 2) for deaths occurring off-treatment; 3) for deaths occurring ≤ 70 days after treatment stopped; 4) for deaths occurring > 70 days after treatment stopped. Primary cause of death will also be presented.

12.4 Analysis of Laboratory, Vital Signs, and ECG Data

Clinical laboratory variables are listed in Table 4.

For laboratory (hematology, chemistry, urinalysis, and coagulation), vital signs, and ECG parameters, changes from baseline are analyzed for each post-baseline visit (as specified in Section 7.0 Analysis of Conventions) and the final visit. If more than one measurement exists for a subject on a particular day, an arithmetic average will be calculated. The average will be considered to be the subject's measurement of that day.

Descriptive statistics will be presented for baseline, each post-baseline, and the final visit by each treatment arm. Mean change from baseline to each post-baseline visit and the final visit within each treatment arm will also be presented. The highest and lowest values of each parameter will be identified for each subject, and descriptive statistics for mean change from baseline within each treatment arm will be presented.

Laboratory grade determinations will be categorized according to NCI CTCAE version 4.0 grades, and shifts from baseline grades to maximum and final post-baseline grades will be assessed. The baseline and final grades will be defined respectively as the grade of the last measurement collected prior to or on the first dose of study drug, and as the grade of the last post-baseline measurement collected no more than 70 days after the last dose of study drug. Frequency and percentage of subjects will be presented by treatment arm: 1) baseline grade vs. maximum post-baseline grades, and 2) baseline grade vs. final post-baseline grade. Frequency and percentage of subjects experiencing a shift from baseline grades of 0 to 2 to maximum post-baseline grades of 3 to 4, and from baseline grades of 0 to 2 to final post-baseline grades of 3 to 4 will be presented by treatment arm.

Detailed listings of data for subjects experiencing NCI CTCAE grade 3 to 4 biochemistry and hematology values will be provided. All measurements collected, regardless of the number of days after the last dose of study drug, will be included in these listings. A

listing will be provided for out-of-normal range as well as clinically significant abnormal lab values.

Descriptive summary statistics for categorical ECG data will be presented for baseline and post-baseline visits; change from baseline in ECG measurements (eg QTcF) will also be summarized. Shift tables will also be provided.

Table 4. 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)

12.5 Analysis of 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 will be tabulated.

12.6 Analysis of Vital Signs Using Criteria for Potentially Clinically Significant Vital Sign Values

Vital signs values will be assessed for potential clinical significance through the application of criteria developed by the sponsor as detailed in the table below.

Systolic Blood Pressure	> 150 mmHg and > 20 mmHg higher than baseline < 70 mmHg and a decrease of ≥ 30 mmHg from baseline
Diastolic Blood Pressure	> 100 mmHg and higher than baseline < 50 mmHg and a decrease of ≥ 20 mmHg from baseline
Pulse Rate	> 120 bpm and an increase of ≥ 30 bpm from baseline < 50 bpm and a decrease of ≥ 30 bpm from baseline
Temperature	≥ 38.9°C ≤ 35.6°C

The number and percentage of subjects with post baseline values meeting Criteria for Potentially Clinically Significant Vital Signs values will be summarized. Except for the temperature, subjects who have a baseline measurement and at least one post-baseline measurement will be included in the summary. A separate listing will be provided that presents all of the subjects and values that meeting the criteria. No comparisons of the rates of subjects met the above criteria between the treatment arms will be performed.

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Appendix A. 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[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			

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)
	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			
	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										

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)
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 Protocol 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 in the Protocol 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 Protocol 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 in the Protocol). 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).

Appendix B. 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[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]											

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)
	Urinalysis[i]	X	X[j]											
	Pregnancy Test[k]	X	X								X	X		
	Electrocardiogram (ECG)[–l]	X									X			
	Echocardiogram	X	X[m]								X			
	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							

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)
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
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 in the Protocol 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 Protocol 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 in the Protocol). 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).