THE LANCET Oncology

Supplementary appendix

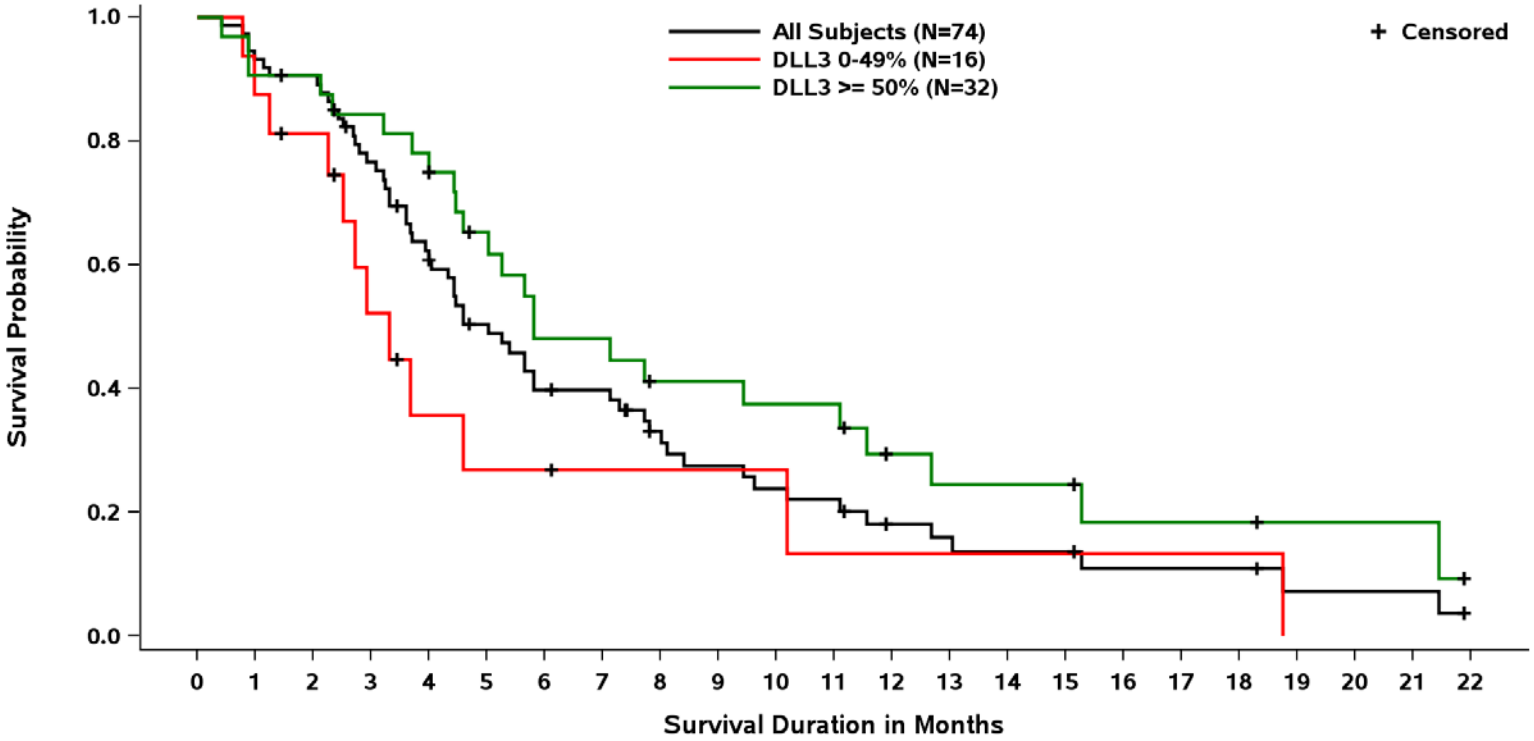
This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Rudin CM, Pietanza MC, Bauer TM, et al, for the SCRX16-001 investigators. Rovalpituzumab tesirine, a DLL3-targeted antibody-drug conjugate, in recurrent small-cell lung cancer: a first-in-human, first-in-class, open-label, phase 1 study. *Lancet Oncol* 2016; published online Dec 5. http://dx.doi.org/10.1016/S1470-2045(16)30565-4.

Supplementary Appendix

Item	Page
Figure S1. Kaplan-Meier Overall Survival of all SCLC Subjects	2
Figure S2. Kaplan-Meier Overall Survival of all SCLC Subjects Dosed 0.2-0.4 mg/kg	3
Table S1. Sites, Investigators, and Enrolment	4
Table S2. Dose Regimen Cohorts in the Study	5
Table S3. Single-Dose Pharmacokinetics of Rovalpituzumab Tesirine Antibody-Drug Conjugate	6
Table S4. Single-Dose Pharmacokinetics of Total Antibody (TAb)	7
Table S5. Multiple-Dose Pharmacokinetics of the Rovalpituzumab Tesirine Antibody-Drug Conjugate	8
Table S6. Activity Outcomes in All Response-Evaluable Subjects per Investigator	9
Table S7. Activity Outcomes in Response-Evaluable Subjects by Line of Therapy per Investigator	10
Table S8. Summary of Treatment-Emergent Adverse Events	11
Table S9. Incidence of Treatment-Emergent Adverse Events by Highest Reported Severity	12
Table S10. Incidence of Drug-Related Treatment-Emergent Adverse Events by Highest Reported Severity	19
Table S11. Incidence of Treatment-Emergent Serious Adverse Events by Highest Reported Severity	23
Table S12. Incidence of Drug-Related Treatment-Emergent Serious Adverse Events by Highest Reported Severity	25
Table S13. Adverse Events Leading to Drug Withdrawal	26
Table S14. Table of Deaths	27

Figure S1. Kaplan-Meier Overall Survival of all SCLC Subjects



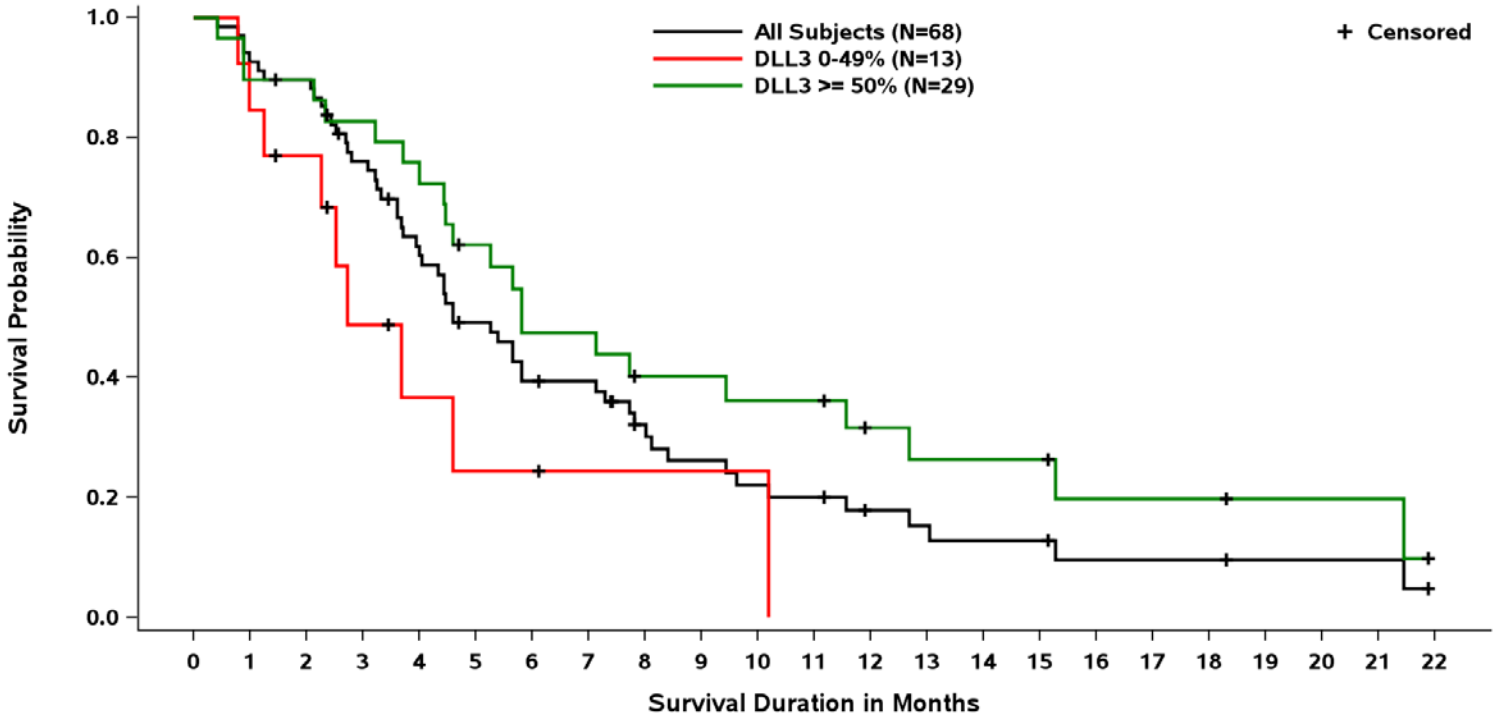
(At Risk)

All Subjects	74	69	66	54	43	33	26	25	18	15	13	12	8	7	6	6	4	4	4	2	2	2	0
DLL3 0-49%	16	14	12	7	4	3	3	2	2	2	2	1	1	1	1	1	1	1	1	0			
DLL3 >= 50%	32	29	29	27	25	19	14	14	11	11	10	10	6	5	5	5	3	3	3	2	2	2	0

(Censored)

All Subjects	0	0	1	3	4	6	6	7	10	10	10	10	12	12	12	12	13	13	13	14	14	14	15
DLL3 0-49%	0	0	1	2	3	3	3	4	4	4	4	4	4	4	4	4	4	4	4	4			
DLL3 >= 50%	0	0	0	0	0	2	2	2	3	3	3	3	5	5	5	5	6	6	6	7	7	7	8

Figure S2. Kaplan-Meier Overall Survival of all SCLC Subjects Dosed 0.2-0.4 mg/kg



(At Risk)

All Subjects	68	63	60	49	39	30	24	23	16	13	11	10	7	6	5	5	3	3	3	2	2	2	0
DLL3 0-49%	13	11	9	5	3	2	2	1	1	1	1	0											
DLL3 >= 50%	29	26	26	24	22	17	13	13	10	10	9	9	6	5	5	5	3	3	3	2	2	2	0

(Censored)

All Subjects	0	0	1	3	4	5	5	6	9	9	9	9	11	11	11	11	12	12	12	13	13	13	14
DLL3 0-49%	0	0	1	2	3	3	3	4	4	4	4	4											
DLL3 >= 50%	0	0	0	0	0	1	1	1	2	2	2	2	4	4	4	4	5	5	5	6	6	6	7

Table S1. Sites, Investigators, and Enrolment

Site / Institution	Investigator(s)	Number of Patients Treated
Memorial Sloan Kettering Cancer Center, New York, NY	Charles M. Rudin M. Catherine Pietanza	21
Tennessee Oncology, PLLC., Nashville, TN / Sarah Cannon Research Institute, Nashville, TN	David R. Spigel Todd M. Bauer Melissa L. Johnson Howard A. Burris III	20
Duke University Medical Center, Durham, NC	Neal Ready	10
Washington University School of Medicine in St. Louis, St. Louis, MO	Daniel Morgensztern Ramaswamy Govindan	6
The University of Texas MD Anderson Cancer Center, Houston, TX	Bonnie S. Glisson Lauren A. Byers	6
Florida Cancer Specialists, Sarasota, FL	Manish Patel	6
University of Chicago, Chicago, IL	Ravi Salgia	5
The University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL	Francisco Robert	4
Blue Ridge Cancer Care, Roanoke, VA	Mark Kochendorfer	4

Table S2. Dose Regimen Cohorts in the Study

				Doses Received			
Dose (mg/kg)	**Schedule**	**n**	**Purpose**	**1**	**2**	**3**	**4+**
0.05	q3w	3	Dose escalation	-	-	-	3
0.1	q3w	1	Dose escalation	-	1	-	-
0.2	q3w	25	Dose escalation and expansion	4	9	6	6
0.4	q3w	3	Dose escalation	0	2	1	-
0.8	q3w	2	Dose escalation	2	-	-	-
0.4	q6w	3	Dose (de)escalation	1	1	-	1
0.3	q6w	45	Dose (de)escalation and expansion	16	18	8	3

q3w, every 3 weeks; q6w, every 6 weeks
Dose escalation and expansion included both SCLC (n=74) and LCNEC (n=8) subjects.

Table S3. Single-Dose Pharmacokinetics of Rovalpituzumab Tesirine Antibody-Drug Conjugate

Dose	Schedule	N	$AUC_{0-\tau}$ (d·μg/mL)	$AUC_{0-\infty}$ (d·μg/mL)	C_{max} (μg/mL)	T_{max} (d)	Half-life (d)	CL (mL/d/kg)	V_{ss} (mL/kg)
0.05	q3w	3	9.0 (17)	12.1 (20)	1.3 (13)	0.042 (179)	11.3 (12)	4.4 (16)	67.9 (12)
0.1	q3w	1	16.7 (-)	26.2 (–)	2.4 (–)	0.024 (–)	15.6 (–)	3.9 (–)	80.5 (–)
0.2	q3w	11	31.5 (20)	47.8 (28)	4.9 (22)	0.040 (166)	13.9 (37)	4.2 (28)	78.6 (27)
0.4	q3w	3	65.9 (18)	99.1 (27)	8.8 (7)	0.042 (179)	12.6 (15)	4.0 (26)	74.0 (13)
0.8	q3w	2	110.2 (13)	142.2 (19)	18.8 (27)	0.023 (6)	9.7 (14)	5.6 (20)	77.3 (6)
0.2	q6w	8	40.5 (30)	43.5 (33)	5.6 (16)	0.038 (115)	10.2 (30)	4.7 (33)	63.5 (19)
0.3	q6w	10	58.7 (31)	66.5 (38)	7.7 (20)	0.027 (86)	12.6 (51)	4.5 (38)	74.2 (24)
0.4	q6w	3	96.2 (39)	109.5 (38)	11.4 (27)	0.021 (32)	14.3 (1)	3.6 (37)	68.1 (40)

τ = 21 d for the q3w schedule and 42 d for the q6w schedule. Geometric mean (% coefficient of variation of the geometric mean) are presented.

Table S4. Single-Dose Pharmacokinetics of Total Antibody (TAb)

Dose	Schedule	N	$AUC_{0-\tau}$ (d·µg/mL)	$AUC_{0-\infty}$ (d·µg/mL)	C_{max} (µg/mL)	T_{max} (d)	Half-life (d)	CL (mL/d/kg)	V_{ss} (mL/kg)
0.05	q3w	3	10.8 (9)	16.5 (8)	1.4 (8)	0.042 (179)	14.2 (15)	3.2 (5)	63.3 (12)
0.1	q3w	1	17.3 (–)	37.2 (–)	2.2 (–)	0.024 (–)	25.1 (–)	2.7 (–)	93.8 (–)
0.2	q3w	11	34.6 (21)	58.1 (37)	4.6 (18)	0.047 (180)	15.4 (47)	3.4 (37)	75.2 (23)
0.4	q3w	3	76.4 (11)	118.0 (18)	9.8 (21)	0.021 (3)	13.3 (15)	3.4 (18)	65.9 (14)
0.8	q3w	2	128.4 (17)	200.1 (44)	19.0 (20)	0.023 (6)	13.7 (47)	4.0 (46)	78.0 (1)
0.2	q6w	8	50.1 (28)	55.8 (35)	5.9 (13)	0.047 (141)	11.8 (40)	3.6 (35)	58.0 (21)
0.3	q6w	10	70.6 (34)	87.5 (45)	7.6 (19)	0.033 (119)	16.9 (65)	3.4 (46)	74.7 (29)
0.4	q6w	3	108.0 (18)	135.4 (19)	10.4 (17)	0.021 (32)	18.5 (19)	2.9 (18)	74.2 (21)

τ = 21 d for the q3w schedule and 42 d for the q6w schedule. Geometric mean (% coefficient of variation of the geometric mean) are presented.

Table S5. Multiple-Dose Pharmacokinetics of the Rovalpituzumab Tesirine Antibody-Drug Conjugate

Dose	Schedule	N	$AUC_{0-\tau}$ (d·μg/mL)	C_{max} (μg/mL)	T_{max} (d)	Half-life (d)
0.05	q3w	3	14.3 (8)	1.5 (1)	0.046 (154)	12.4 (8)
0.1	q3w	1	-[a]	2.9 (–)	0.024 (-)	6.6 (–)
0.2	q3w	2	53.4 (35)	6.3 (16)	0.027 (18)	11.8 (39)
0.2	q6w	2	52.0 (3)	7.2 (3)	0.019 (15)	6.0 (4)
0.3	q6w	1	69.1 (–)	6.6 (–)	0.015 (–)	15.2 (–)

τ = 21 d for the q3w schedule and 42 d for the q6w schedule. Geometric mean (% coefficient of variation of the geometric mean) are presented.

a) Insufficient data to estimate

Table S6. Activity Outcomes in All Response-Evaluable Subjects per Investigator

	Per Investigator			Per Central Review		
DLL3 Expression	**All**	**0-49%**	**≥ 50%**	**All**	**0-49%**	**≥ 50%**
Number Evaluable	65	10	29	59	7	28
Confirmed Objective Response (CR+PR)	11 (17%)	0 (0%)	10 (34%)	9 (15%)	0 (0%)	8 (29%)
Confirmed Disease control (CR+PR+SD)	46 (71%)	6 (60%)	26 (90%)	39 (66%)	3 (43%)	24 (86%)
Duration of Response, months (95% CI)	5.6 (2.5-8.3)	0 (-)	4.3 (2.2-15)	4.4 (2.2-6.5)	0 (-)	4.6 (2.2-6.9)
Progression-Free Survival, months (95% CI)	3.1 (2.7-4.1)	2.3 (1.3-3.3)	4.5 (3.0-5.4)	4.1 (2.9-4.9)	2.3 (1.1-3.7)	4.7 (4.1-5.7)

Responses reflect confirmed responses assessed by the investigator or by central review via RECIST version 1.1, based upon two consecutive assessments at least 4 weeks apart, in subjects dosed with any dose of rovalpituzumab tesirine.

Table S7. Activity Outcomes in Response-Evaluable Subjects by Line of Therapy per Investigator

Line of Therapy	**Second Line**			**Third Line**		
DLL3 Expression	**All**	**0-49%**	**≥ 50%**	**All**	**0-49%**	**≥ 50%**
Number Evaluable	32	5	14	28	3	12
Confirmed Objective Response (CR+PR)	4 (13%)	0 (0%)	4 (29%)	7 (25%)	0 (0%)	6 (50%)
Confirmed Disease control (CR+PR+SD)	23 (72%)	2 (40%)	12 (86%)	18 (64%)	2 (67%)	11 (92%)
Duration of Response, months (95% CI)	4.0 (2.9-5.6)	0 (-)	4.0 (2.9-5.6)	6.2 (2.2-15)	0 (-)	5.4 (2.2-15)
Progression-Free Survival, months (95% CI)	3.3 (2.7-4.2)	2.2 (1.3-2.3)	4.3 (2.8-4.9)	2.7 (1.7-4.4)	2.5 (1.7-2.7)	5.6 (2.1-7.8)

Responses reflect confirmed responses assessed by the investigator via RECIST version 1.1, based upon two consecutive assessments at least 4 weeks apart, in subjects dosed 0.2-0.4 mg/kg.

Table S8. Summary of Treatment-Emergent Adverse Events

	All Subjects		Drug-Related		Grade 3+		Drug-Related Grade 3+	
All Treatment Emergent Adverse Event	81	(99%)	73	(89%)	57	(70%)	35	(43%)
Serious Treatment Emergent Adverse Event	41	(50%)	24	(29%)	33	(40%)	17	(21%)
Maximum Severity of Adverse Event								
Grade 1	2	(2%)	10	(12%)	0	(0%)	0	(0%)
Grade 2	22	(27%)	28	(34%)	0	(0%)	0	(0%)
Grade 3	43	(52%)	26	(32%)	43	(52%)	26	(32%)
Grade 4	9	(11%)	7	(9%)	9	(11%)	7	(9%)
Grade 5	5	(6%)	2	(2%)	5	(6%)	2	(2%)
Drug Withdrawal Due to Adverse Event	18	(22%)	14	(17%)	14	(17%)	11	(13%)
Dose Reduced Due to Adverse Event	6	(7%)	6	(7%)	3	(4%)	3	(4%)

Table S9. Incidence of Treatment-Emergent Adverse Events by Highest Reported Severity

SYSTEM ORGAN CLASS Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	21	(28%)	27	(36%)	13	(18%)	0	(0%)	0	(0%)	61	(82%)
Fatigue	10	(14%)	22	(30%)	6	(8%)	0	(0%)	0	(0%)	38	(51%)
Oedema Peripheral	14	(19%)	8	(11%)	2	(3%)	0	(0%)	0	(0%)	24	(32%)
Pyrexia	11	(15%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	12	(16%)
Asthenia	4	(5%)	2	(3%)	3	(4%)	0	(0%)	0	(0%)	9	(12%)
Pain	4	(5%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	6	(8%)
Face Oedema	4	(5%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	5	(7%)
Oedema	1	(1%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Chills	3	(4%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Peripheral Swelling	1	(1%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Local Swelling	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Malaise	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Application Site Irritation	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Catheter Site Pain	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Chest Pain	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Generalised Oedema	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Localised Oedema	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Non-Cardiac Chest Pain	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Performance Status Decreased	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
GASTROINTESTINAL DISORDERS	32	(43%)	15	(20%)	3	(4%)	0	(0%)	0	(0%)	50	(68%)
Constipation	18	(24%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	20	(27%)
Nausea	16	(22%)	5	(7%)	0	(0%)	0	(0%)	0	(0%)	21	(28%)
Vomiting	15	(20%)	4	(5%)	0	(0%)	0	(0%)	0	(0%)	19	(26%)
Diarrhoea	10	(14%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	12	(16%)
Abdominal Pain	6	(8%)	3	(4%)	1	(1%)	0	(0%)	0	(0%)	10	(14%)
Abdominal Distension	2	(3%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	4	(5%)
Dysphagia	4	(5%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	5	(7%)
Dyspepsia	4	(5%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	4	(5%)
Ascites	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Abdominal Discomfort	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Abdominal Pain Upper	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Abdominal Tenderness	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Stomatitis	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Anal Fistula	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Dry Mouth	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Gastrooesophageal Reflux Disease	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Haematochezia	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Haemorrhoids	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Hiatus Hernia	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Lip Blister	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Lip Dry	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)

SYSTEM ORGAN CLASS Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
Lip Swelling	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Mouth Ulceration	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Noninfective Gingivitis	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Odynophagia	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Tongue Ulceration	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	14	(19%)	16	(22%)	18	(24%)	0	(0%)	2	(3%)	50	(68%)
Pleural Effusion	5	(7%)	17	(23%)	6	(8%)	0	(0%)	0	(0%)	28	(38%)
Dyspnoea	5	(7%)	6	(8%)	12	(16%)	0	(0%)	0	(0%)	23	(31%)
Cough	8	(11%)	5	(7%)	0	(0%)	0	(0%)	0	(0%)	13	(18%)
Hypoxia	0	(0%)	1	(1%)	5	(7%)	0	(0%)	1	(1%)	7	(9%)
Productive Cough	3	(4%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	5	(7%)
Dyspnoea Exertional	4	(5%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	4	(5%)
Nasal Congestion	4	(5%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	4	(5%)
Sinus Congestion	4	(5%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	4	(5%)
Epistaxis	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Oropharyngeal Pain	3	(4%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Haemoptysis	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Pulmonary Embolism	0	(0%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	2	(3%)
Dysphonia	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Hiccups	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Lower Respiratory Tract Congestion	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Nasal Discharge Discolouration	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Pneumonitis	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Pulmonary Oedema	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Respiratory Failure	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)
Rhinitis Allergic	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Upper-Airway Cough Syndrome	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Wheezing	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	27	(36%)	12	(16%)	6	(8%)	0	(0%)	0	(0%)	45	(61%)
Rash Maculo-Papular	10	(14%)	1	(1%)	2	(3%)	0	(0%)	0	(0%)	13	(18%)
Erythema	9	(12%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	11	(15%)
Photosensitivity Reaction	2	(3%)	6	(8%)	1	(1%)	0	(0%)	0	(0%)	9	(12%)
Dry Skin	7	(9%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	9	(12%)
Erythema Multiforme	4	(5%)	2	(3%)	1	(1%)	0	(0%)	0	(0%)	7	(9%)
Dermatitis Acneiform	2	(3%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	4	(5%)
Skin Exfoliation	3	(4%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	4	(5%)
Swelling Face	2	(3%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Pruritus	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Skin Hyperpigmentation	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Alopecia	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Dermatitis Bullous	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Palmar-Plantar Erythrodysaesthesia Syndrome	0	(0%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	2	(3%)
Petechiae	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Rash	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)

SYSTEM ORGAN CLASS Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
Rash Erythematous	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Blister	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Blister Rupture	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Ecchymosis	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Pruritus Generalised	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Purpura	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Rash Pruritic	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Skin Discolouration	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Skin Fissures	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Skin Irritation	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Skin Lesion	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Skin Ulcer	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
METABOLISM AND NUTRITION DISORDERS	14	(19%)	13	(18%)	4	(5%)	1	(1%)	0	(0%)	32	(43%)
Decreased Appetite	12	(16%)	6	(8%)	0	(0%)	0	(0%)	0	(0%)	18	(24%)
Hypoalbuminaemia	7	(9%)	7	(9%)	0	(0%)	0	(0%)	0	(0%)	14	(19%)
Dehydration	2	(3%)	1	(1%)	2	(3%)	0	(0%)	0	(0%)	5	(7%)
Hypokalaemia	3	(4%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	5	(7%)
Hyponatraemia	2	(3%)	1	(1%)	1	(1%)	1	(1%)	0	(0%)	5	(7%)
Hyperglycaemia	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Hyperkalaemia	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Hypomagnesaemia	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	25	(34%)	7	(9%)	2	(3%)	0	(0%)	0	(0%)	34	(46%)
Arthralgia	12	(16%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	13	(18%)
Back Pain	4	(5%)	4	(5%)	1	(1%)	0	(0%)	0	(0%)	9	(12%)
Musculoskeletal Chest Pain	5	(7%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	7	(9%)
Pain In Extremity	4	(5%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	6	(8%)
Myalgia	5	(7%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	5	(7%)
Muscular Weakness	2	(3%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Neck Pain	2	(3%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Muscle Spasms	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Musculoskeletal Discomfort	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Musculoskeletal Pain	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Bone Pain	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Coccydynia	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
INVESTIGATIONS	15	(20%)	3	(4%)	10	(14%)	4	(5%)	0	(0%)	32	(43%)
Lipase Increased	2	(3%)	0	(0%)	3	(4%)	4	(5%)	0	(0%)	9	(12%)
Aspartate Aminotransferase Increased	4	(5%)	1	(1%)	1	(1%)	1	(1%)	0	(0%)	7	(9%)
Blood Alkaline Phosphatase Increased	2	(3%)	1	(1%)	2	(3%)	0	(0%)	0	(0%)	5	(7%)
Amylase Increased	2	(3%)	2	(3%)	1	(1%)	0	(0%)	0	(0%)	5	(7%)
Blood Albumin Decreased	4	(5%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	4	(5%)
Weight Decreased	3	(4%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Alanine Aminotransferase Increased	2	(3%)	0	(0%)	1	(1%)	1	(1%)	0	(0%)	4	(5%)

SYSTEM ORGAN CLASS Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
Blood Creatinine Increased	0	(0%)	3	(4%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Platelet Count Decreased	1	(1%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	3	(4%)
Weight Increased	2	(3%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Blood Bilirubin Increased	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Ammonia Increased	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Aspartate Aminotransferase	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Blood Testosterone Decreased	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Blood Urea Increased	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Electrocardiogram St Segment Elevation	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Grip Strength Decreased	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Haemoglobin Decreased	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Liver Function Test Abnormal	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Liver Function Test Increased	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Lymphocyte Count Decreased	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Neutrophil Count Decreased	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Renal Function Test Abnormal	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Troponin Increased	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
White Blood Cell Count Decreased	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	9	(12%)	6	(8%)	5	(7%)	5	(7%)	0	(0%)	25	(34%)
Anaemia	7	(9%)	4	(5%)	3	(4%)	0	(0%)	0	(0%)	14	(19%)
Thrombocytopenia	1	(1%)	3	(4%)	3	(4%)	5	(7%)	0	(0%)	12	(16%)
Neutropenia	0	(0%)	3	(4%)	1	(1%)	0	(0%)	0	(0%)	4	(5%)
Lymphadenopathy	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Pancytopenia	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Thrombotic Thrombocytopenic Purpura	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
INFECTIONS AND INFESTATIONS	7	(9%)	11	(15%)	4	(5%)	2	(3%)	1	(1%)	25	(34%)
Upper Respiratory Tract Infection	2	(3%)	3	(4%)	0	(0%)	0	(0%)	0	(0%)	5	(7%)
Pneumonia	0	(0%)	1	(1%)	3	(4%)	0	(0%)	0	(0%)	4	(5%)
Urinary Tract Infection	2	(3%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	4	(5%)
Sinusitis	1	(1%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Bronchitis	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Conjunctivitis	1	(1%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	2	(3%)
Candida Infection	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Cellulitis	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Cholangitis Infective	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Eye Infection	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Fungal Skin Infection	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Gastroenteritis Viral	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Infection	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Oral Candidiasis	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Otitis Externa	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Pneumocystis Jirovecii Pneumonia	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Respiratory Tract Infection	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Sepsis	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)

SYSTEM ORGAN CLASS Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
Skin Infection	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Tooth Infection	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
NERVOUS SYSTEM DISORDERS	19	(26%)	5	(7%)	3	(4%)	0	(0%)	0	(0%)	27	(36%)
Dizziness	8	(11%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	9	(12%)
Headache	8	(11%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	8	(11%)
Dysgeusia	4	(5%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	4	(5%)
Balance Disorder	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Hypoaesthesia	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Neuropathy Peripheral	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Syncope	0	(0%)	0	(0%)	2	(3%)	0	(0%)	0	(0%)	2	(3%)
Ataxia	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Dementia	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Presyncope	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Sciatica	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Seizure	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Somnolence	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Tremor	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Trigeminal Nerve Disorder	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
EYE DISORDERS	17	(23%)	3	(4%)	1	(1%)	0	(0%)	0	(0%)	21	(28%)
Periorbital Oedema	6	(8%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	6	(8%)
Vision Blurred	5	(7%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	7	(9%)
Lacrimation Increased	3	(4%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	4	(5%)
Eye Pruritus	3	(4%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Eye Irritation	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Eye Swelling	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Eyelid Oedema	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Visual Acuity Reduced	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Dry Eye	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Erythema Of Eyelid	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Eye Allergy	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Eye Pain	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Photophobia	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
PSYCHIATRIC DISORDERS	9	(12%)	5	(7%)	1	(1%)	0	(0%)	0	(0%)	15	(20%)
Insomnia	6	(8%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	6	(8%)
Confusional State	3	(4%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	4	(5%)
Anxiety	3	(4%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Depression	2	(3%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Mental Status Changes	0	(0%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Agitation	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Irritability	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Psychotic Disorder	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Restlessness	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)

SYSTEM ORGAN CLASS Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
VASCULAR DISORDERS	3	(4%)	7	(9%)	5	(7%)	1	(1%)	0	(0%)	16	(22%)
Hypotension	3	(4%)	1	(1%)	3	(4%)	1	(1%)	0	(0%)	8	(11%)
Capillary Leak Syndrome	0	(0%)	3	(4%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Deep Vein Thrombosis	0	(0%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Hypertension	0	(0%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	2	(3%)
Embolism	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Flushing	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Orthostatic Hypotension	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Thrombosis	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
CARDIAC DISORDERS	2	(3%)	9	(12%)	1	(1%)	2	(3%)	0	(0%)	14	(19%)
Pericardial Effusion	1	(1%)	7	(9%)	0	(0%)	2	(3%)	0	(0%)	10	(14%)
Atrial Fibrillation	0	(0%)	2	(3%)	1	(1%)	0	(0%)	0	(0%)	3	(4%)
Sinus Tachycardia	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Cardiac Tamponade	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Tachycardia	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	4	(5%)	2	(3%)	2	(3%)	0	(0%)	0	(0%)	8	(11%)
Fall	3	(4%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	5	(7%)
Contusion	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Eye Injury	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Hip Fracture	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Overdose	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Tendon Injury	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
RENAL AND URINARY DISORDERS	2	(3%)	2	(3%)	0	(0%)	0	(0%)	1	(1%)	5	(7%)
Urinary Incontinence	0	(0%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Acute Kidney Injury	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)
Dysuria	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Pollakiuria	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
EAR AND LABYRINTH DISORDERS	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Deafness	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Ear Congestion	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Hypoacusis	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Vertigo	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
HEPATOBILIARY DISORDERS	0	(0%)	1	(1%)	2	(3%)	0	(0%)	0	(0%)	3	(4%)
Cholelithiasis	0	(0%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	2	(3%)
Bile Duct Stenosis	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Cholangitis Acute	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Hepatitis	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Hyperbilirubinaemia	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Jaundice Cholestatic	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)

SYSTEM ORGAN CLASS Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	(0%)	0	(0%)	1	(1%)	1	(1%)	1	(1%)	3	(4%)
Metastases To Spine	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Myelodysplastic Syndrome	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Tumour Haemorrhage	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)
IMMUNE SYSTEM DISORDERS	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Seasonal Allergy	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Breast Pain	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
SURGICAL AND MEDICAL PROCEDURES	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Endotracheal Intubation	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
UNCODED	2	(3%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Bilateral Lower Extremity Tenderness	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Thrush Of Mouth	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Urinary Retention Secondary To Cauda Equine Syndrome	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)

Table S10. Incidence of Drug-Related Treatment-Emergent Adverse Events by Highest Reported Severity

SYSTEM ORGAN CLASS Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	14	(19%)	23	(31%)	6	(8%)	0	(0%)	0	(0%)	43	(58%)
Fatigue	8	(11%)	15	(20%)	3	(4%)	0	(0%)	0	(0%)	26	(35%)
Oedema Peripheral	11	(15%)	7	(9%)	2	(3%)	0	(0%)	0	(0%)	20	(27%)
Face Oedema	3	(4%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	4	(5%)
Oedema	1	(1%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Pyrexia	3	(4%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Asthenia	0	(0%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	2	(3%)
Pain	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Peripheral Swelling	0	(0%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Generalised Oedema	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Localised Oedema	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Malaise	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	21	(28%)	11	(15%)	6	(8%)	0	(0%)	0	(0%)	38	(51%)
Rash Maculo-Papular	9	(12%)	1	(1%)	2	(3%)	0	(0%)	0	(0%)	12	(16%)
Erythema	8	(11%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	10	(14%)
Photosensitivity Reaction	2	(3%)	5	(7%)	1	(1%)	0	(0%)	0	(0%)	8	(11%)
Dry Skin	5	(7%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	7	(9%)
Erythema Multiforme	3	(4%)	2	(3%)	1	(1%)	0	(0%)	0	(0%)	6	(8%)
Dermatitis Acneiform	2	(3%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	4	(5%)
Swelling Face	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Dermatitis Bullous	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Palmar-Plantar Erythrodysaesthesia Syndrome	0	(0%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	2	(3%)
Petechiae	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Pruritus	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Skin Exfoliation	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Blister	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Blister Rupture	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Pruritus Generalised	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Purpura	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Rash	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Rash Erythematous	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Rash Pruritic	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Skin Hyperpigmentation	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Skin Ulcer	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
GASTROINTESTINAL DISORDERS	15	(20%)	9	(12%)	0	(0%)	0	(0%)	0	(0%)	24	(32%)
Nausea	11	(15%)	3	(4%)	0	(0%)	0	(0%)	0	(0%)	14	(19%)
Vomiting	9	(12%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	10	(14%)
Abdominal Distension	1	(1%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Abdominal Pain	0	(0%)	3	(4%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Diarrhoea	3	(4%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Ascites	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)

SYSTEM ORGAN CLASS Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
Constipation	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Abdominal Discomfort	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Abdominal Tenderness	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Gastrooesophageal Reflux Disease	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Lip Blister	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Lip Dry	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Lip Swelling	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Mouth Ulceration	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Stomatitis	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Tongue Ulceration	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5	(7%)	14	(19%)	7	(9%)	0	(0%)	0	(0%)	26	(35%)
Pleural Effusion	4	(5%)	13	(18%)	6	(8%)	0	(0%)	0	(0%)	23	(31%)
Dyspnoea	3	(4%)	3	(4%)	2	(3%)	0	(0%)	0	(0%)	8	(11%)
Cough	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Haemoptysis	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Hypoxia	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Pulmonary Oedema	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
INVESTIGATIONS	10	(14%)	3	(4%)	7	(9%)	3	(4%)	0	(0%)	23	(31%)
Aspartate Aminotransferase Increased	4	(5%)	1	(1%)	1	(1%)	1	(1%)	0	(0%)	7	(9%)
Lipase Increased	1	(1%)	0	(0%)	2	(3%)	3	(4%)	0	(0%)	6	(8%)
Blood Alkaline Phosphatase Increased	2	(3%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	4	(5%)
Alanine Aminotransferase Increased	2	(3%)	0	(0%)	1	(1%)	1	(1%)	0	(0%)	4	(5%)
Blood Albumin Decreased	3	(4%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Weight Decreased	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Amylase Increased	1	(1%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	3	(4%)
Platelet Count Decreased	1	(1%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	3	(4%)
Weight Increased	2	(3%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Blood Creatinine Increased	0	(0%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Aspartate Aminotransferase	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Electrocardiogram St Segment Elevation	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Haemoglobin Decreased	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Liver Function Test Abnormal	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Neutrophil Count Decreased	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Troponin Increased	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
White Blood Cell Count Decreased	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
METABOLISM AND NUTRITION DISORDERS	14	(19%)	8	(11%)	0	(0%)	0	(0%)	0	(0%)	22	(30%)
Hypoalbuminaemia	7	(9%)	6	(8%)	0	(0%)	0	(0%)	0	(0%)	13	(18%)
Decreased Appetite	10	(14%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	12	(16%)
Hyperkalaemia	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Hypokalaemia	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Hypomagnesaemia	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Hyponatraemia	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)

SYSTEM ORGAN CLASS Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
BLOOD AND LYMPHATIC SYSTEM DISORDERS	6	(8%)	5	(7%)	3	(4%)	5	(7%)	0	(0%)	19	(26%)
Thrombocytopenia	1	(1%)	3	(4%)	3	(4%)	5	(7%)	0	(0%)	12	(16%)
Anaemia	5	(7%)	2	(3%)	2	(3%)	0	(0%)	0	(0%)	9	(12%)
Neutropenia	0	(0%)	3	(4%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Pancytopenia	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Thrombotic Thrombocytopenic Purpura	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	12	(16%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	14	(19%)
Arthralgia	8	(11%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	9	(12%)
Myalgia	3	(4%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Pain In Extremity	2	(3%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Back Pain	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Musculoskeletal Chest Pain	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Bone Pain	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Muscle Spasms	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Musculoskeletal Discomfort	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
EYE DISORDERS	11	(15%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	12	(16%)
Periorbital Oedema	6	(8%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	6	(8%)
Eye Irritation	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Eye Pruritus	2	(3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Eyelid Oedema	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Lacrimation Increased	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Dry Eye	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Erythema Of Eyelid	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Eye Pain	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Eye Swelling	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Photophobia	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
CARDIAC DISORDERS	1	(1%)	7	(9%)	0	(0%)	2	(3%)	0	(0%)	10	(14%)
Pericardial Effusion	1	(1%)	6	(8%)	0	(0%)	2	(3%)	0	(0%)	9	(12%)
Atrial Fibrillation	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Cardiac Tamponade	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Sinus Tachycardia	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
NERVOUS SYSTEM DISORDERS	10	(14%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	12	(16%)
Dysgeusia	4	(5%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	4	(5%)
Dizziness	3	(4%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Neuropathy Peripheral	1	(1%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Balance Disorder	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Headache	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Trigeminal Nerve Disorder	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
VASCULAR DISORDERS	1	(1%)	2	(3%)	2	(3%)	1	(1%)	0	(0%)	6	(8%)
Hypotension	1	(1%)	0	(0%)	2	(3%)	1	(1%)	0	(0%)	4	(5%)

SYSTEM ORGAN CLASS Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
Capillary Leak Syndrome	0	(0%)	3	(4%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
INFECTIONS AND INFESTATIONS	0	(0%)	0	(0%)	1	(1%)	1	(1%)	0	(0%)	2	(3%)
Conjunctivitis	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Eye Infection	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Infection	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
HEPATOBILIARY DISORDERS	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Hepatitis	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)
Tumour Haemorrhage	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)
PSYCHIATRIC DISORDERS	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Insomnia	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Mental Status Changes	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
RENAL AND URINARY DISORDERS	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)
Acute Kidney Injury	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)
UNCODED	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Thrush Of Mouth	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)

Table S11. Incidence of Treatment-Emergent Serious Adverse Events by Highest Reported Severity

SYSTEM ORGAN CLASS Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1	(1%)	7	(9%)	11	(15%)	0	(0%)	2	(3%)	21	(28%)
Pleural Effusion	0	(0%)	8	(11%)	6	(8%)	0	(0%)	0	(0%)	14	(19%)
Dyspnoea	0	(0%)	0	(0%)	5	(7%)	0	(0%)	0	(0%)	5	(7%)
Haemoptysis	1	(1%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Hypoxia	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)
Respiratory Failure	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)
CARDIAC DISORDERS	0	(0%)	3	(4%)	1	(1%)	2	(3%)	0	(0%)	6	(8%)
Pericardial Effusion	0	(0%)	3	(4%)	0	(0%)	2	(3%)	0	(0%)	5	(7%)
Atrial Fibrillation	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Cardiac Tamponade	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	(0%)	1	(1%)	5	(7%)	0	(0%)	0	(0%)	6	(8%)
Oedema Peripheral	0	(0%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	2	(3%)
Asthenia	0	(0%)	0	(0%)	2	(3%)	0	(0%)	0	(0%)	2	(3%)
Fatigue	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Oedema	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Pain	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
VASCULAR DISORDERS	0	(0%)	5	(7%)	2	(3%)	1	(1%)	0	(0%)	8	(11%)
Capillary Leak Syndrome	0	(0%)	3	(4%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Hypotension	0	(0%)	0	(0%)	2	(3%)	1	(1%)	0	(0%)	3	(4%)
Deep Vein Thrombosis	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Thrombosis	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
GASTROINTESTINAL DISORDERS	0	(0%)	3	(4%)	1	(1%)	0	(0%)	0	(0%)	4	(5%)
Ascites	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Abdominal Pain	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Anal Fistula	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Diarrhoea	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Dysphagia	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
INFECTIONS AND INFESTATIONS	0	(0%)	0	(0%)	3	(4%)	2	(3%)	1	(1%)	6	(8%)
Pneumonia	0	(0%)	0	(0%)	3	(4%)	0	(0%)	0	(0%)	3	(4%)
Infection	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Pneumocystis Jirovecii Pneumonia	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Sepsis	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	(0%)	0	(0%)	0	(0%)	4	(5%)	0	(0%)	4	(5%)
Thrombocytopenia	0	(0%)	0	(0%)	0	(0%)	4	(5%)	0	(0%)	4	(5%)
Pancytopenia	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)

SYSTEM ORGAN CLASS Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0	(0%)	1	(1%)	2	(3%)	0	(0%)	0	(0%)	3	(4%)
Fall	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Hip Fracture	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Overdose	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
METABOLISM AND NUTRITION DISORDERS	0	(0%)	0	(0%)	2	(3%)	0	(0%)	0	(0%)	2	(3%)
Hypokalaemia	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Dehydration	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
PSYCHIATRIC DISORDERS	0	(0%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Confusional State	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Psychotic Disorder	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
HEPATOBILIARY DISORDERS	0	(0%)	0	(0%)	2	(3%)	0	(0%)	0	(0%)	2	(3%)
Bile Duct Stenosis	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Cholelithiasis	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)	2	(3%)
Myelodysplastic Syndrome	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Tumour Haemorrhage	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)
INVESTIGATIONS	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Liver Function Test Abnormal	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
NERVOUS SYSTEM DISORDERS	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
Dementia	0	(0%)	0	(0%)	1	(1%)	0	(0%)	0	(0%)	1	(1%)
RENAL AND URINARY DISORDERS	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)
Acute Kidney Injury	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)
UNCODED	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Urinary Retention Secondary To Cauda Equine Syndrome	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)

Table S12. Incidence of Drug-Related Treatment-Emergent Serious Adverse Events by Highest Reported Severity

SYSTEM ORGAN CLASS Preferred Term	Grade 1		Grade 2		Grade 3		Grade 4		Grade 5		Total	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0	(0%)	8	(11%)	6	(8%)	0	(0%)	0	(0%)	14	(19%)
Pleural Effusion	0	(0%)	8	(11%)	6	(8%)	0	(0%)	0	(0%)	14	(19%)
Dyspnoea	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
CARDIAC DISORDERS	0	(0%)	3	(4%)	0	(0%)	2	(3%)	0	(0%)	5	(7%)
Pericardial Effusion	0	(0%)	3	(4%)	0	(0%)	2	(3%)	0	(0%)	5	(7%)
Cardiac Tamponade	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	0	(0%)	2	(3%)	1	(1%)	0	(0%)	0	(0%)	3	(4%)
Oedema Peripheral	0	(0%)	1	(1%)	1	(1%)	0	(0%)	0	(0%)	2	(3%)
Fatigue	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)
Oedema	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
VASCULAR DISORDERS	0	(0%)	3	(4%)	1	(1%)	1	(1%)	0	(0%)	5	(7%)
Capillary Leak Syndrome	0	(0%)	3	(4%)	0	(0%)	0	(0%)	0	(0%)	3	(4%)
Hypotension	0	(0%)	0	(0%)	1	(1%)	1	(1%)	0	(0%)	2	(3%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	0	(0%)	0	(0%)	0	(0%)	4	(5%)	0	(0%)	4	(5%)
Thrombocytopenia	0	(0%)	0	(0%)	0	(0%)	3	(4%)	0	(0%)	3	(4%)
Pancytopenia	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
GASTROINTESTINAL DISORDERS	0	(0%)	2	(3%)	0	(0%)	0	(0%)	0	(0%)	2	(3%)
Ascites	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
Abdominal Pain	0	(0%)	1	(1%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)
INFECTIONS AND INFESTATIONS	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Infection	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
INVESTIGATIONS	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
Liver Function Test Abnormal	0	(0%)	0	(0%)	0	(0%)	1	(1%)	0	(0%)	1	(1%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)
Tumour Haemorrhage	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)
RENAL AND URINARY DISORDERS	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)
Acute Kidney Injury	0	(0%)	0	(0%)	0	(0%)	0	(0%)	1	(1%)	1	(1%)

Table S13. Adverse Events Leading to Drug Withdrawal

Preferred Term	All Subjects	
Number of Subjects Reporting at Least One TEAE	18	(22%)
Pleural Effusion	4	(5%)
Pericardial Effusion	2	(2%)
Rash Maculo-Papular	2	(2%)
Abdominal Pain	1	(1%)
Alanine Aminotransferase Increased	1	(1%)
Anal Fistula	1	(1%)
Ascites	1	(1%)
Aspartate Aminotransferase Increased	1	(1%)
Blood Alkaline Phosphatase Increased	1	(1%)
Capillary Leak Syndrome	1	(1%)
Dyspnoea	1	(1%)
Fatigue	1	(1%)
Hypotension	1	(1%)
Liver Function Test Abnormal	1	(1%)
Oedema	1	(1%)
Pain	1	(1%)
Sepsis	1	(1%)
Thrombocytopenia	1	(1%)
Tumour Haemorrhage	1	(1%)

Table S14. Table of Deaths

Cause of Death	**N (%) of All Subjects (N=82)**
Death Due to Disease	56 (68%)
Death Due to AE	4 (5%)
- Death Due to Drug-Related AE	2 (2%)
Unknown	4 (5%)
Other (Bleeding Ulcer)	1 (1%)

Stemcentrx

Clinical Study Protocol

Title:	Phase I/II Open Label Dose Escalation Study of the Safety, Pharmacokinetics, and Preliminary Efficacy of SC16LD6.5 as a Single Agent in Patients with Recurrent Small Cell Lung Cancer
Protocol Number:	SCRX16-001
Investigational Product:	SC16LD6.5 (rovalpituzumab tesirine)
Sponsor:	Stemcentrx, Inc. 450 E. Jamie Court, 3rd Floor South San Francisco, CA 94080 Telephone: 650-491-0120
IND Number:	117510
Sponsor Representative:	Sreeni Yalamanchili, PharmD Telephone: 650-830-0031 e-mail: sreeni.yalamanchili@stemcentrx.com
Medical Monitor	Donald Strickland, M.D. Telephone: 901-517-6082 email: Donald.Strickland2@scri-innovations.com
Protocol Date:	Amendment Revision 5, October 1, 2015
Institution:	
Investigator Name:	_____
Investigator Signature:	_____ Date (DD/MON/YYYY)

Protocol Synopsis

Title:	**Phase I/II Open Label Dose Escalation Study of the Safety, Pharmacokinetics, and Preliminary Efficacy of SC16LD6.5 as a Single Agent in Patients with Recurrent Small Cell Lung Cancer**
Protocol Number:	SCRX16-001
Phase:	I/II
Indication:	Small cell lung cancer that has recurred or progressed following 1st or 2nd line therapy and large cell neuroendocrine carcinoma that has recurred or progressed following therapy.
Study Objectives:	<u>For the Phase I Dose Escalation Phase and Phase Ib Retreatment/Maintenance:</u> Primary objective: • to determine the tolerability, adverse event profile, the maximum tolerated dose (MTD), and dose limiting toxicities (DLTs) of SC16LD6.5 in patients with recurrent small cell lung cancer (SCLC) Secondary objectives: • to characterize the pharmacokinetics of SC16LD6.5 • to characterize the immunogenicity of SC16LD6.5 • to determine the recommended Phase II dose (RP2D) and schedule based on assessment of MTD and observed pharmacokinetics • to describe any clinical anti-tumor activity observed in patients treated with SC16LD6.5 Exploratory objectives: • to evaluate the expression of DLL3 • to characterize the relationship between DLL3 expression levels and clinical benefit • to characterize the pharmacodynamic biomarker γ-H2AX • to evaluate potential prognostic or predictive gene signatures <u>For the Phase II portion of the study</u> Primary objective: • to estimate the objective response rate (ORR), according to RECIST v1.1 criteria, of SC16LD6.5 in patients with recurrent small cell lung cancer Secondary objectives: • to estimate the duration of response, progression-free survival (PFS) and overall survival (OS) • to further characterize the safety profile at the RP2D • to further characterize the pharmacokinetics of SC16LD6.5 at the RP2D • to further characterize the immunogenicity of SC16LD6.5 Exploratory objectives: • to further evaluate the expression of DLL3 • to further characterize the relationship between DLL3 expression levels and clinical benefit • to further characterize the pharmacodynamic biomarker γ-H2AX • to further evaluate potential prognostic or predictive gene signatures

Methods of Assessment:	Standard safety monitoring including physical examination, performance status, vital signs, hematology and clinical chemistry, urinalysis, pharmacokinetic sampling, and standard radiographic tumor assessments (CT or MRI).
Population:	Patients with small cell lung cancer that have progressed during or following 1st or 2nd line therapy for either limited or extensive stage disease or with large cell neuroendocrine carcinoma • ≥ 18 years • life expectancy ≥ 12 weeks • Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 • no 'uncontrolled' CNS metastases • adequate organ function • measurable disease (for phase II portion only)
Drug Description & Study Rationale:	SC16LD6.5 is an antibody drug conjugate comprised of a humanized monoclonal antibody conjugated to a linker-drug. The humanized monoclonal antibody specifically recognizes DLL3 (delta-like ligand 3), a single pass type I transmembrane protein that is expressed on the cell surface of SCLC tumor cells. Conjugated to the antibody is a linker-drug (LD6.5), which is comprised of a pyrrolobenzodiazepine (PBD) derivative drug (D6.5) containing a serum-stable linker. Upon binding to DLL3, SC16LD6.5 internalizes and D6.5 is released via proteolysis of the linker, thereby allowing the drug to exert its cytotoxic effects inside the target tumor cell.
Treatment Regimen:	Phase I-Dose Escalation Portion: SC16LD6.5 will be administered intravenously (IV) to patients with recurrent SCLC. SC16LD6.5 will be given on day 1 of 21 or 42 day treatment cycles. Patients may continue to receive SC16LD6.5 infusions after cycle 1 at their assigned dose level until disease progression, unacceptable toxicity, deterioration of performance status to > 2, or other reasons for study withdrawal develop. A 3-week dosing interval was determined by extrapolating data from the efficacy, PK, and multi-dose Good Laboratory Practice (GLP) toxicology studies in cynomolgus monkeys to humans. Following the initial preliminary assessment of PK in human subjects, a half-life of approximately 11-14 days was identified for SC16LD6.5. Thus, a longer dosing interval of 6 weeks will also be evaluated. Phase Ib-Retreatment and Maintenance: SC16LD6.5 will be administered IV to patients with recurrent SCLC or LCNEC in two cohorts: retreatment and maintenance. In both cohorts, patients will be given a Treatment Course comprising of 0.3 mg/kg on Day 1 of a 42 day (6 week) cycle for two cycles. All patients will be followed for progression and overall survival. Patients who are currently active on study will be re-consented to the retreatment cohort with observation. Patients that progress ≥ 12 weeks from last treatment cycle may be eligible for retreatment with sponsor approval. For the retreatment cohort, patients will be observed on day 1 of every 6 weeks following the completion of the first Treatment Course (2 cycles). Patients will not be eligible to receive additional doses of SC16LD6.5 should disease progression occur within 12 weeks of first Treatment Course completion or unacceptable toxicity, deterioration of ECOG performance status to > 2, or other

reasons for study withdrawal develop. If no unacceptable toxicity develops and patients remain on study, patients will be given another Treatment Course (2 cycles) at the time of documented progression followed by observation for progression and overall survival on day 1 of every six weeks.

For the maintenance cohort, starting with cycle 3, patients will be treated with SC16LD6.5 at 0.1 mg/kg q6week following the first Treatment Course completion. The maintenance dose will be administered until progressive disease, unacceptable toxicity, deterioration of ECOG performance status > 2 or other reasons for study withdrawal develop. All patients will be followed for progression and overall survival.

Phase II-RP2D portion: SC16LD6.5 will be administered intravenously (IV) to patients with recurrent SCLC. SC16LD6.5 will be given at the selected optimal dose and schedule as determined during the phase I portion of the study. Patients will undergo regular tumor assessments and continue to receive SC16LD6.5 infusions at the RP2D until disease progression, unacceptable toxicity, deterioration of performance status to > 2, or other reasons for study withdrawal develop.

Planned Sample Size:

Phase 1-Dose Escalation Portion

In the absence of dose-limiting toxicities this study will evaluate 6 pre-determined dose levels equating to 100% dose escalation steps. Planned dose levels will be 0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg, 0.8 mg/kg, and 1.6 mg/kg. If >1 DLTs are encountered, a dose level mid-way between the last tolerated dose level and the current dose level may be evaluated. No intra-patient dose escalation will occur.

Each dose cohort will enroll approximately 1-6 patients. Once the last evaluable patient has completed 1 cycle of SC16LD6.5 at their allocated dose level, a decision to enroll patients at the next dose level will be made based on toxicity data.

An accelerated titration dose escalation design will be utilized. The first dose level will enroll 3 patients. If no ≥ grade 2 related AEs is noted, subsequent dose cohorts will involve 1-3 patients. Cohorts comprising 1-3 patients will continue until a ≥ grade 2 related AE is observed. At that point a standard “3+3” design will be adopted. If a DLT is seen in any of the 3 patients during the first cycle of a cohort, 3 additional patients will complete 1 cycle at this dose. If a second patient develops a DLT, dose escalation will cease. A final dose level, midway between the last dose level evaluated and the prior tolerated dose level, may be evaluated prior to declaring an MTD. In addition, if a dose level is not tolerated on an every 3 week dosing schedule but the dose level immediately lower is tolerable on an every 3 week schedule, the option to increase the dosing interval to 6 weeks may be explored in addition to *or* in place of exploring an intermediate dose level on a 3 week schedule. If the longer dosing interval improves tolerability, dose escalation may resume with the longer dosing interval.

Additional patients may be added to a cohort(s) to further evaluate long term safety, tolerability, PK and PD and relationship to DLL3 expression.

Phase I will assess the overall risk-to-benefit of one, or more, doses and schedules being considered for the RP2D. This overall risk-to-benefit assessment will involve estimating the proportion of patients able to remain on

study drug for ≥ 12 weeks. Discontinuation of study drug prior to 12 weeks would generally be the result of either unacceptable toxicity or disease progression. Historical estimates of 12 week PFS in studies utilizing topotecan for recurrent SCLC are approximately 50%. Enrollment of approximately 20 patients in the phase I portion of the study will provide a reasonable degree of confidence around the point estimate of 12 week tolerability.

It is anticipated that a minimum of 2 to approximately 90 patients will be required, depending on which dose level the MTD is determined, for the Phase I and Phase Ib portion of the study.

Phase Ib-Retreatment and Maintenance

SCLC
Two cohorts will enroll approximately 10 evaluable (completed one Treatment Course) patients with SCLC or LCNEC per cohort for safety, tolerability, PK, and preliminary anti-tumor activity. Patients who discontinue for PD, AE not related to treatment, or causes other than toxicity related to study drug will be replaced.

LCNEC
Two cohorts will enroll approximately 10 evaluable (completed one Treatment Course) patients with LCNEC will be enrolled for safety, tolerability, PK, and preliminary anti-tumor activity. Patients who discontinue for PD, AE not related to treatment, or causes other than toxicity related to study drug will be replaced

Phase II Portion

For this portion of this study, a Simon's minimax two-stage design employing a binomial distribution is used to calculate the required sample size. The statistical assumptions will require 29 evaluable patients in the first stage and 38 evaluable patients in total. In the first stage, if ≤ 1 ORRs are seen in the first 29 patients, the study will stop any further recruitment and the treatment will be considered as not effective in this setting. However, if ≥ 2 ORRs are seen, an additional 9 patients will be recruited. The treatment will be considered worthy of further investigation if 5 or more ORRs are observed in the 38 patients in total. This sample size provides 90% power with a null hypothesis ORR of 5% versus an alternative hypothesis ORR of 20%, using one-sided testing at a 5% significance level. Assuming that approximately 10-15% of enrolled patients will not undergo post-baseline response assessments, it is anticipated that approximately 45 patients will be enrolled in order to achieve 38 evaluable patients.

Investigational Product: SC16LD6.5 is provided in sterile clear USP Type I 10 cc glass vials designed to deliver 50 mg/vial. Each vial is produced nominally using a 5 mL fill volume, with a protein concentration of 10 mg/mL of SC16LD6.5.

Duration of Treatment: Patients can continue to receive SC16LD6.5 infusions at their allocated dose level until demonstrated radiologic and/or clinically assessed progressive disease, deterioration of performance status to > 2, or until another withdrawal criterion is met.

PK, PD and ATA: Pharmacokinetics
Serum or plasma sampling will be employed to allow characterization of SC16LD6.5, SC16, D6.5, and related analytes pharmacokinetics (PK), anti-therapeutic antibodies (ATA), and determine the relationship between the PK and pharmacodynamic (PD) measurements including those of efficacy and

toxicity on all patients enrolled. Pharmacokinetic profiling will be assessed in all treated subjects. Blood for PK measurements will be drawn based on the dosing schedule:

Phase I-Dose Escalation:
3 week dosing schedule: Blood samples for PK will be collected from all subjects entered into study immediately prior to their first dose of SC16LD6.5 and at multiple time points on Day 1 (Day 1 being the day of infusion). Additional blood for PK measurements will be drawn once each on Days 2, 3, 5, 8, and 15 of Cycle 1. In Cycles 2 and 3, blood will be taken immediately pre (trough) and post (peak) infusion on Day 1. In Cycle 4, additional samples will be collected on Day 1, 8 and 15.

6 week dosing schedule: Blood samples for PK will be collected from all subjects entered into study immediately prior to their first dose of SC16LD6.5 and at multiple time points on Day 1 (Day 1 being the day of infusion). Additional blood for PK measurements will be drawn once each on Days 2, 3, 5, 8, 15, 22 and 29 of Cycle 1. In Cycles 2 and 4, blood will be taken immediately pre (trough) and post (peak) infusion on Day 1. In Cycle 3, additional samples will be collected on Day 1, 8, 15, 22 and 29.

Phase Ib-Retreatment and Maintenance:
Blood samples for PK measurements will be taken pre-dose and at end of infusion at Cycle 1 and Cycle 2 for the first treatment course and at end of study.

When feasible, blood for serum measurements will also occur when a subject comes off study. Approximately 5 mL of blood will be drawn per time point.

A similar sample collection design will be implemented in the Phase II expansion phase based on the PK from Phase I.

Pharmacodynamics and Anti-Therapeutic Antibodies

Phase I-Dose Escalation:
3 and 6 week dosing schedule:
Samples will be collected to evaluate the pharmacodynamic biomarker γ-H2AX. Samples will be collected pre-dose on days 1, and on day 8 of Cycle 1, pre-dose Cycle 2, pre-dose Cycle 3, and pre-dose Cycle 4.

Samples to evaluate ATA will be collected pre-dose for Cycles 1 through 4 and at the end of study.

Phase Ib-Retreatment and Maintenance:
Samples to evaluate ATA will be collected pre-dose for Cycles 1 and 2 and at the end of study.

Reference Therapy: Not applicable

Safety Criteria for Evaluation: Routine clinical and laboratory assessments (including physical examination, performance status, hematology and chemistry labs) will be performed. Adverse event (AE) monitoring will be performed using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03 (CTCAE).

Efficacy Criteria for Evaluation: Efficacy assessments should include a baseline assessment and follow-up assessments every 6 weeks while receiving study drug. Tumor response and progression-free survival will be assessed using standard RECIST v1.1 criteria

(with slight modifications for Phase II portion of the study). If response or stable disease is noted after 18 weeks, tumor assessment intervals may increase to 9 - 12 weeks.

Correlative Science:

Blood: Samples will be collected at baseline and just prior to cycle 3. Assays for DLL3 levels in plasma/serum, enumeration of circulating tumor cells (CTCs) and characterization of target (DLL3) expression in CTCs will be conducted.

Archival Tumor Samples: Formalin-fixed, paraffin embedded specimens, either tumor blocks or ≥10 unstained slides (5-micron thick) will be requested and assayed for DLL3 expression via semi-quantitative IHC. *(If available)*

Fresh Tumor Samples: Patients will undergo appropriate procedures (bronchoscopy or percutaneous biopsy) of primary or metastatic disease. Specimens from two additional passes/biopsies will be requested for the following analyses (*Optional)*:

1) One specimen will be split among two tubes enabling:
   a) downstream quantification of target DLL3
   b) disease-specific gene expression to evaluate prognostic or predictive gene signatures
   c) DLL3 protein expression using an emulsion of tumor protein lysate
2) The second specimen will be placed in formalin/ethanol, fixed and embedded in paraffin for target DLL3 IHC analysis.

Statistical Methods:

The dose escalation portion of the study is designed to make a preliminary assessment of safety, tolerability, pharmacokinetics, and anti-tumor activity of SC16LD6.5. The final analysis will be based on patient data collected through the completion of treatment or early termination, whichever occurs first. Statistical analyses will be primarily descriptive in nature. All summaries will be based on data from the safety population (patients who received at least one dose of SC16LD6.5). Continuous data will be summarized using mean, standard deviation, median, minimum, and maximum. Discrete data will be summarized using frequencies and percentages. All summaries will be presented for all patients and by dose level and schedule.

Determination of the MTD will be achieved according to predetermined study rules as described in the protocol. Statistical hypothesis testing will not be performed.

The phase I expanded portion of the study will assess the overall risk-to-benefit of the RP2D by estimating the proportion of patients able to remain on study drug for ≥12 weeks. Discontinuation of study drug prior to 12 weeks would generally be the result of either unacceptable toxicity or disease progression. Historical estimates of 12 week PFS in studies utilizing topotecan for recurrent SCLC are approximately 50%. Enrollment of approximately 20 patients in the phase I portion of the study will provide a reasonable degree of confidence around the point estimate of 12 week tolerability.

The phase Ib retreatment and maintenance portion of the study will assess the tolerability and a preliminary estimate of the risk-to benefit of the RP2D and tolerability of the maintenance schedule by estimating the proportion of patients able to remain on the maintenance or retreatment study drug for ≥12 weeks without occurrence of unacceptable toxicity. Enrollment of approximately 10 patients with SCLC and 10 patients with LCNEC that are evaluable (completed one Treatment Course) for safety with DLL3 expression per cohort in this

portion of the study will provide a reasonable degree of confidence around the tolerability and safety of SC16LD6.5 retreatment and maintenance and preliminary indications of anti-tumor activity. Patients who experience treatment related unacceptable toxicity during the retreatment or maintenance phase will be discontinued from the study.

The phase II portion of the study will utilize a Simon's minimax 2-stage design based on a primary endpoint of ORR. The statistical assumptions include a null hypothesis of 5%, an alternate hypothesis of 20%, $\alpha = 0.05$, and 90% power. All other efficacy, pharmacokinetic, and safety analyses will be descriptive and based on the appropriately defined study populations (safety, pharmacokinetic, and efficacy populations). Data will be summarized as described above for the dose escalation portion of the study.

Primary Pharmacokinetic Analysis:

For ADC (SC16LD6.5), total antibody (SC16) and free drug (D6.5), the following PK parameters will be estimated: AUC, Cmax, clearance, volume of distribution, Tmax, and half-life. For SC16, AUC, Cmax, half-life, and the ratio of SC16 AUC to SC16LD6.5 AUC will be estimated. For all three analytes, the concentrations below the lower limit of quantification of the assay will be excluded or assigned a numeric value based on the lower reporting limit of the assay. Serum concentrations of SC16LD6.5, D6.5, SC16, and computed PK parameters will be listed by patient and dose group cohort and summarized descriptively (mean, standard deviation, percent coefficient of variation, minimum, maximum). Individual and mean concentration versus time plots will be presented on both linear and logarithmic scales. PK parameters will be determined by the best available techniques that can be applied to all available data. Both non-compartmental analyses and compartmental-based analyses methods will be considered.

Table of Contents

PROTOCOL SYNOPSIS **2**

TABLE OF CONTENTS **9**

ABBREVIATIONS **11**

1 INTRODUCTION **14**

1.1 BACKGROUND 14
1.2 NON-CLINICAL SUMMARY OF SC16LD6.5 19
1.3 SC16LD6.5: TOXICOLOGY STUDIES 22
1.4 DOSE AND SCHEDULE RATIONALE 24
1.5 SMALL CELL LUNG CANCER 24
1.6 CORRELATIVE SCIENCE 25
1.7 POTENTIAL RISKS 26
1.8 STUDY OBJECTIVES 27
1.9 OUTLINE OF STUDY 29

2 INVESTIGATIONAL PLAN **32**

2.1 STUDY TREATMENT 32
2.2 DEFINITION AND DETERMINATION OF DOSE LIMITING TOXICITY (DLT) AND MAXIMUM TOLERATED DOSE (MTD) 33
2.3 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS 35
2.4 STUDY EVALUATIONS 36

3 SELECTION OF STUDY POPULATION **40**

3.1 INCLUSION CRITERIA 40
3.2 EXCLUSION CRITERIA 41

4 TREATMENT PLAN **42**

4.1 AGENT ADMINISTRATION 42
4.2 PRE-MEDICATION 42
4.3 CONCOMITANT MEDICATIONS 42
4.4 DURATION OF THERAPY 42
4.5 TREATMENT DOSE MODIFICATIONS 43

5 AGENT FORMULATIONS AND PROCUREMENT **44**

5.1 PRODUCT NAME 44
5.2 CHEMICAL NAME AND STRUCTURE 44
5.3 MOLECULAR WEIGHT 44
5.4 PHYSICAL CHARACTERISTICS 44
5.5 DOSAGE AND FORMULATION 44
5.6 STUDY AGENT PROCUREMENT 45
5.7 SAFETY PRECAUTIONS 45
5.8 STUDY AGENT STORAGE 45
5.9 SC16LD6.5 PREPARATION 45
5.10 SC16LD6.5 ADMINISTRATION 45

6 STUDY PROCEDURES **46**

6.1 EVALUATIONS AND PROCEDURES 46
6.2 SCREENING VISIT 53
6.3 BLOOD DRAWING FOR PLASMA PHARMACOKINETIC AND PHARMACODYNAMICS ANALYSIS 54
6.4 CLINICAL MONITORING 58
6.5 PROTOCOL VIOLATION DEFINITIONS 58
6.6 PROTOCOL REVISIONS 59

6.7 CLINICAL LABORATORIES 59
6.8 PREGNANCY 59
6.9 REGULATORY COMPLIANCE 59

7 SAFETY 60

7.1 STUDY DRUG WITHDRAWAL CRITERIA/STOPPING RULES 60
7.2 DATA SAFETY MONITORING 60
7.3 ADVERSE EVENTS 60
7.4 SERIOUS ADVERSE EVENTS 61
7.5 SPECIFIC ADVERSE EVENTS 63
7.6 NOTIFICATION ABOUT SERIOUS OR UNEXPECTED ADVERSE EVENTS 63

8 ASSESSMENT OF DISEASE STATUS 66

8.1 RADIOLOGIC ASSESSMENTS 66
8.2 ASSESSMENT OF RESPONSE IN PATIENTS WITH MEASURABLE DISEASE 66

9 ETHICS 67

9.1 ETHICAL CONDUCT OF THE STUDY 67
9.2 PATIENT INFORMED CONSENT AND AUTHORIZATION FOR USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION (PHI) 67

10 STATISTICAL METHODS AND PLANNED ANALYSES 69

10.1 STATISTICAL METHODS 69
10.2 DATA QUALITY ASSURANCE 74

11 STUDY ADMINISTRATION 75

11.1 STUDY INITIATION 75
11.2 STUDY COMPLETION 75
11.3 CLINICAL SUPPLIES 75
11.4 RETENTION OF STUDY RECORDS 75
11.5 PUBLICATION OF STUDY RESULTS 76
11.6 CASE REPORT FORMS (CRFS) AND MONITORING 76
11.7 CONFIDENTIALITY 76

12 REFERENCES 78

13 APPENDICES 79

Abbreviations

Abbreviation	Meaning
ADC	Antibody Drug Conjugate
AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute neutrophil count
AST	Aspartate Transaminase
ATA	Anti-Therapeutic Antibodies
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
C_{max}	Maximum Plasma Concentration
CL	Clearance
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CRO	Contract Research Organization
CTC	Circulating Tumor Cell
CTCAE	Common Terminology Criteria for Adverse Events
D6.5	Stemcentrx's drug toxin, a PBD cytotoxic agent
DAR	Drug-to-Antibody Ratio
DLL3	Delta-Like Ligand 3
DLT	Dose Limiting Toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group (ECOG)
ESA	Erythropoiesis-Stimulating Agent
FDA	Food and Drug Administration
g	Gram(s)
GI50	50% Growth Inhibition
GLP	Good Laboratory Practice(s)
GMP	Good Manufacturing Practice(s)
HR	Heart Rate
Hr	Hour

Abbreviation	Meaning
HNSTD	Highest Non-Severely Toxic Dose
ICF	Informed Consent Form
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
IC_{50}	Concentration at 50% inhibition
IV	Intravenous
kg	Kilogram
LCNEC	Large Cell Neuroendocrine Carcinoma
LD6.5	A PBD derivative, D6.5, containing a serum stable linker
LPI	Last Patient In
µM	Micromolar
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
Min	Minute(s)
mL	Millilitre(s)
msec	Millisecond
MSD	Meso Scale Discovery
MTD	Maximum Tolerated Dose
µ	Micro
NCI	National Cancer Institute
NSCLC	Non Small Cell Lung Cancer
NOAEL	No Observed Adverse Effect Level
ORR	Objective Response Rate
PBD	Pyrrolobenzodiazepine
PDX	Patient-Derived Xenograft
PE	Physical Examination
PFS	Progression Free Survival
PHI	Protected Health Information
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PR	Partial Response

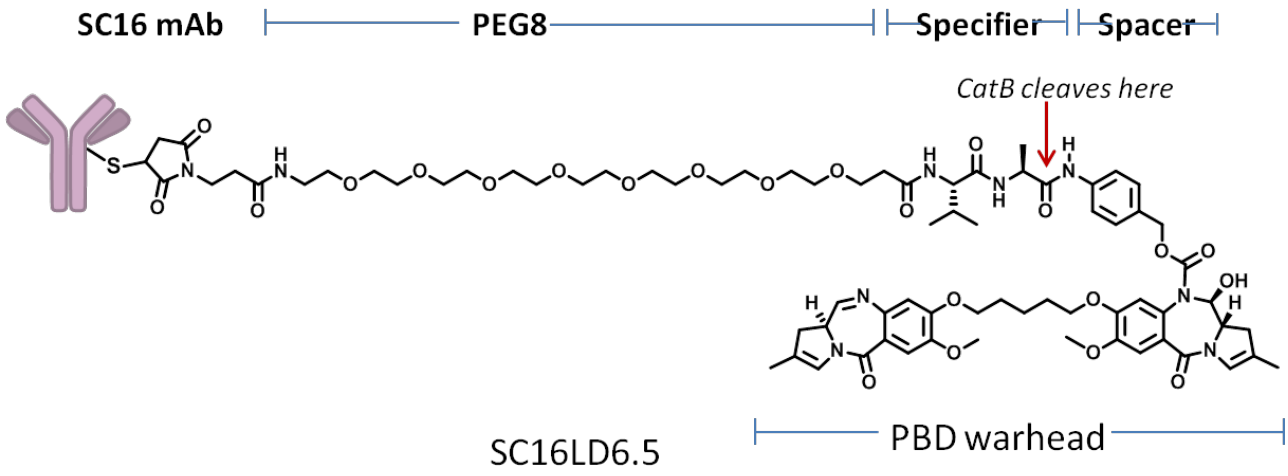
Abbreviation	Meaning
RP2D	Recommended Phase II Dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SC16	Stemcentrx's humanized mAb against the human DLL3 antigen
SC16LD6.5	Stemcentrx's Antibody Drug Conjugate
SCLC	Small Cell Lung Cancer
SCRI	Sarah Cannon Research Institute
SCRX	Stemcentrx
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SLD	Sum of the Longest Diameters
STD	Severe Toxicity Dose
T_{max}	Time of maximum plasma concentration
T½ , t½	Elimination half-life
TTP	Time to Tumor Progression
TPC	Tumor Perpetuating Cells
ULN	Upper Limit of Normal
Vd	Volume of Distribution
Λt	Elimination rate constant

1 INTRODUCTION

1.1 Background

SC16LD6.5 is an antibody-drug conjugate (ADC) consisting of a humanized monoclonal antibody against delta-like ligand 3 (DLL3) conjugated to a pyrrolobenzodiazepine (PBD) dimer (D6.5) via a serum stable linker. It is constructed utilizing a maleimide group for conjugation to the antibody, a PEG linker that serves as a spacer, and a serum stable valine-alanine dipeptide, which serves as a cathepsin B cleavage site for release of the cytotoxic drug (D6.5). Upon binding to DLL3, SC16LD6.5 internalizes and D6.5 is released via proteolysis of the cathepsin B cleavage site (see Figure 1.1). ADCs theoretically enable the precise delivery of highly potent cytotoxic agents to cells expressing the target antigen, thereby combining the best characteristics of biologics (target specificity) and chemotherapy (potent killing activity) and improving the therapeutic index.

Figure 1.1 SC16LD6.5



1.1.1 Pyrrolobenzodiazepines (PBDs)

PBDs are naturally occurring compounds first isolated in the 1960s from Streptomyces. They exhibit antitumor activity via DNA minor groove binding which inhibits both transcription and DNA replication. Synthetic PBD monomers were subsequently developed to remove the cardiotoxic effects of the natural compounds and to enhance potency. More recently, so called ‘PBD dimers’ have been created. These compounds retain the properties of PBD monomers, but can span greater lengths of DNA and form covalent adducts to guanine bases forming both intra-strand and inter-strand cross-links in the DNA resulting in significant increases in *in vitro* cytotoxicity.

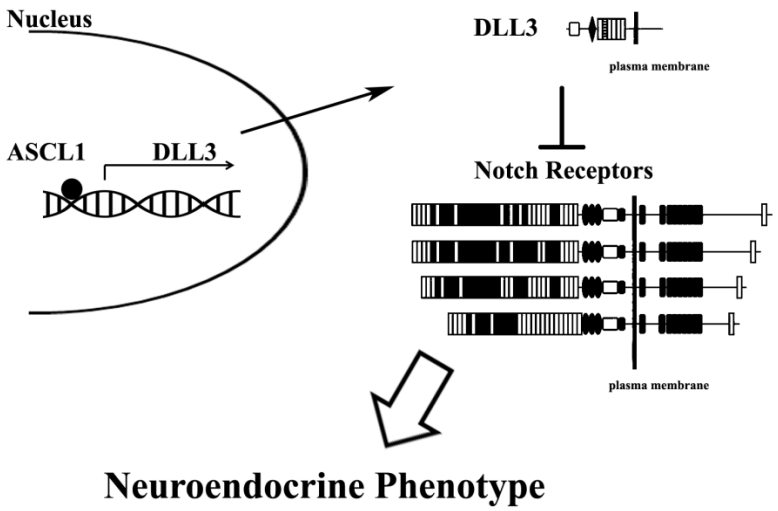
SJG-136 is a second-generation PBD dimer, with a mean *in vitro* GI50 of 7.4 nmol/L that has been studied in humans across multiple doses and schedules (Puzanov et al., 2011; Hartley et al., 2004). Consistent DLTs include vascular leak syndrome, hepatotoxicity, and fatigue and a dose

of 30µg/m^2 daily x 3 every 21 days is currently being evaluated in phase II studies. D6.5, a third-generation PBD dimer, represents further refinement of the chemistry to optimize both selectivity and potency of minor groove binding and DNA cross-links. D6.5 has not been studied in humans; however, a non-human primate repeated dose toxicology study has been conducted (see Section 1.3).

1.1.2 DLL3

The Notch pathway plays a key role in cellular development and fate decisions, including in the diffuse neuroendocrine system and pulmonary neuroendocrine cells. In the developing lung, Notch signalling regulates the differentiation of an airway epithelial precursor with potential for neuroendocrine or Clara cell phenotype. The transcription factor ASCL1 promotes development of pulmonary neuroendocrine cells and its expression peaks near birth and declines in adulthood. Distinctive features of neuroendocrine lung cancer *i.e.* small cell lung cancer (SCLC) and large cell neuroendocrine cancer (LCNEC) are aberrant expression of ASCL1, suppression of the Notch pathway, and expression of a neuroendocrine phenotype (reviewed by Ball DW, 2004; Kunnimalaiyaan M et al., 2007). One transcriptional target of ASCL1 is DLL3, a ligand that suppresses the Notch signalling pathway (see Figure 1.2; Jiang T et al., 2009; Henke RM et al., 2009; Geffers I et al., 2007). DLL3 was identified as a potential ADC target by interrogating next-generation whole transcriptome RNA-sequencing data from a large library of patient-derived explanted human tumors. This analysis revealed DLL3 to be highly overexpressed in SCLC and LCNEC, but with minimal-to-no expression in normal tissues or other non-neuroendocrine tumor types in the library. Therefore, targeting of DLL3-expressing neuroendocrine lung tumors with a therapeutic antibody should selectively kill tumor cells. Blocking DLL3 activity could release suppression of the Notch pathway in poorly-differentiated neuroendocrine tumors, promoting growth arrest, differentiation or other forms of cellular maturation.

Figure 1.2 DLL3 Pathway



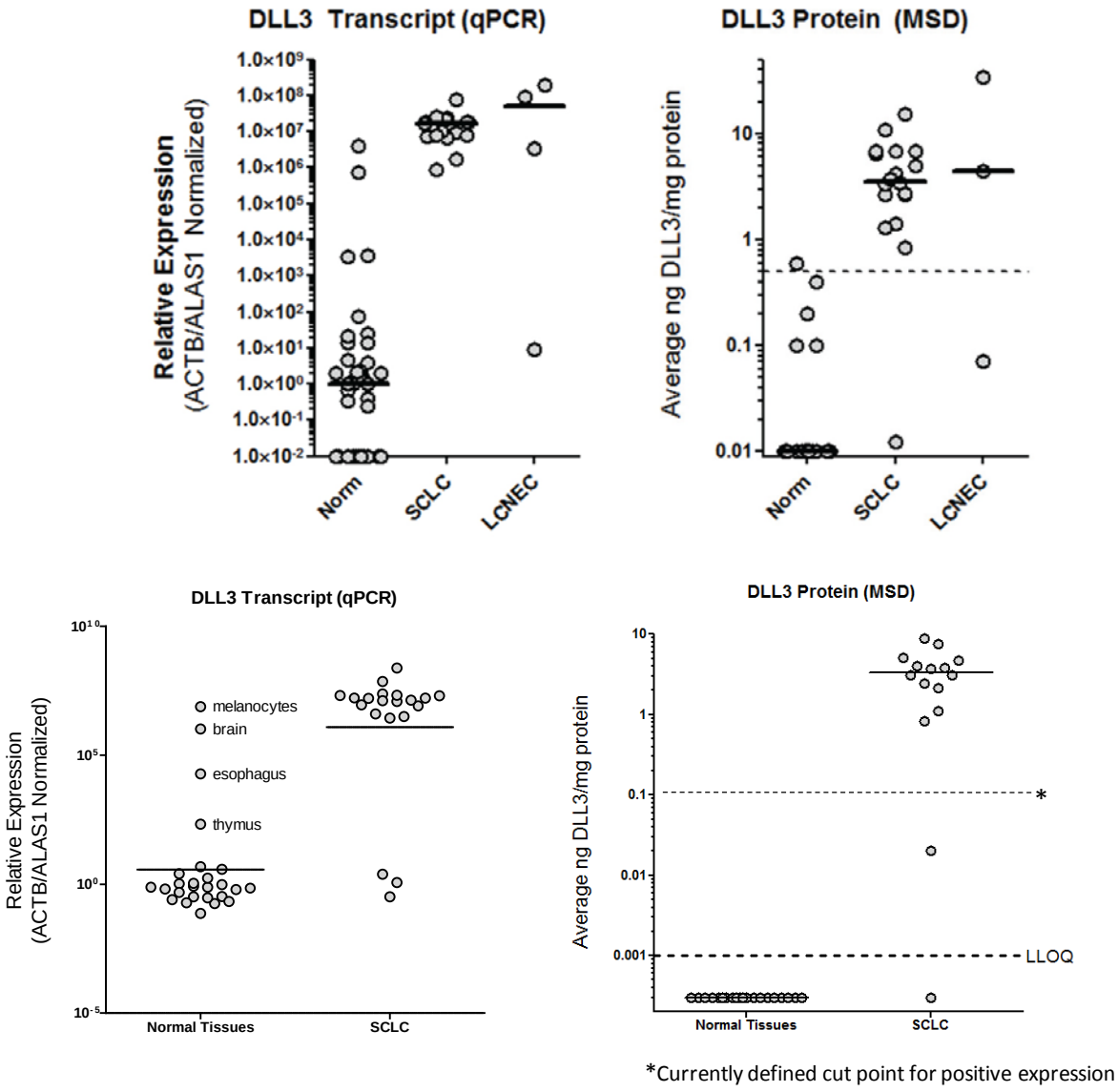
We confirmed that DLL3 mRNA transcript and protein are highly expressed in both SCLC and LCNEC tumors, with minimal expression in normal tissues. Specifically, quantitative PCR (qPCR) measured mRNA transcript levels in patient derived xenograft (PDX) tumors and normal tissues, a Meso Scale Discovery (MSD) antibody sandwich ELISA assay measured protein levels in lysates of PDX tumors and normal tissues, and immunohistochemistry (IHC) measured protein expression and cellular localization of DLL3 (see Table 1.1-1 and Figure 1.3). Additionally, IHC was performed on tissue microarrays (TMA) consisting of cores from SCLC and LCNEC tumors and normal tissues. Analysis of the TMA sections demonstrated that 36 of 44 SCLC and 3 of 3 LCNEC tumors were positive for DLL3 protein expression by IHC, whereas 0 of 27 normal tissues (evaluated in duplicate from two donors) had expression (data not shown). DLL3 mRNA transcript was identified in normal melanocytes, brain, thymus and esophagus; however, DLL3 protein was not detected at levels significantly higher than the limit of detection in these normal tissues by MSD or IHC.

Table 1.1-1 DLL3 Expression in Patient Derived Xenograft Tumors

DLL3 Expression in PDX Tumors			
Tumor Type	**qPCR (Transcript)**	**MSD (Protein)**	**Immunohistochemistry (Protein)**
SCLC	21/21	17/18	8/11
Breast	0/10	0/15	ND
Colon	1/18	1/34	ND
Gastric	3/6	2/4	ND
Kidney	6/10	6/8	2/4
LCNEC	3/4	2/3	2/2
LU-Ad	1/8	1/5	0/1
LU-SCC	5/13	0/5	0/5
Melanoma	9/19	9/14	1/6
Ovarian	4/16	5/11	1/5
Pancreatic	0/9	2/7	ND

*ND = not done

Figure 1.3 DLL3 Expression in Normal Tissues, SCLC, and LCNEC Tumors



SCLC and LCNEC tumors express DLL3 on the cell surface and can be engaged by the DLL3 specific monoclonal antibody SC16, thereby promoting internalization of the SC16LD6.5 ADC and enabling subsequent release of the cytotoxic drug inside the tumor cell. Specifically, SC16LD6.5 reduced both SCLC and LCNEC PDX tumor volumes in mice bearing these tumors, and in many cases prevented tumor recurrence during follow-up observations that extended as long as 200 days after cessation of treatment (see Section 1.2.2). In addition to SCLC and LCNEC, other tumors with neuroendocrine phenotypes express DLL3 and are killed by

SC16LD6.5, including rare gastric, colon, pancreatic, endometrial, kidney and ovarian neuroendocrine subtype tumors.

Tumor perpetuating cells (TPC) are a cell population that has unlimited self-renewal capacity, can initiate new tumors upon serial transplantation, and can differentiate into the heterogeneous mix of cells seen in the originating whole tumor. *In vivo* treatment of mice bearing SCLC tumors with SC16LD6.5 reduced the frequency of TPC that could initiate a new tumor upon serial transplant by 16 - 100 fold compared to the same SCLC tumors treated with a control ADC. Thus, targeting tumor cells expressing DLL3 will kill the critical TPC that have self-renewal capacity and appear relatively resistant to traditional chemotherapies, thereby preventing tumor recurrence.

1.1.3 Anti-DLL3 antibody development

A large library of murine anti-human DLL3 antibodies was generated via immunization of mice with recombinant DLL3-Fc or DLL3-His antigen purified from the supernatant of overexpressing cells. The library was then screened for optimal candidates to identify both a lead therapeutic antibody and a lead formalin fixed, paraffin embedded (FFPE)-compatible diagnostic antibody. Therapeutic optimization was based on binding affinity, internalization, the potency of *in vitro* cytotoxicity with Saporin utilizing DLL3 transfected cell lines, and SCLC PDX tumor cells that endogenously express DLL3. A lead clone was selected, humanized into an IgG1 framework, and maintenance of affinity, internalization, and cytotoxicity was verified. A lead diagnostic antibody was also selected based on sufficient sensitivity and specificity of binding, particularly when utilized within the context of an immunohistochemical (IHC) assay performed with FFPE tissue.

1.2 Non-Clinical Summary of SC16LD6.5

1.2.1 *In Vitro* Summary

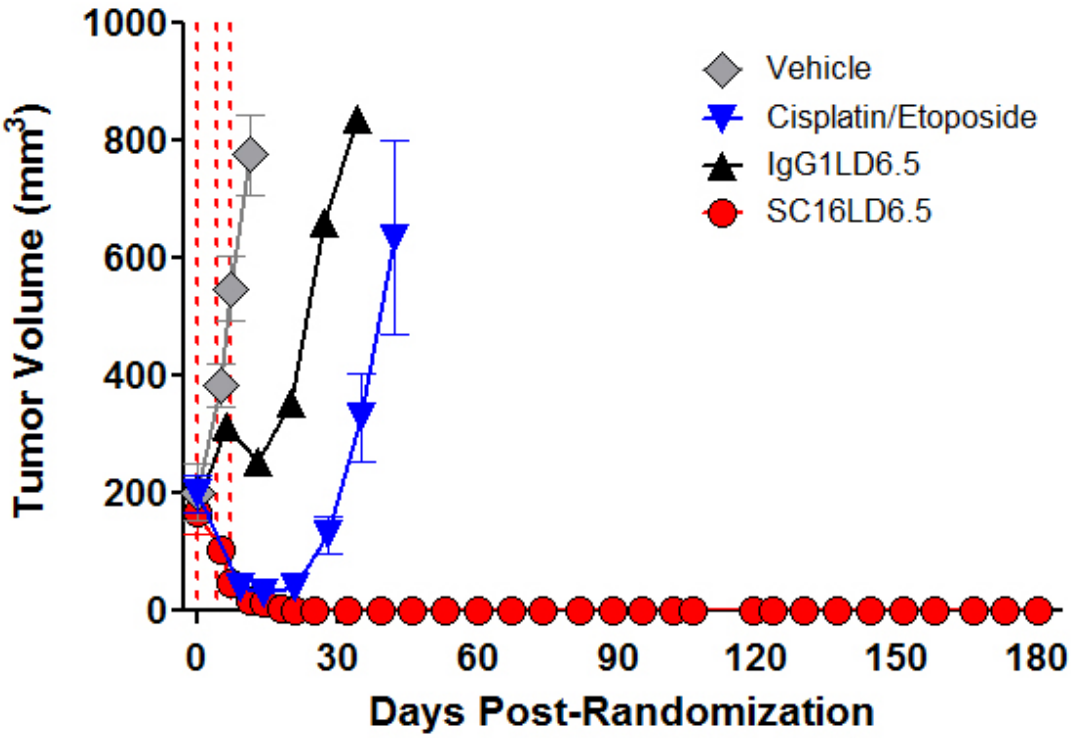
The ADC SC16LD6.5 was generated via proprietary technology conjugating the humanized SC16 antibody and LD6.5. The drug-to-antibody ratio (DAR) is approximately 2. SC16LD6.5 was evaluated *in vitro* and shown to bind, with a nanomolar affinity, specifically to DLL3 on human 293 cells engineered to overexpress human, cynomolgus monkey or rat DLL3, but not naïve parental 293 cells. Additionally, SC16LD6.5 binds to dissociated SCLC tumor cells, but not tumor cells negative for DLL3 expression. To confirm that SC16LD6.5 is internalized via the endocytic route, antibodies against SC16LD6.5 were confirmed to co-localize with SLP-1, a marker of late endosomal compartments. To explore cytotoxic potential, the ability of SC16LD6.5 to kill 293 cells overexpressing human DLL3 was evaluated. SC16LD6.5 killed 293 cells overexpressing DLL3 with an IC50 of 6pM, and had no ability to kill naïve parental 293 cells. It was further demonstrated that SC16LD6.5 mediated the killing of SCLC tumor cells from two patient-derived xenografts that endogenously express DLL3, with an IC50 between 6-8pM. Finally, specificity of SC16LD6.5 for DLL3 was demonstrated by knocking down endogenous DLL3 protein expression on tumor cells using DLL3-targeting hairpins delivered to tumor cells using lentivirus, and demonstrating that SC16LD6.5 was no longer able to mediate killing on these tumors cells lacking DLL3 expression.

1.2.2 *In vivo* Summary

SC16LD6.5 efficacy was evaluated in immunodeficient NOD/SCID mice bearing SCLC patient derived xenografts (PDX) (Figure 1.4). Eleven PDX tumors originating from different SCLC patients, with varying levels of DLL3 expression (Table 1.2-1), were evaluated for *in vivo* efficacy of SC16LD6.5 (1 mg/kg dose; regimen: once every 4 days for total of 3 doses) and compared with *in vivo* response to standard of care (SOC) therapy (dosed near maximum tolerated dose in mice: Cisplatin (5 mg/kg) single dose; Etoposide (8 mg/kg) daily doses for total of 3 doses) (Figure 1.4). In summary, tumor regression and time to progression (TTP; analyzed by the time to tumor recurrence measured in days post initial treatment; Table 1.2-1) was significant ($P < 0.01$) following SC16LD6.5 treatment (average ± SEM TTP: > 95 ± 18 days) compared with SOC therapy (average ± SEM TTP: 20 ± 4 days).

In contrast to SC16LD6.5, response to control ADC (hIgG1LD6.5; 1 mg/kg) was minimal in the majority of SCLC PDX, indicating that the observed SC16LD6.5 therapeutic response was specific to DLL3 targeted therapy and not the conjugated drug. Treatment with excess naked SC16 antibody (30 mg/kg) or drug alone (D6.5) did not result in tumor regression, indicating that the response was specific to the targeted SC16LD6.5 ADC. Taken together, these data show that SC16LD6.5 treatment of DLL3-expressing SCLC PDX tumor-bearing mice results in significant *in vivo* efficacy with longer remission (TTP) compared with standard of care therapy.

Figure 1.4 SCLC PDX Tumor (LU102) Response to SC16LD6.5



SC16LD6.5 1 mg/kg results in durable remission, whereas response to standard of care therapy (Cisplatin, 5 mg/kg single dose; Etoposide 8 mg/kg total of three daily doses) is transient and results in recurrence with short latency.

Table 1.2-1 Summary of DLL3 Expression and *in vivo* Efficacy of SC16LD6.5 Therapy

SCLC PDX	DLL3 Protein Expression		SC16LD6.5 (1 mg/kg Q4Dx3) Efficacy			SOC (Cisplatin-Etoposide) Efficacy	
	IHC	MSD	%TGI	FFP (day 28)	Absolute TTP (days)	FFP (day 28)	Absolute TTP (days)
LU102	HIGH	HIGH	96%	YES	> 181	NO	28
LU95	MED	MED	92%	YES	> 168	NO	2
LU117	HIGH	MED	94%	YES	> 167	NO	21
LU111	MED	HIGH	99%	YES	> 140	NO	22
LU64	HIGH	HIGH	99%	YES	> 119	NO	12
LU124	MED	MED	88%	YES	47	NO	19
LU149	TBD	LOW	91%	YES	> 64	NO	18
LU129	TBD	HIGH	84%	NO	43	YES	52
LU73	LOW	HIGH	75%	NO	47	NO	28
LU80	LOW	LOW	75%	NO	37	NO	14
LU86	MED	MED	95%	NO	32	NO	0

TBD, To Be Determined (experiments are ongoing).
IHC – Low: < 30% positive or negative; Med: 30-60% positive; High: > 60% positive
MSD – Low: < 2.0; Med: 2.0 – 3.5; High: > 3.5 ng/mg
%TGI: percent tumor growth inhibition compared with control-treated animals (vehicle-treated) on the day that the first control animal was sacrificed (tumor volume reached 1000 mm^3). FFP: freedom from progression at 28 days post-initial treatment was scored as YES/NO. TTP: time elapsed between day of first treatment and confident tumor recurrence; TTP with ">" indicate experiments where tumor regrowth has not occurred to date (taken as study end date or 3/25/13 for ongoing studies).

1.3 SC16LD6.5: Toxicology studies

SC16LD6.5 recognizes human, rat and cynomolgus monkey DLL3. The cynomolgus monkey is considered the more pharmacologically relevant species based on binding affinity and sequence homology of DLL3 to human SC16LD6.5 was evaluated in both cynomolgus monkey (GLP) and rat (non-GLP) toxicity studies. The toxicology findings were generally consistent across the two non-human species.

SC16LD6.5 doses in the cynomolgus monkey study were 0.5, 1 and 3 mg/kg and the dosing schedule was every 3 weeks for a total of 3 doses. A subset of animals were allowed a 6-week recovery period to understand the reversibility, persistence, or delayed occurrence of any effects. The relevant findings included:

- Myelosuppression: Transient, dose-related, tri-lineage cytopenias were observed, most notably in the 3 mg/kg group. A single animal in this group exhibited findings consistent with fatal neutropenic sepsis at the end of the first dosing cycle and was euthanized in moribund condition. Similar myelosuppressive dose-dependent findings were observed in animals treated with unconjugated D6.5, suggesting that the toxicity of SC16LD6.5 on the hematopoietic system is antigen-independent and consistent with toxicity due to the cytotoxic component (D6.5) of SC16LD6.5. Additional findings compatible with the mechanism of action of D6.5 and its effect on rapidly proliferating cells included dose dependent cellular necrosis, depletion and/or apoptosis in the thymus, bone, bone marrow, liver, pancreas, and testes. Myelosuppression resolved during the recovery period while other effects on rapidly proliferating cells persisted.

- Renal: Dose-related renal findings were observed at both terminal and recovery necropsies. These findings were characterized by minimal to moderate degeneration in the proximal tubule and glomerulus. With the exception of a single animal at 1 and 3 mg/kg, with moderate tubular and glomerular degeneration, these findings were generally not accompanied by clinical chemistry changes (BUN and creatinine). No abnormalities were observed in routine urinalyses.

- Skin: Dose related skin lesions, in all SC16LD6.5 dose groups, appeared near the end of the first dosing cycle. These were grossly characterized by scattered areas of hyperpigmentation ranging in size from <1 to ~10 cm and predominantly located in the inner thighs and antecubital areas, often near venipuncture sites, but also on the trunk. The number of lesions and apparent clinical severity increased with dose. All of the animals dosed at 3 mg/kg became less mobile, presumably related to pain, and two animals demonstrated sufficient debility to warrant euthanasia. The veterinary staff at the GLP testing facility deemed the remaining 3 mg/kg animals too unfit to receive their second dose of SC16LD6.5. Their general clinical condition improved during a 6 week 'recovery' period prior to necropsy. Skin lesions in animals receiving ≤ 1 mg/kg SC16LD.5 were characterized by hyperpigmentation and acanthosis. Gross clinical

characteristics of skin lesions in the 0.5 and 1 mg/kg animals did not progress in severity during subsequent doses of SC16LD6.5. Hemorrhage, ulceration and dermatitis were only observed in the 3 mg/kg dose group. Further, animals dosed with 3 mg/kg SC16LD6.5 had sections of skin clefts forming at the basal cell and/or basement membrane of the epidermis, leading to epidermal loss and ulceration. Similar lesions of basement membrane clefting were not noted at doses ≤ 1 mg/kg SC16LD.5 and were limited to the 3 mg/kg animals euthanized in moribund condition. Of note, acanthosis was also observed in a single monkey treated with 0.004 and 0.008 mg/kg D6.5, suggesting that the toxicity of SC16LD6.5 associated with the skin lesions may be antigen-independent.

Based on these findings, the highest non-severely toxic dose level (HNSTD) in cynomolgus monkeys was 1 mg/kg.

SC16LD6.5 doses in the rat study were 0, 1, 3 and 5 mg/kg administered every 2-weeks for a total of 2 doses. A subset of animals were allowed a 4-week recovery period to understand the reversibility, persistence, or delayed occurrence of any effects. The relevant findings included:

- Similar, dose-dependent effects on hematopoiesis, rapidly proliferating cellular compartments, and renal tissues were noted. The 5 mg/kg dose level resulted in substantial toxicity/debilitation, including mortality, such that recovery could not be assessed. Skin findings were limited to the 5mg/kg dose level and not considered dose limiting.

- Alveolar histiocytosis was noted in the lungs across all SC16LD6.5 dose groups. The lesion was characterized as ‘sub-acute’ (involving macrophage and neutrophils) or ‘chronic’ (involving alveolar collapse and/or evidence of fibrosis) and scored as minimal, mild, moderate, or marked with respect to the proportion of involved lung. At terminal necropsy (1 week following the second dose), this lesion was not observed at 1 mg/kg, but was noted as a sub-acute, mild lesion in 2/10 animals at 3 mg/kg. At recovery necropsy (4 weeks following the second dose), 1/6 animals had moderate sub-acute lesions and an additional 2/6 animals had chronic, mild lesions at 1 mg/kg; 0/6 animals had sub-acute changes while 6/6 animals had chronic lesions, 5 moderate and 1 marked at 3 mg/kg.

Based on these findings, the STD_{10} in rats was 3 mg/kg.

In summary, intravenous administration of SC16LD6.5 resulted in monitorable and reversible myelosuppression as well as monitorable effects on rapidly proliferating cellular compartments, kidneys, and skin. Lung findings were limited to the rat and judged to be severe in a single animal in the 3 mg/kg dose group.

1.4 Dose and Schedule Rationale

The cynomolgus monkey is considered to be the most pharmacologically relevant of the two species evaluated in pre-clinical toxicology studies. The HNSTD of SC16LD6.5 in this species was established as 1 mg/kg. Higher doses resulted in severe myelosuppression and, in some animals, debilitating skin toxicity. Although toxic effects were noted at the 1 mg/kg dose level, they were generally milder and not considered to be severe. Repeated dosing on a 3 week schedule did not result in worsening, or cumulative, toxicities and full recovery from nadir neutrophil and platelet counts was uniformly observed in the 1 mg/kg dose group at each 3 week post-dose time point. Based on these findings, an initial dosing interval/schedule of 21 days (q3 week cycles) was utilized. However, based on the observation of delayed toxicity along with a preliminary estimated SC16LD6.5 half-life of 11-14 days, a longer dosing interval (6 weeks) will also be assessed.

Based on the study population of advanced, life-threatening recurrent small cell lung cancer, the phase I starting dose will be set using the HNSTD in cynomolgus monkeys using a safety factor of 6. Following standard allometric scaling across species, 1/6 of a 1mg/kg dose in cynomolgus monkeys would correspond to a calculated human dose of ~0.05 mg/kg, which will be the starting dose in this study.

Due to the life-threatening nature of the study population, an accelerated titration dose escalation scheme with 100% increases in dose levels is appropriate in order to more rapidly reach dose levels which may provide therapeutic benefit. Once DLT's are observed, smaller (25-50%) changes in dose levels may be considered.

1.5 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 in the United States. These cancers arise from epithelial cells with neuroendocrine differentiation and, typically, are positive for both cytokeratin and neuroendocrine markers (chromogranin A, NCAM/CD56, etc.); however the diagnosis is usually made by morphologic examination. Unlike non-small cell lung cancer (NSCLC), SCLC can only rarely be cured with local therapy (surgery and/or radiotherapy) alone and systemic chemotherapy remains the cornerstone of therapy for all stages of disease. Historically, SCLC has been divided into 'limited' and 'extensive' stage disease; the former pragmatically defined as disease limited to the chest that can be encompassed by a radiation field while the latter includes all other patients. Approximately 1/3 of newly diagnosed patients will have limited stage disease while 2/3 will be extensive. Standard initial therapy for all patients with a suitable performance status is systemic chemotherapy with a doublet of a platinum salt (carboplatin or cisplatin) in combination with second agent, usually etoposide. For patients with limited stage disease, concurrent or sequential involved field thoracic radiotherapy is indicated. Response rates to initial therapy are quite high, ranging from 70-90% for limited stage and 60-70% for extensive

stage; however recurrence is uniform in the extensive group and very high (~80%) in the limited group leading to median survivals of 9-11 months and 14-20 months respectively. Recurrent SCLC is rapidly fatal (median survival < 6 months) and is typically divided into 2 groups; 'refractory' patients who recur during or shortly after (within 2-3 months) completing a 4-6-cycle course of initial therapy versus 'sensitive' patients, those with later (>2-3 months) recurrences following primary therapy. Although many single agents and chemotherapy combinations have shown some transient evidence of activity in recurrent patients, only topotecan has received FDA approval. This approval was initially for an IV formulation for the sensitive population based on response rates that range between 11% and 31% in the sensitive population, and between 2% and 7% in the refractory population, with a duration of response and overall time to progression of 3-4 months. Subsequently, an oral formulation was approved for both the sensitive and refractory populations, but only for patients 'not deemed suitable for IV chemotherapy', based on a modest survival benefit compared to best supportive care (25.9 versus 13.9 weeks, HR=0.64). The overall response rate in this study was 7% (O'Brien et al., 2006). Based on the very limited clinical benefit provided by topotecan, it is clear that newer approaches are indicated for patients with recurrent SCLC, including both sensitive and resistant groups.

1.6 Correlative Science

Several exploratory correlative science studies are planned as adjuncts to this therapeutic study. Study participants will be required to provide ~ 14-20 mL (2 x 7-10 mL tubes) of whole blood prior to cycle 1 and archival (FFPE) tumor samples (if available) from either the primary, or subsequent tumor biopsies. In addition, all patients will be required to provide an additional 14-20 mL (2 x 7-10 mL tubes) of whole blood just prior to cycle 3, or at study discontinuation, whichever time point occurs first (see the Correlative Science Lab Manual for detailed collection and handling procedures). In addition, study participants will be encouraged to participate in the optional submission of fresh tumor material obtained prior to cycle 1 via a medically appropriate biopsy procedure (bronchoscopy, percutaneous biopsy, FNA, etc.). These specimens will be used to evaluate potential diagnostic and/or prognostic biomarkers by exploring their relationship with baseline disease characteristics and outcome variables:

Blood: Samples will be collected at baseline and just prior to cycle 3. Assays for DLL3 levels in plasma/serum, enumeration of circulating tumor cells (CTCs) and characterization of target (DLL3) expression in CTCs will be conducted. (Required)

Archival Tumor Samples: Formalin-fixed, paraffin embedded specimens, either tumor blocks or≥ 10 unstained slides (5-micron thick) will be requested and assayed for DLL3 expression via semi-quantitative IHC. (*If available*)

Fresh Tumor Samples: Patients will undergo appropriate procedures (bronchoscopy or percutaneous biopsy) of primary or metastatic disease. Specimens from two additional passes/biopsies will be requested for the following analyses (*Optional)*:

1) One specimen will be split among two tubes enabling:
    a. downstream quantification of target DLL3
    b. disease-specific gene expression to evaluate prognostic or predictive gene signatures
    c. DLL3 protein expression using an emulsion of tumor protein lysate
2) The second specimen will be placed in formalin/ethanol, fixed and embedded in paraffin for target DLL3 IHC analysis.

1.7 Potential Risks

The potential risk of toxicity from the starting dose of SC16LD6.5 is low based on the pre-clinical IND enabling toxicology studies. The dose escalation scheme is reasonable and adequate controls are in place to detect, monitor and control any toxicity reported in a timely fashion.

Careful monitoring will be conducted in this study, including frequent clinical assessments, hematologic, chemistry, and urine evaluations. Attention should be paid to the organ systems identified in the GLP toxicology study as potential sources of adverse events; specifically skin, blood counts, lung, and renal effects.

1.8 Study Objectives

Dose Escalation (Phase I) and Retreatment/Maintenance (Phase Ib):

Primary objective:

- to determine the tolerability, adverse event profile, the maximum tolerated dose (MTD), and dose limiting toxicities (DLTs) of SC16LD6.5 in patients with recurrent small cell lung cancer (SCLC)

Secondary objectives:

- to characterize the pharmacokinetics of SC16LD6.5
- to characterize the immunogenicity of SC16LD6.5
- to determine the recommended Phase II dose (RP2D) and schedule based on assessment of MTD and observed pharmacokinetics
- to describe any clinical anti-tumor activity observed in patients treated with SC16LD6.5

Exploratory objectives:

- to evaluate the expression of DLL3
- to characterize the relationship between DLL3 expression levels and clinical benefit
- to characterize the pharmacodynamic biomarker γ-H2AX
- to evaluate potential prognostic or predictive gene signatures

Phase II Portion of the Study:

Primary objective:

- to estimate the objective response rate (ORR) according to RECIST criteria of SC16LD6.5 in patients with recurrent small cell lung cancer

Secondary objectives:

- to estimate the duration of response, progression-free survival (PFS) and overall survival (OS)
- to further characterize the safety profile at the RP2D
- to further characterize the pharmacokinetics of SC16LD6.5 at the relevant clinical dose
- to further characterize the immunogenicity of SC16LD6.5

Exploratory objectives:

- to further evaluate the expression of DLL3
- to further characterize the relationship between DLL3 expression levels and clinical benefit
- to further characterize the pharmacodynamic biomarker γ-H2AX
- to further evaluate potential prognostic or predictive gene signatures

1.9 Outline of Study

SCRX16-001 is a phase I/II, open-label, single agent, non-comparative study that will be conducted at 5-10 clinical sites. The phase I portion is a dose-escalation study with SC16LD6.5 alone for patients with recurrent small cell lung cancer.

Patients will receive SC16LD6.5 intravenously (IV) on day 1 of each 21 or 42 day treatment cycle. If no DLTs are encountered during cycle 1, patients may continue to receive SC16LD6.5 every 21 or 42 days at their allocated dose level until clinical benefit, as assessed by the Investigator, is no longer present or other reasons for study withdrawal develop (see Section 7.1). Deterioration of performance status to > 2 will require study drug discontinuation. No intra-subject dose escalation will be allowed.

Planned dose levels will be 0.05 mg/kg, 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg, 0.8 mg/kg, and 1.6 mg/kg. If DLTs are experienced in ≥ 2 patients at any dose level, dose escalation will cease and a dose level midway between the last tolerated dose level and the current dose level may be evaluated prior to the maximum tolerated dose (MTD) being declared. For instance, if 0.8 mg/kg is tolerated but 1.6 mg/kg is not, then a dose level between 0.8 and 1.6 mg/kg will be evaluated.

For the phase I portion of the study, an accelerated titration design will be utilized. Each cohort will enroll approximately1-6 patients. Once the last evaluable patient has completed 1 cycle of SC16LD6.5 at their allocated dose level, a decision to enroll patients at the next dose level will be made based on toxicity data. During the single patient dose cohorts, if a single ≥ grade 2 related AE is observed, that dose cohort and all subsequent dose cohorts will enroll a minimum of 3 patients. If a DLT is seen in any of the 3 patients during cycle 1, 3 additional patients will complete 1 cycle at that dose level before enrollment would open at the next dose level. If a second patient develops a DLT, dose escalation will cease and an intermediate dose level midway between the last tolerated dose level and the current dose level will be evaluated. In addition, if a dose level is not tolerated on an every 3 week dosing schedule but the dose level immediately lower is tolerable on an every 3 week schedule, the option to increase the dosing interval to 6 weeks may be explored in addition to *or* in place of exploring an intermediate dose level on a 3 week schedule. If the longer dosing interval improves tolerability, dose escalation may resume with the longer dosing interval. Once MTD/RP2D has been established, and a minimum of 6 patients complete at least 1 cycle of therapy at that dose level.

Although DLT will be defined by cycle 1, late toxicity and tolerability will also be assessed by the investigators and Sponsor before determining the RP2D and schedule.

Additional patients may be enrolled as an expansion phase during Phase 1 to further explore PK, PD, tolerability and anti-tumor activity related to the expression of DLL3.

The expanded phase I portion of the study will assess the overall risk-to-benefit of one, or more, doses and schedules being considered for the RP2D. This overall risk-to-benefit assessment will involve estimating the proportion of patients able to remain on study drug for ≥12 weeks. Discontinuation of study drug prior to 12 weeks would generally be the result of either unacceptable toxicity or disease progression. Historical estimates of 12 week PFS in studies utilizing topotecan for recurrent SCLC are approximately 50%. Enrollment of approximately 20 evaluable patients with SCLC and 20 evaluable patients with LCNEC in the phase Ib portion of the study will provide a reasonable degree of confidence around the point estimate of 12 week tolerability.

The phase Ib portion is designed to evaluate SC16LD6.5 in the retreatment and maintenance setting. SC16LD6.5 will be administered IV to patients with recurrent SCLC and LCNEC in two cohorts: retreatment and maintenance. In both cohorts, patients will be given a Treatment Course comprising of 0.3 mg/kg on Day 1 of a 42 day (6 week) cycle for two cycles.

For the retreatment cohort, patients will be observed on day 1 every 6 weeks following the completion of the first Treatment Course (2 cycles). Patients will not be eligible to receive additional doses of SC16LD6.5 should disease progression occur within 12 weeks of first Treatment Course completion or unacceptable toxicity, deterioration of ECOG performance status to > 2, or other reasons for study withdrawal develop (Section 7.1). If no unacceptable toxicity develops and patients remain on study, patients will be given another Treatment Course (2 cycles) at the time of documented progression followed by observation on day 1 every 6 weeks.

For the maintenance cohort, starting at Cycle 3, patients will be treated with SC16LD6.5 at 0.1 mg/kg q6week following the first Treatment Course completion. The maintenance dose will be administered until progressive disease, unacceptable toxicity, deterioration of ECOG performance status > 2 or other reasons for study withdrawal develop (Section 7.1).

The phase Ib retreatment and maintenance portion of the study will assess the tolerability and a preliminary estimate of the risk-to benefit of the RP2D and tolerability of the maintenance schedule by estimating the proportion of patients able to remain on the maintenance or retreatment study drug for ≥12 weeks unacceptable toxicity. Enrollment of approximately 10 patients with SCLC and 10 patients with LCNEC that are evaluable (completed one Treatment Course) for safety with DLL3 expression per cohort in this portion of the study will provide a reasonable degree of confidence around the tolerability and safety of SC16LD6.5 retreatment

and maintenance and preliminary indications of anti-tumor activity. Patients who experience treatment related unacceptable toxicity during the retreatment or maintenance phase will be discontinued from the study. The maintenance arm will be dose reduced to 0.05 mg/kg q6weeks and enrollment will continue.

For the phase II portion of the study, Simon's minimax two-stage design employing a binomial distribution is used to calculate the required sample size. In this portion, the statistical assumptions will require 29 evaluable patients in the first stage and 38 evaluable patients in total. In the first stage, if ≤1 ORRs are seen in the first 29 patients, the study will stop any further recruitment and the treatment will be considered as not effective in this setting. However, if ≥2 ORRs are seen, an additional 9 patients will be recruited. The treatment will be considered worthy of further investigation if 5 or more ORRs are observed in the 38 patients in total

It is anticipated that a minimum of 2 to a maximum of ~135 patients will be required for the phase I and phase II portion of the study. The total sample size of the Phase II will be driven by the safety and tolerability of schedules determined in Phase I. It is anticipated that no more than two schedules will be tested.

Patients will be assessed using standard clinical, laboratory, and radiological assessments for safety monitoring according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03. Efficacy assessments will be based on standard RECIST v1.1 criteria with some modifications [Eisenhauer et al., 2009, (see Section 2.4.3)]. Drug levels will be measured at appropriate time points in order to estimate typical pharmacokinetic values (V_d, CL, C_{max}, AUC, $T_{1/2}$, etc.).

2 INVESTIGATIONAL PLAN

2.1 Study Treatment

For the phase I portion of the study, SC16LD6.5 will be administered intravenously (IV) to patients with recurrent small cell lung cancer and large cell neuroendocrine carcinoma of the lung. SC16LD6.5 will be given on day 1 every 21 or 42 days. At least 6 dose cohorts are planned; the first cohort will introduce a starting dose of 0.05 mg/kg, increasing as shown in Table 2.1-1. If DLTs are experienced in > 2 patients at any dose level, an intermediate dose level midway between the last tolerated dose level and the current dose level may be evaluated prior to the MTD/RP2D being declared. In addition, an MTD/RP2D may be determined for both a 21 day (3 week) and a 42 day (6 week) dosing schedule. Patients in the phase I portion of the study may continue to receive SC16LD6.5 infusions after cycle 1, at their assigned dose level, provided there is clinical benefit to the patient as determined by the Investigator. The Sponsor may further expand the cohorts to evaluate safety, tolerability and explore anti-tumor activity related to DLL3 expression.

Table 2.1-1 SC16LD6.5 Planned Dose Levels by Cohort

Cohort No.	SC16LD6.5 IV
1	0.05 mg/kg
2	0.1 mg /kg
3	0.2 mg /kg
4	0.4 mg/kg
5	0.8 mg/kg
6	1.6 mg/kg

For the phase Ib portion of the study, SC16LD6.5 will be administered IV to patients with recurrent SCLC in two cohorts: retreatment and maintenance. In both cohorts, patients will be given a Treatment Course comprising of 0.3 mg/kg on Day 1 of a 42 day (6 week) cycle for two cycles.

Patients who are currently active on study will be re-consented to the retreatment cohort with observation. Patients that progress ≥ 12 weeks from last treatment cycle may be eligible for retreatment with medical monitor approval provided the patient meets the original study inclusion and exclusion criteria.

For the retreatment cohort, patients will be observed on day 1 every 6 weeks following the completion of the first Treatment Course (2 cycles). Patients will not be eligible to receive additional doses of SC16LD6.5 should disease progression occur within 12 weeks of first Treatment Course completion or unacceptable toxicity, deterioration of ECOG performance status to > 2, or other reasons for study withdrawal develop. If no unacceptable toxicity develops

and patients remain on study, patients will be given another Treatment Course (2 cycles) at the time of documented progression per RECIST 1.1 followed by observation on day 1 every 6 weeks.

For the maintenance cohort starting with cycle 3, patients will be treated with 0.1 mg/kg q6week following the first Treatment Course completion. Maintenance will be administered until progressive disease, unacceptable toxicity, deterioration of ECOG performance status > 2 or other reasons for study withdrawal develop (Section 7.1).

For the phase II portion of the study, SC16LD6.5 will be administered intravenously to patients with recurrent SCLC and LCNEC. SC16LD6.5 will be given at the recommended dose and scheduled determined in the phase I portion of the study. Patients will undergo regular tumor assessments and continue to receive SC16LD6.5 infusions at the RP2D until disease progression, unacceptable toxicity, deterioration of performance status to > 2, or other reasons for study withdrawal develop (see Section 7.1).

2.2 Definition and Determination of Dose Limiting Toxicity (DLT) and Maximum Tolerated Dose (MTD)

The MTD will be defined as the dose level immediately below the dose level at which ≥ 2 of the first 3 patients per cohort (or ≥ 2 of 6 patients) during the first cycle experience a DLT (related to study drug; see Section 7.3 for definition of related adverse events). At least 6 patients must be treated at the designated MTD, with no more than 1 DLT observed among the 6 patients. The MTD will be defined in terms of NCI-CTCAE v4.03 graded toxicity during the patients' first treatment cycle (21 days).

A DLT will be defined as any one of the following occurring during cycle 1 and assessed as related to study drug (see Section 7.3 for definition of related adverse events):

- NCI-CTCAE Grade 4 neutropenia lasting ≥ 7 days OR febrile neutropenia (single oral temperature measurement of ≥ 38.3ºC (101ºF) or a temperature of ≥ 38ºC (100.4ºF) sustained over a 1-hour period.), Grade 4 thrombocytopenia or anemia;
- NCI-CTCAE ≥ Grade 3 abnormal laboratory values (except anemia, neutropenia, thrombocytopenia, and hyperglycemia that can be medically managed) that are assessed as clinically significant;
- AST/ALT > 3x ULN AND concomitant Bilirubin > 2x UNL (whether related or unrelated to study drug)
- NCI-CTCAE ≥ Grade 3 non-laboratory toxicity; (excluding rash, nausea, diarrhea, and vomiting if controlled with standard supportive therapy).

Patients experiencing a DLT should be removed from the study treatment. If no ≥ grade 2 related AEs are observed in the first three patients during cycle 1 at dose level 1, escalation will proceed to the next dose level utilizing subsequent single patient cohorts. During the single patient dose cohorts, once the initial patient receives their first dose of study drug, if up to two additional patients are identified, meet the eligibility criteria, and sign informed consent they may be offered the opportunity to enroll at that dose level provided they are able to start treatment within 7 days of the initial patient. Single patient cohorts will continue until a single ≥ grade 2 related AE is observed and then cohorts will revert to 3-6 in planned size. Once any DLT is reported, up to 6 patients will be enrolled at the same dose level. Escalation will continue only if a DLT is limited to one of six patients. If a DLT occurs in 2 or more patients, further dose escalation on that dosing schedule will cease. If DLTs are experienced in > 2 patients at any dose level, an intermediate dose level midway between the last tolerated dose level and the current dose level will be evaluated prior to the MTD/RP2D being declared. An MTD/RP2D may be determined for both a 21 day (3 week) and a 42 day (6 week) dosing schedule.

Table 2.2-1 Dose Limiting Toxicity (DLT) Escalation Decision Rules

Number of Patients with DLT at a Given Dose Level During the First Cycle	Escalation Decision Rule
0 out of 3 or 0 out of 1	Enter 1 or 3 patients at the next dose level.
1 out of 3	・Enter at least 3 more patients at this dose level. ・If 0 of these 3 patients (1 of 6 total dosed for cohort) experience DLT, proceed to the next dose level. ・If 1 or more of this group experience DLT (2 of 6 total dosed for cohort), then dose escalation is stopped and an intermediate dose level will be evaluated prior to declaring the MTD/RP2D
≥2 out of 3	Dose escalation will be stopped and an intermediate dose level will be evaluated prior to declaring the MTD/RP2D

If there is clinical benefit to the patient, as determined by the Investigator, the patient may continue to receive every 21 or 42 day infusions of SC16LD6.5 at their allocated dose level provided ANC ≥1000 x 10^9/L and platelets ≥75 x 10^9/L on the day of treatment. These patients will be followed for safety and tolerability, and will be monitored and assessed by laboratory testing values as outlined in Section 2.4.1.

DLT is defined by cycle 1; however the safety and tolerability from later cycles will also be evaluated before determining the recommended Phase II dose.

2.3 Method of Assigning Patients to Treatment Groups

SCRX16-001 is a Phase I/II open-label, single agent, non-comparative, dose-escalation study of SC16LD6.5. Patients will be screened and identified as eligible for the study by the Investigator at each site. Eligible patients will be registered to the study centrally by the CRO, Sarah Cannon Research Institute. Site personnel must notify the study CRO of any patients in screening to verify dose levels and openings available for enrollment.

2.3.1 Registration Process

Once a patient is determined as fulfilling the study eligibility criteria by the Investigator, the 'SCRX16-001 Registration and Enrollment Form' should be completed by the Study Coordinator or appropriately delegated site staff member and faxed or emailed to Sarah Cannon Research Institute, CRO. On receipt of the "SCRX16-001 Registration and Enrollment Form", the CRO will confirm the patient study identification (ID) number, the dose cohort that the

subject is assigned to, and return it to the site. Completed Registration and Enrollment Form must be received by the site prior to patient dosing and stored with site files.

The patient's ID will be determined by a three digit site number, plus a three digit patient number, which will be allocated chronologically and will be site specific, e.g. Site 001 first patient will be number: 001-001, then sequentially 001-002, 001-003 etc. Likewise, Site 002 the first patient would be 002-001, second patient would be 002-002, etc. Study numbers will be assigned by the site at consent and only be used once and will not be reallocated to any other patient during the study.

Once a patient is registered, issues that would cause treatment delays longer than 72 hours should be discussed with the CRO. If a patient does not proceed to receive protocol therapy following registration, the patient's study registration may be cancelled and the patient will be considered a screen failure. The CRO should be notified of screen failures as soon as possible.

Once a cohort has enrolled 1-3 patients, recruitment to that cohort will be suspended until the final evaluable patient completes 21 to 42 days of safety follow-up, or any of the 1-3 patients experience a DLT, whichever comes first. Sites will be notified that enrollment to a cohort has been suspended so no further patients are approached to join the study, until it is determined that either additional patients will be enrolled at the existing dose level or that enrollment to the next cohort may commence.

2.4 Study Evaluations

Study evaluations and assessments are summarized in Table 6.1-1, Table 6.1-2, and Table 6.1-3 and Section 6.

2.4.1 Safety and Tolerability

The safety and tolerability of SC16LD6.5 will be assessed by careful monitoring (detailed in Table 6.1-1, Table 6.1-2, and Table 6.1-3) and evaluation as noted below:

Physical examination, inclusive of Eastern Cooperative Oncology Group (ECOG) performance status, and vital signs including weight, blood pressure, pulse rate, and body temperature; complete blood count with differential (CBC); serum chemistry panel; urinalysis microscopic and dipstick; 12-lead electrocardiogram (ECG); adverse event (AE) monitoring using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03.

2.4.2 Pharmacokinetics, Pharmacodynamics, and ATA (See also Section 6.3)

Pharmacokinetics

A combination of intensive, semi-intensive, and sparse sampling will be used to characterize the PK of SC16LD6.5 and related analytes.

Phase I:

For a 3 week dosing schedule, intensive and semi-intensive PK sampling (8 and 5 time points, respectively as defined in Table 6.3-1) will be employed during Cycle 1 and Cycle 4 to determine PK parameters of all patients enrolled on study. Sparse PK sampling (two time points/cycle, as defined in Table 6.3-1) will be employed for cycles 2 and 3.

For a 6 week dosing schedule, intensive and semi-intensive PK sampling (10 and 7 time points, respectively as defined in Table 6.3-2) will be employed during Cycle 1 and Cycle 3 to determine PK parameters of all patients enrolled on study. Sparse PK sampling (two time points/cycle, as defined in Table 6.3-2) will be employed for cycles 2 and 4.

If feasible, blood for PK measurements will also occur when a subject comes off study during any post-treatment visit.

Phase Ib-Retreatment and Maintenance:

Blood samples for PK measurements will be taken pre-dose and end of infusion at Cycle 1 and Cycle 2 for the first treatment course and at end of study.

Pharmacodynamics and Anti-Therapeutic Antibodies

A biomarker (γ-H2AX) of SC16LD6.5 pharmacodynamics will be evaluated. γ-H2AX has been shown to be a sensitive biomarker of DNA damage induced by an analogue of D6.5, SJG-136, in Phase 1 clinical studies [http://www.ncbi.nlm.nih.gov/pubmed/23251007].

Phase I:

3 and 6 week dosing schedule:

Samples will be collected pre-dose on day 1, and on Day 8 of Cycle 1, pre-dose Cycle 2, pre-dose Cycle 3, and pre-dose Cycle 4.

Samples to evaluate ATA will be collected pre-dose for Cycles 1 through 4 and at the end of study.

Phase Ib-Retreatment and Maintenance:

Blood samples for ATA measurements will be taken pre-dose Cycle 1 and Cycle 2 for the first treatment course and at the end of study.

2.4.3 Efficacy analyses

Efficacy evaluation will be conducted via standard radiographic methods (CT or MRI imaging) and assessed by RECIST v1.1 criteria.

The specific methodology utilized to evaluate response and progression will be at the discretion of the Investigator, but the same methodology should be used for follow-up assessments as was

used for the baseline assessment. The frequency of follow-up assessments will be every 6 weeks for 18 weeks and then every 9 -12 weeks thereafter or as clinically indicated. Response determination should be made according to RECIST v1.1 criteria, including the requirement to confirm responses at ≥ 4 weeks. Baseline radiology should be performed as close as possible to the start of treatment but no longer than 21 days (3 weeks) before cycle 1, day 1. Only those patients who have measurable disease at baseline, have received at least one dose of therapy, and have had their disease re-evaluated will be evaluable for response.

Although RECIST v1.1 considers a ≥ 20% increase in SLD, or new lesions, as evidence for disease progression, the following modifications will be utilized only during the phase II portion of this study:

- Progression will require a ≥ 50% increase in SLD, or new lesions. Patients with a SLD increase of < 50% may be allowed to remain on study drug unless they are demonstrating evidence of clinical progression. If the investigator feels the patient is benefiting and should continue on study, this should be documented in the medical record and the Medical Monitor should be informed.
- Isolated evidence of CNS progression will not constitute disease progression. These patients should undergo appropriate palliative CNS therapy, at the discretion of the investigator, and continue to receive study therapy until systemic (non-CNS) progression develops (see specific instructions in Section 2.4.3.1).

2.4.3.1 Rationale for Modifications to RECIST Criteria

SC16LD6.5 is an antibody-drug conjugate which targets DLL3 expressed in both TPC and non-TPC populations in SCLC. Because pre-clinical studies of more specific TPC targeted ADCs sometimes suggest a ‘delay’ of *in vivo* efficacy (that is, a short period of transient tumor growth prior to cytoreduction), presumably due to the low frequency of TPCs within established tumors, this study will allow the option of continued dosing of study drug in patients with SLD increases of < 50% at the discretion of the investigator. Efficacy assessments in the statistical analysis plan (SAP) will include both standard RECISTv1.1 criteria in addition to this modification.

Because it is well known that other monoclonal antibodies (notably trastuzumab) fail to penetrate the blood-brain barrier resulting in isolated CNS progression despite systemic disease control, this protocol will also allow continued administration of study drug (after palliative CNS therapy as described below) for patients demonstrating isolated CNS progression at the discretion of the investigator.

If isolated CNS progression is observed patients should be fully evaluated for other sites of progression. If none is detected, study drug should be held until palliative CNS therapy is completed. A ‘standard course’ (30Gy delivered over 10 fractions) of whole brain radiotherapy (WBRT) is strongly suggested. Study therapy should be re-started 1 week after the completion of

CNS therapy. The total treatment break cannot exceed 6 weeks, or the patient will be required to discontinue therapy.

All patients who agree to continue on study therapy despite either 1) an increase in SLD of >20% but <50% or 2) the development of isolated CNS metastases must be discussed with the Medical Monitor and re-consented.

2.4.4 Determination of the Recommended Phase II Dose

The recommended Phase II dose level will be at or below the MTD and at or above a dose that either confers exposure consistent with that needed for efficacy in the nonclinical models or has resulted in a confirmed objective tumor response. Tolerability will also be evaluated with various dosing schedules. The recommended Phase II dose and schedule will be determined based on the above factors as well as an evaluation of the safety profile and tolerability beyond cycle 1.

3 SELECTION OF STUDY POPULATION

3.1 Inclusion Criteria

Patients must fulfill all of the following inclusion criteria to be eligible to enroll into the study:

1. Provision of informed consent
2. Male or female ≥18 years of age
3. Histologic or cytologic confirmed diagnosis of small cell lung cancer, either limited or extensive disease at initial presentation is allowed (large cell neuroendocrine permitted with approval from medical monitor)
4. Evidence of progressive disease during or following 1 or 2 prior chemotherapy regimens)
    - At least 1 prior regimen must have contained a platinum salt
    - 'Adjuvant therapy' will constitute a prior treatment regimen
    - No more than 2 prior regimens are allowed
5. Measurable disease (only for the phase II portion)
6. ECOG Performance status 0-1 (Appendix A)
7. A minimum life expectancy of 12 weeks
8. Adequate bone marrow, hepatic and renal function as evidenced by:
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
    - Platelet count ≥ 100 x 10^9/L
    - Hemoglobin ≥ 9.0 g/dL
    - Serum bilirubin < 1.5 x ULN
    - AST/ALT (SGOT/SGPT) < 2.5 x ULN for the reference laboratory or < 5 x ULN in the presence of liver metastases
    - Serum creatinine < 1.5 x ULN
9. No 'active' CNS metastases. Prior CNS metastases are allowed, provided adequate palliative therapy has been administered and CNS disease control has been established prior to study entry.
    - A brain MRI scan, ≤ 28 days from day 1, is required
10. Female patients who are not of child-bearing potential, and female patients of child-bearing potential who agree to use adequate contraceptive measures and who have a negative serum pregnancy test within 1 week prior to initial study treatment. (See Appendix B)

11. Male patients willing to use adequate contraceptive. (See Appendix B)

12. At least 21 days must have elapsed prior to day 1 cycle 1, from chemotherapy, radiotherapy, immunotherapy or following major surgery and any surgical incision should be completely healed. At least 14 days must have elapsed prior to Day 1 Cycle 1 for "limited palliative radiotherapy", defined as a course of therapy encompassing < 25% total bone marrow volume and not exceeding 30 Gy.

13. At least 14 days must have elapsed for chemotherapy regimens, biologic, and targeted therapy given continuously or on a weekly basis with limited potential for delayed toxicity

14. Patients currently active on study will be eligible for retreatment provided they did not progress within 12 weeks of their last treatment cycle.

3.2 Exclusion Criteria

Patients who have any of the following exclusion criteria are not eligible to participate in the study:

1. Patients who are pregnant or breastfeeding.

2. Active involvement of the Central Nervous System (CNS).

3. Uncontrolled infection or systemic disease.

4. AST/ALT > 3x UNL AND concomitant Bilirubin > 2x UNL

5. Clinically significant cardiac disease not well controlled with medication (*e.g.*, congestive heart failure, symptomatic coronary artery disease e.g. angina, and cardiac arrhythmias) or myocardial infarction within the last 12 months.

6. Chemotherapy regimens within the last 21 days (or within 6 weeks for prior nitrosourea or mitomycin C). Chemotherapy regimens, biologic, and targeted therapy given continuously or on a weekly basis with limited potential for delayed toxicity within the last 14 days.

7. No concurrent systemic chemotherapy or anticancer biologic therapy is allowed.

Note: Patients on hormonal treatment for breast cancer or prostate cancer may continue on treatment and enter into study.

8. Known hypersensitivity to any components of SC16LD6.5 study drug product.

9. Patients with known human immunodeficiency virus (HIV) or Hepatitis B or C (active, previously treated or both), a history of solid organ or bone marrow transplantation would generally be considered to have met exclusion criteria, however exceptions may be considered on a case-by-case basis by the medical monitor.

10. Psychiatric disorder or social or geographic situation that would preclude study participation.

11. QT_cF interval of >450 msec (males) or >470 msec (females)

4 TREATMENT PLAN

4.1 Agent Administration

SC16LD6.5 will be administered intravenously (IV) to patients with recurrent SCLC. SC16LD6.5 will be given on day 1 every 21 or 42 days. All patients may continue to receive SC16LD6.5 infusions at their assigned dose level as long as there is clinical benefit to the patient as determined by the Investigator and the performance status is ≤ 2.

If patients develop signs or symptoms compatible with an infusion reaction, the infusion should be stopped and standard supportive care administered. If the infusion reaction was grade 1 or grade 2 in severity and the signs and symptoms have fully resolved, the infusion can be restarted at a slower rate (over 60-90 minutes). If the reaction is ≥ grade 3, treatment should be permanently discontinued. For patients that experience infusion reactions, subsequent infusions should be administered over 60 minutes.

4.2 Pre-Medication

All patients must receive pre-medication consisting of oral dexamethasone 8mg b.i.d. given on the day prior to, the day of, and the day following each dose of study drug.

4.3 Concomitant Medications

Supportive care measures and treatment for symptom control or drug related toxicity are permitted including analgesics, anti-emetics, *etc*. Erythropoiesis-Stimulating Agents (ESAs) are permitted and will be allowed during cycle 1 provided the patient is receiving ESAs at study entry. No other hematopoietic growth factors will be allowed during cycle 1 of therapy. After cycle 1, the use of hematopoietic growth factors per the ASCO guidelines for use is permitted, at the discretion of the treating physician. Patients on hormonal treatment for breast cancer or prostate cancer may continue on treatment and enter into study.

Prophylactic and clinical management of skin rash is required for patients participating in the trial (see Appendix C).

Patients will be medically monitored so that any adverse events will be identified promptly and treated appropriately.

4.4 Duration of Therapy

For the Phase I dose escalation, Phase Ib retreatment/maintenance, and Phase II portion of this study, patients can continue to receive SC16LD6.5 infusions at their allocated dose level, schedule, and treatment course until demonstrated radiologic and/or clinically assessed progressive disease (i.e. symptomatic deterioration) or until another withdrawal criterion is met (See Section 7.1).

4.5 Treatment Dose Modifications

No intra-patient dose escalation will be permitted in the phase I dose escalation portion.

If a patient experiences a DLT during cycle 1 of the phase I portion of the study, the patient should be withdrawn from the study. If a patient experiences a DLT after cycle 1 of the phase I portion of the study, the patient may continue on study drug at one dose level below their assigned dose provided:

1) they are not assigned to dose level 1; patients at the 0.05 mg/kg dose level will be required to discontinue study treatment.

2) the adverse event has resolved to < Grade 1 or to baseline prior to re-treatment with any subsequent cycle

3) the performance status is ≤ 2

4) the DLT was not AST/ALT > 3x UNL AND concomitant bilirubin > 2x UNL

If a patient experiences a ≥ grade 3 AE or a clinically intolerable grade 2 AE at any time during the phase II portion of the study, the patient may continue on study drug at one dose level below their assigned dose provided the adverse event has resolved to < Grade 1 or to baseline within 2 weeks of the scheduled subsequent dose (dose delay of > 2 weeks will require discontinuation), the performance status is ≤ 2 and the adverse event is not a AST/ALT > 3x UNL AND concomitant Bilirubin > 2x UNL.

Only a single dose reduction will be allowed during the study; however, further dose reductions or an additional delay in re-treatment with a subsequent dose may be considered on a case by case basis following discussion with the medical monitor for patients who are responding to therapy and are in need of toxicity management. If a patient experiences a second episode of a ≥ grade 3 related AE after dose reduction, they should be discontinued from study therapy. “Re-escalation” after dose reduction will not be permitted.

5 AGENT FORMULATIONS AND PROCUREMENT

5.1 Product Name

Codename: SC16LD6.5

5.2 Chemical Name and Structure

SC16LD6.5 is an antibody-drug conjugate (ADC). The humanized IgG1 monoclonal antibody (SC16) is produced by recombinant DNA technology from Chinese hamster ovary (CHO) cells and is then covalently conjugated to a pyrrolobenzodiazepine (PBD) molecule via a linker to produce the bulk drug substance (SC16LD6.5).

5.3 Molecular Weight

Molecular Weight: 147,768 Da

5.4 Physical Characteristics

On visual inspection, the solution for infusion should be clear, colorless and free from extraneous visible particulates.

5.5 Dosage and Formulation

SC16LD6.5 drug product is provided in a sterile clear USP Type I 10 cc glass vials designed to deliver 50 mg/vial. Each vial contains a 5.0 mL nominal fill volume. Each vial is filled with a 5.3 mL fill volume that includes a 0.3 mL overfill in order to consistently deliver 5 mL per vial. The liquid formulation is nominally 10 mg/mL SC16LD6.5 in 20 mM histidine hydrochloride, 0.175M sucrose and 0.04% w/v polysorbate 20, pH 6.0. The drug product is stored and shipped frozen at ≤ -70°C prior to its use in clinical trials.

Each container will be labeled with:

- Stem CentRx
- SC16LD6.5 (50 mg/vial; 10 mg/mL)
- Lot number
- Store ≤ -70°C
- Single use only, refer to protocol
- Protect from light
- Caution Statement: "Caution: New Drug - Limited by United States Law to Investigational Use”

Investigational product containers are to be accounted for at monitoring visits.

5.6 Study Agent Procurement

SC16LD6.5 investigational study agent will be provided by Stemcentrx, Inc., the Sponsor, via a third party distributor.

5.7 Safety Precautions

SC16LD6.5 is a cytotoxic agent that causes chronic alkylation of DNA. Wear protective clothing and gloves while handling.

5.8 Study Agent Storage

SC16LD6.5 vials should be stored at the study center in a secure area with limited access at ≤ -70°C, and protected from light. Any breach of investigational product storage conditions should be reported to the sponsor on detection, and the medication should be quarantined until the Sponsor authorizes usage or otherwise.

5.9 SC16LD6.5 Preparation

SC16LD6.5 should be diluted in normal saline (0.9% NaCl) prior to intravenous use.

Calculate the amount of SC16LD6.5 drug product required for dosing the patient based on body weight. Use aseptic techniques for preparation.

Use an appropriate size sterile syringe to extract the calculated amount of SC16LD6.5 out of the vial(s) as required, and insert into the injection port of the IV infusion bag containing normal saline. For dose levels ≤ 0.1 mg/kg a 50mL IV infusion bag should be used. For doses > 0.1 mg/kg a 100mL IV infusion bag should be used. Dispose of the needle and syringe into a sharps bin. On visual inspection, the solution for infusion should be clear, colorless and free of particles.

5.10 SC16LD6.5 Administration

Administer the infusion of SC16LD6.5 study drug and saline solution over 30 minutes.

Monitor vital signs (including blood pressure, heart rate, and body temperature) as well as signs and symptoms of infusion reactions pre-infusion, at 15 minutes, immediately post infusion and 30 minutes post infusion. (See Table 6.1-1)

The study drug infusion bag should be used following preparation. If not used immediately, the bag can be stored at 5°C for up to 8 hours.

6 STUDY PROCEDURES

6.1 Evaluations and Procedures

A summary of the assessments and procedures to be performed for Phase I is provided in Table 6.1-1 for a 3 week dosing interval and Table 6.1-2 for a 6 week dosing interval. A summary of the assessments and procedures to be performed for Retreatment/Maintenance is provided in Table 6.1-3.

Table 6.1-1 Schedule of Assessments for Phase I-Dose Escalation 3 Week Dosing Interval

Assessment	*Screening*[1]		*Treatment Cycle 1 (21 days)*			*Subsequent Cycles*	*End of Study Visit*	*Long Term Follow-up*[14]
Week	***-4***	***-1***	***1***	***2***	***3***			
Study Day [2]	***-28***	***-7***	***1***	***8***	***15***		***At study treatment withdrawal***	***Monthly after study treatment withdrawal***
Obtain Informed Consent [3]	x							
Review Inclusion/Exclusion Criteria		x						
Medical history		x						
Physical examination		x		x[6]	x[6]	x[7]	x	
12 Lead ECG		x	x[15]			x[15]	x	
ECOG Performance Status		x	x			x	x	
Vital signs [4]		x	x	x	x	x	x	
Brain MRI	x							
Clinical laboratory tests								
Complete Blood Count (CBC) [5]		x		x	x	x[7]	x	
Serum Chemistry [5]		x		x[16]	x[16]	x[7]	x	
Pregnancy test (if applicable) [8]		x						
Urinalysis (dipstick and microscopic)		x				x[7]		
Concomitant medication review		x				x	x	
Tumor imaging	x[1]					x[9]		
Administering SC16LD6.5 study medication			x			x[17]		
PK, PD, and ATA Sampling [10]			x	x	x	x[10]	x	
Adverse events/toxicity assessment [11]			x	x	x	x	x	
Correlative Science								
Blood samples [12]			x			x[12]	x	
Archival (FFPE) tumor tissue [12]		x						
Fresh tumor tissue [13]		x						
Survival Status								x

Footnotes for Phase I-Dose Escalation 3 Week Dosing Interval

[1] Screening Visit should occur ≤ 7 days before commencement of Cycle 1, Day 1; Radiologic assessment may be performed within 21 days of Cycle 1, Day 1.

[2] There is ± 3 day window allowable for each clinic visit.

[3] Informed Consent must be obtained prior to any study related procedure being initiated within 28 days of Cycle 1, Day 1.

[4] Vital signs to include height (at Screening only), weight, blood pressure, pulse, and body temperature. On study dosing days, vital signs including blood pressure, heart rate and temperature will be taken pre-infusion, at 15 minutes during infusion, immediately post infusion and 30 minutes post infusion.

[5] Perform lab tests at site's local lab. Patient should be fasting prior to lab draw for serum chemistry. See Section 6.2 for list of blood tests.

[6] Limited physical examination as required for any signs/symptoms of possible adverse events.

[7] Subsequent Cycles: CBC, Physical exams, Serum Chemistry, Urinalysis to be performed only Day 1 of each 3 week cycle (21 days).

[8] Serum β-hCG test for women of childbearing potential. Additional testing should be performed per the Investigator when deemed necessary.

[9] Tumor burden to be assessed by CT/MRI every 2 cycles (6 weeks) until 6 cycles (18weeks) of treatment has been completed at which time assessments should be made at 3 cycle (9 week) intervals.

[10] Blood samples for serum or plasma PK, PD, and ATA will be collected according to the schedules outlined in Section 6.3.

[11] Monitor for adverse events for 30 days after last dose of SC16LD6.5.

[12] Study participants will be required to provide ~14-20mL (2 x 7-10mL tubes) of whole blood pre-dose on C1D1 and archival (FFPE) tumor samples (if available) from either the primary, or subsequent, tumor biopsies. In addition, all patients will be required to provide an additional 14-20mL of whole blood just prior to cycle 3, or at study discontinuation, whichever time point occurs first.

[13] (Optional) Study participants will be encouraged to participate in the optional submission of fresh tumor material obtained prior to cycle 1 via a medically appropriate biopsy procedure (bronchoscopy, percutaneous biopsy, FNA, etc.).

[14] Patients will be followed up monthly upon study withdrawal for survival.

[15]ECGs should be performed in triplicate pre-dose and +/- 15 minutes from the 'peak' PK timepoint (30 minutes following completion of the infusion) on Cycle 1 Day 1 and Cycle 4 Day 1.

[16]Additional serum chemistry for AST/ALT, bilirubin, alkaline phosphatase, amylase and lipase to be performed on Cycle 1 Day 8 and Cycle 1 Day 15.

[17] See Section 2.1 for doses to be administered in subsequent cycles.

Table 6.1-2 Schedule of Assessments for Phase I-Dose Escalation 6 Week Dosing Interval

Assessment	*Screening*[1]		*Treatment Cycle 1 (42 days)*					*Subsequent Cycles*		*End of Study Visit*	*Long Term Follow-up*
Week	***-4***	***-1***	***1***	***2***	***3***	***4***	***5***	***1***	***4***		
Study Day [2]	***-28***	***-7***	***1***	***8***	***15***	***22***	***29***	***1***	***22***	***At study treatment withdrawal***	***Monthly After Study Treatment Withdrawal***
Obtain Informed Consent [3]	x										
Review Inclusion/Exclusion Criteria		x									
Medical history		x									
Physical examination		x		x[6]	x[6]			x[7]		x	
12 Lead ECG		x	x[15]					x[15]		x	
ECOG Performance Status		x	x					x		x	
Vital signs [4]		x	x	x	x			x		x	
Brain MRI	x										
Clinical laboratory tests											
Complete Blood Count (CBC) [5]		x		x	x			x[7]	x[7]	x	
Serum Chemistry [5]		x		x[16]	x[16]			x[7]	x[7]	x	
Pregnancy test (if applicable) [8]		x									
Urinalysis (dipstick and microscopic)		x						x[7]			
Concomitant medication review		x						x		x	
Tumor imaging	x[1]							x[9]			
Administering SC16LD6.5 study medication			x					x[17]			
PK, PD, and ATA Sampling [10]			x	x	x	x	x	x[10]	X[10]	x	
Adverse events/toxicity assessment [11]			x	x	x	x	x	x	x	x	
Correlative Science											
Blood samples [12]			x					x[12]		x	
Archival (FFPE) tumor tissue [12]		x									
Fresh tumor tissue [13]		x									
Survival Status											x

Footnotes for Phase I-Dose Escalation 6 Week Dosing Interval

[1] Screening Visit should occur ≤ 7 days before commencement of Cycle 1, Day 1; Radiologic assessment may be performed within 21 days of Cycle 1, Day 1.

[2] There is ± 3 day window allowable for each clinic visit.

[3] Informed Consent must be obtained prior to any study related procedure being initiated within 28 days of Cycle 1, Day 1.

[4] Vital signs to include height (at Screening only), weight, blood pressure, pulse, and body temperature. On study dosing days, vital signs including blood pressure, heart rate and temperature will be taken pre-infusion, at 15 minutes during infusion, immediately post infusion and 30 minutes post infusion.

[5] Perform lab tests at site's local lab. Patient should be fasting prior to lab draw for serum chemistry. See Section 6.2 for list of blood tests.

[6] Limited physical examination as required for any signs/symptoms of possible adverse events.

[7] Subsequent Cycles: CBC, Physical exams, Serum Chemistry, Urinalysis to be performed Day 1 of each 6 week cycle (42 days). In addition, CBC and Serum Chemistry will also be performed on Day 22 (week 4) of every 6 week cycle.

[8] Serum β-hCG test for women of childbearing potential. Additional testing should be performed per the Investigator when deemed necessary.

[9] Tumor burden to be assessed by CT/MRI every cycle (6 weeks) until 3 cycles (18 weeks) of treatment has been completed at which time assessments should be made at 2 cycle (12 weeks) intervals.

[10] Blood samples for serum or plasma PK, PD, and ATA will be collected according to the schedules outlined in section 6.3.

[11] Monitor for adverse events for 30 days after last dose of SC16LD6.5.

[12] Study participants will be required to provide ~14-20mL (2 x 7-10mL tubes) of whole blood pre-dose on C1D1 and archival (FFPE) tumor samples (if available) from either the primary, or subsequent, tumor biopsies. In addition, all patients will be required to provide an additional 14-20mL of whole blood just prior to cycle 3, or at study discontinuation, whichever time point occurs first.

[13] (Optional) Study participants will be encouraged to participate in the optional submission of fresh tumor material obtained prior to cycle 1 via a medically appropriate biopsy procedure (bronchoscopy, percutaneous biopsy, FNA, etc.).

[14] Patients will be followed up monthly upon study withdrawal for survival.

[15]ECGs should be performed in triplicate pre-dose and +/- 15 minutes from the 'peak' PK timepoint (30 minutes following completion of the infusion) on Cycle 1 Day 1 and Cycle 3 Day 1.

[16]Additional serum chemistry for AST/ALT, bilirubin, alkaline phosphatase, amylase and lipase to be performed on Cycle 1 Day 8 and Cycle 1 Day 15.

[17] See Section 2.1 for doses to be administered in subsequent cycles.

Table 6.1-3 Schedule of Assessments for Retreatment/Maintenance 6 Week Dosing Interval

Assessment	*Screening*[1]		*Treatment Cycle 1 (42 days)*					*Subsequent Cycles*		*Observation Visits*[18]	*End of Study Visit*	*Long Term Follow-up*
Week	***-4***	***-1***	***1***	***2***	***3***	***4***	***5***	***1***	***4***	***Every 6 weeks***		
Study Day [2]	***-28***	***-7***	***1***	***8***	***15***	***22***	***29***	***1***	***22***	***Day 1 of every 6 weeks***	***At study treatment withdrawal***	***Monthly After Study Treatment Withdrawal***
Obtain Informed Consent [3]	x											
Review Inclusion/Exclusion Criteria		x										
Medical history		x										
Physical examination		x		x[6]	x[6]			x[7]		x	x	
12 Lead ECG		x	x[15]					x[15]			x	
ECOG Performance Status		x	x					x		x	x	
Vital signs [4]		x	x	x	x			x		x	x	
Brain MRI	x											
Clinical laboratory tests												
Complete Blood Count (CBC) [5]		x		x	x			x[7]	x[7]	x	x	
Serum Chemistry [5]		x		x[16]	x[16]			x[7]	x[7]	x	x	
Pregnancy test (if applicable) [8]		x										
Urinalysis (dipstick and microscopic)		x						x[7]		x		
Concomitant medication review		x						x			x	
Tumor imaging	x[1]							x[9]		x		
Administering SC16LD6.5 study medication			x					x[17]				
PK, PD, and ATA Sampling [10]			x[10]					x[10]			x[10]	
Adverse events/toxicity assessment [11]			x	x	x	x	x	x	x	x	x	
Correlative Science												
Blood samples [12]			x					x[12]			x	
Archival (FFPE) tumor tissue [12]		x										
Fresh tumor tissue [13]		x										
Survival Status												x

Footnotes for Retreatment/Maintenance 6 Week Dosing Interval

[1] Screening Visit should occur ≤ 7 days before commencement of Cycle 1, Day 1; Radiologic assessment may be performed within 14 days of Cycle 1, Day 1.

[2] There is ± 3 day window allowable for each clinic visit.

[3] Informed Consent must be obtained prior to any study related procedure being initiated within 28 days of Cycle 1, Day 1.

[4] Vital signs to include height (at Screening only), weight, blood pressure, pulse, and body temperature. On study dosing days, vital signs including blood pressure, heart rate and temperature will be taken pre-infusion, at 15 minutes during infusion, immediately post infusion and 30 minutes post infusion.

[5] Perform lab tests at site's local lab. Patient should be fasting prior to lab draw for serum chemistry. See Section 6.2 for list of blood tests.

[6] Limited physical examination as required for any signs/symptoms of possible adverse events.

[7] Subsequent Cycles: CBC, Physical exams, Serum Chemistry, Urinalysis to be performed Day 1 of each 6 week cycle (42 days). In addition, CBC and Serum Chemistry will also be performed on Day 22 (week 4) of every 6 week cycle.

[8] Serum β-hCG test for women of childbearing potential. Additional testing should be performed per the Investigator when deemed necessary.

[9] Tumor burden to be assessed by CT/MRI every cycle (6 weeks).

[10] Blood samples for serum or plasma PK, PD, and ATA will be collected according to the schedules outlined in section 6.3.

[11] Monitor for adverse events for 30 days after last dose of SC16LD6.5.

[12] Study participants will be required to provide ~14-20mL (2 x 7-10mL tubes) of whole blood pre-dose on C1D1 and archival (FFPE) tumor samples (if available) from either the primary, or subsequent, tumor biopsies. In addition, all patients will be required to provide an additional 14-20mL of whole blood at cycle 2, or at study discontinuation, whichever time point occurs first.

[13] (Optional) Study participants will be encouraged to participate in the optional submission of fresh tumor material obtained prior to cycle 1 via a medically appropriate biopsy procedure (bronchoscopy, percutaneous biopsy, FNA, etc.).

[14] Patients will be followed up monthly upon study withdrawal for survival.

[15]ECGs should be performed in triplicate pre-dose and +/- 15 minutes from the 'peak' PK timepoint (30 minutes following completion of the infusion) on Cycle 1 Day 1 and Cycle 3 Day 1.

[16]Additional serum chemistry for AST/ALT, bilirubin, alkaline phosphatase, amylase and lipase to be performed on Cycle 1 Day 8 and Cycle 1 Day 15.

[17]See Section 2.1 for doses to be administered in subsequent cycles.

[18]Retreatment arm only. Patients will be observed on day 1 of every 6 weeks following the completion of their Treatment Course(s). Observation visits will continue until study discontinuation criterion is met.

6.2 Screening Visit

The purpose and the procedures of the study will be fully explained to participants by the Principal Investigator and support staff and every patient approached regarding the study will be provided with the Informed Consent Form (ICF). Patients wishing to enroll in the study will sign the ICF prior to initiating any study related investigations or procedures. Radiological scans performed *prior* to consent can be utilized for the purposes of the study if they have been performed as part of routine clinical practice and the patient consents for their medical records to be reviewed by the Sponsor.

All screened patients who sign the informed consent form (ICF) must be recorded on the Screening/Enrollment Log. If a subject who signs an ICF is not enrolled in the study, please provide the reason for exclusion on the log. The Screening/Enrollment Log will be retained within the Investigator Site File.

The screening visit should occur ≤ 7 days before day 1 cycle 1.

The following procedures are to be performed at the screening visit:

- Review Inclusion and Exclusion Criteria
- Review and record medical history including previous anti-cancer therapy
- Physical examination
- 12-lead ECG
- Determination of ECOG performance status.
- Vital signs (height [at screening visit only], weight, blood pressure, heart rate, and body temperature)
- Brain MRI (MRI may be performed within 28 days of cycle 1 day 1)
- Laboratory assessments: Complete Blood Count including: WBCs with differential, hematocrit, hemoglobin and platelets; Chemistry including: sodium, potassium, calcium, creatinine, total protein, albumin, bilirubin (total, direct), AST/SGOT, ALT/SGPT, alkaline phosphatase, amylase, lipase, glucose; urinalysis (dipstick and microscopic). *NOTE: Clinical laboratory testing will be performed by each site's local laboratory.*
- Serum β-hCG Pregnancy test (if female is of child bearing potential)
- Review and record all concomitant medications
- Tumor imaging including all areas of disease involvement (tumor imaging may be performed anytime within 14 days of cycle 1 day 1.)

6.3 Blood Drawing for Plasma Pharmacokinetic and Pharmacodynamics Analysis

6.3.1 Timing

The timing of blood samples collection is detailed in Table 6.3-1 (Phase I 3 week dosing interval), in Table 6.3-2 (Phase I 6 week dosing interval), and in Table 6.1-3 (Phase Ib 6 week dosing interval) below.

Free toxin does not need to be collected for the expansion cohorts on Phase I and Phase Ib.

Table 6.3-1 PK and PD Sampling Schedule for Phase I 3 Week Dosing Interval

Study Visit	Time	Planned Assays
Cycle 1, Day 1	Pre-dose	Serum anti-SC16LD6.5 antibody PK and PD sample[1]
	30 minutes (± 15 minutes) after the end of infusion	PK sample
	4 hours (± 15 minutes) after the end of infusion	PK sample
Cycle 1, Day 2	24 hours after end of infusion (± 2 hours)	PK sample
Cycle 1, Day 3	48 hours after end of infusion (± 2 hours)	PK sample
Cycle 1, Day 5	96 hours after end of infusion (± 2 hours)	PK sample
Cycle 1, Day 8	7 days after end of infusion (± 6 hours)	PK and PD sample
Cycle 1, Day 15	14 days after end of infusion (± 6 hours)	PK sample

Table 6.3-1 PK and PD Sampling Schedule for Phase I 3 Week Dosing Interval (cont'd)

Study Visit	Time	Planned Assays
Cycle 2, Day 1	Pre-dose	Serum anti-SC16LD6.5 antibody PK and PD sample
	30 minutes (± 15 minutes) after the end of infusion	PK sample
Cycle 3, Day 1	Pre-dose	Serum anti-SC16LD6.5 antibody PK and PD sample
	30 minutes (± 15 minutes) after the end of infusion	PK sample
Cycle 4, Day 1	Pre-dose	Serum anti-SC16LD6.5 antibody PK and PD sample
	30 minutes (± 15 minutes) after the end of infusion	PK sample
	4 hours (± 15 minutes) after the end of infusion	PK sample
Cycle 4, Day 8	7 days after end of infusion (± 6 hours)	PK sample
Cycle 4, Day 15	14 days after end of infusion (± 6 hours)	PK sample

*If feasible, blood for PK measurements will also occur when a subject comes off study during any post-treatment visit.
[1]PK samples will be analyzed for SC16LD6.5, SC16, D6.5, and related species.

Table 6.3-2 PK and PD Sampling Schedule for Phase I 6 Week Dosing Interval

Study Visit	Time	Planned Assays
Cycle 1, Day 1	Pre-dose	Serum anti-SC16LD6.5 antibody PK and PD sample[1]
	30 minutes (± 15 minutes) after the end of infusion	PK sample
	4 hours (± 15 minutes) after the end of infusion	PK sample
Cycle 1, Day 2	24 hours after end of infusion (± 2 hours)	PK sample
Cycle 1, Day 3	48 hours after end of infusion (± 2 hours)	PK sample
Cycle 1, Day 5	96 hours after end of infusion (± 2 hours)	PK sample
Cycle 1, Day 8	7 days after end of infusion (± 6 hours)	PK and PD sample
Cycle 1, Day 15	14 days after end of infusion (± 6 hours)	PK sample
Cycle 1, Day 22	21 days after end of infusion (± 6 hours)	PK sample
Cycle 1, Day 29	28 days after end of infusion (± 6 hours)	PK sample

Table 6.3-2 PK and PD Sampling Schedule for Phase I 6 Week Dosing Interval (cont'd)

Study Visit	Time	Planned Assays
Cycle 2, Day 1	Pre-dose	Serum anti-SC16LD6.5 antibody PK and PD sample
	30 minutes (± 15 minutes) after the end of infusion	PK sample
Cycle 3, Day 1	Pre-dose	Serum anti-SC16LD6.5 antibody PK and PD sample
	30 minutes (± 15 minutes) after the end of infusion	PK sample
	4 hours (± 15 minutes) after the end of infusion	PK sample
Cycle 3, Day 8	7 days after end of infusion (± 6 hours)	PK sample
Cycle 3, Day 15	14 days after end of infusion (± 6 hours)	PK sample
Cycle 3, Day 22	21 days after end of infusion (± 6 hours)	PK sample
Cycle 3, Day 29	28 days after end of infusion (± 6 hours)	PK sample
Cycle 4, Day 1	Pre-dose	Serum anti-SC16LD6.5 antibody PK and PD sample
	30 minutes (± 15 minutes) after the end of infusion	PK sample

*If feasible, blood for PK measurements will also occur when a subject comes off study during any post-treatment visit.
[1]PK samples will be analyzed for SC16LD6.5, SC16, D6.5, and related species.

Table 6.3-3 PK and PD Sampling Schedule for Phase Ib 6 Week Dosing Interval

Study Visit	Time	Planned Assays
Cycle 1, Day 1	Pre-dose	Serum anti-SC16LD6.5 antibody and Total antibody PK and PD sample
	30 minutes (± 15 minutes) after the end of infusion	PK sample
Cycle 2, Day 1	Pre-dose	Serum anti-SC16LD6.5 antibody and Total antibody PK and PD Sample
	30 minutes (± 15 minutes) after the end of infusion	PK sample
End of Study	End of Study	Serum anti-SC16LD6.5 antibody and Total antibody PK Sample

6.3.2 Procedure for Collection of Samples for Pharmacokinetic Analysis

The detailed collection and handling procedures are described in the laboratory manual for collection of serum and plasma samples for PK analysis.

6.4 Clinical Monitoring

The Sponsor/CRO will provide clinical monitoring services and data management services in accordance with Monitoring SOPs and Data Management Plans.

A monitoring visit to each site will occur within 3 weeks of the first patient starting investigational product. In addition to routine data monitoring at qualified sites approximately every 4-6 weeks, an initiation visit and a study closeout visit will be performed for each site that participates in the study. Clinical monitors will review documentation to confirm that the study is being conducted in compliance with the clinical study protocol, ICH-GCP and local regulatory and ethical standards.

6.5 Protocol Violation Definitions

Protocol violations are defined as any deviation from this protocol, and include items such as a study required evaluation not completed according to the protocol, a study visit completed outside of the defined visit window, etc.

A major protocol violation would include, but not be limited to, the following:

- enrollment of a patient who does not meet the inclusion/exclusion criteria.
- enrollment of a patient who has not provided informed consent

- the non-reporting of serious adverse events according to the procedure described in Section 7.4

6.6 Protocol Revisions

With the exception of emergency situations, no changes to the protocol will be permitted without approval from the Sponsor. Notify the Institutional Review Board (IRB) of changes in the protocol as appropriate, and provide documented approval of any change or deviation that may increase risk to the Patient, and/or that may adversely affect the rights of the Patient or validity of the investigation.

In the event of an emergency, the Principal Investigators will institute any medical procedures deemed appropriate. However, all such procedures must be promptly reported to the Sponsor, the Medical Monitor, and the IRB.

6.7 Clinical Laboratories

Clinical laboratory tests will be performed by accredited laboratories. PK related assays and all correlative science assays will be performed by Stemcentrx, Inc. or designated laboratories.

6.8 Pregnancy

If a patient becomes pregnant while enrolled in the study, a Pregnancy Form should be completed and faxed to the SCRI Safety Department expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, planned, accidental, or therapeutic) must also be reported to the SCRI Safety Department.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and must be updated to reflect the outcome of the pregnancy.

6.9 Regulatory Compliance

This study will be conducted in accordance with national and local Regulatory Guidelines, Good Clinical Practice-ICH guidelines, the National Statement on Ethical Conduct in Human Research 2007 and The Declaration of Helsinki (October 2000) with notes of Clarification in 2002 (Washington) and 2004 (Tokyo).

7 SAFETY

7.1 Study Drug Withdrawal Criteria/Stopping Rules

It is planned that all enrolled patients will complete 1 cycle, consisting of 1 IV infusion of SC16LD6.5 on day 1 and 21 or 42 days of safety follow-up. Patients can continue on SC16LD6.5 at their allocated dose level every 3 or 6 weeks after cycle 1 until demonstrated progressive disease, as defined in Section 2.4.3, or a study withdrawal criterion is met.

Withdrawal criteria, other than progressive disease, can be defined as one or more of the following:

- deterioration of performance status to > 2
- an inter-current illness that prevents further administration of SC16LD6.5;
- a DLT as defined in Section 2.2 (For Phase 1a);
- an adverse event related to SC16LD6.5 (see Section 7.3 for definition of related adverse events) that is intolerable;
- an adverse event of AST/ALT > 3x UNL AND concomitant Bilirubin > 2x UNL;
- the patient withdraws consent;
- the patient dies;
- general or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

In all cases, the Medical Monitor should be notified of the reason for withdrawal and this must be recorded in the CRF and in the patient's medical records. The patient must be followed to establish whether the reason was an adverse event related to SC16LD6.5, and, if so, this must be reported in accordance with the procedures in Section 6.5.

7.2 Data Safety Monitoring

The Medical Monitor will review and evaluate all toxicities related to SC16LD6.5 (see Section 7.3 for definition of related adverse events). Once the first (for single patient dose cohorts) or third patient of each dose level has completed 1 cycle or when appropriate, depending on the DLTs experienced, a determination will be made that enrollment at the next dose level may commence.

7.3 Adverse Events

Adverse events (AE) reported by the patient or observed by the Investigator will be listed individually on an adverse event form in the CRF. The signs and symptoms, time of onset,

duration, treatment (if any), and follow-up procedures (if any) will be reported, and the criteria for assessing causality to study drug (Table 7.4-1) and outcome categories should be defined (Table 7.4-2).

All grades of adverse events will be reported from the start of study treatment through the 30-day follow-up period after the last dose of SC16LD6.5. The causality, or relatedness, of adverse events to study drug are typically subdivided into "probably", "possibly", or "not related". In this study, AE's assessed by the Investigator as definitely, probably or possibly related to study drug will be considered as related and those assessed as unlikely or not related will be considered unrelated.

An AE is any un-anticipated or unintended medical occurrence or worsening of a sign or symptom (including an abnormal laboratory finding that requires medical intervention) or disease in a study participant, which does not necessarily have a causal relationship with the study condition, procedures or study agent(s) that occurs after the start of study treatment.

Lab values are not considered adverse events unless clinically significant.

Pre-existing conditions or illnesses which are expected to exacerbate or worsen are not considered adverse events and will be accounted for in the subject's medical history. All adverse events are to be followed up for 30 days post the last dose of study drug or until resolution (whichever is sooner).

7.4 Serious Adverse Events

The definitions of SAEs are given below. The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

An SAE is defined as any untoward medical occurrence that results in death, is immediately life-threatening, requires at least a 24-hour in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

The definition of SAE also includes any important medical event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the previous definition. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Progression of malignancy (including fatal outcomes), if documented by the use of an appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as an SAE. Deaths due to progression of malignancy are to be reported on the appropriate eCRF page.

Treatment within or admission to the following facilities does not meet the criteria of "in-patient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, custodial care or respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study), does not require reporting as a SAE to the SCRI Safety Department.

The definition of "related" is that there is a reasonable possibility that the drug caused any of the adverse events described in Table 7.4-1.

Table 7.4-1 Criteria for Assessing Causality to Study Drug

An adverse event is considered related to study drug if any of the following apply:
follows a reasonable temporal sequence from drug administration.
abates upon discontinuation of the study drug.
is confirmed by reappearance of the reaction on repeat exposure (re-challenge).
cannot be reasonably explained by the known characteristics of the patient's clinical state.

Table 7.4-2 Adverse Event Outcome Categories

'Resolved'	The patient has fully recovered from the adverse event with no residual effects observable.
'Resolved w/ Sequelae'	The patient has recovered from the adverse event, however there are residual effects observable.
'Ongoing'	The adverse event is still present and observable.
'Death'	The patient died as a result of the adverse event.
'Unknown'	The outcome of the adverse is unknown at the time of report.

7.5 Specific Adverse Events

7.5.1 Serosal Effusions

Serosal effusions (pleural or pericardial, or ascites) have been observed with SC16LD6.5, alone or in combination with peripheral edema and/or hypoalbuminemia. These events have the potential to be life-threatening (e.g. pericardial tamponade). Therefore, development of any of these events or worsening from baseline warrants prompt evaluation by the Investigator or designee. Alternative causes, such as infection, congestive heart failure, or disease progression, should be ruled out.

In the event of a grade 2 or higher AE in this group (effusions, edema, hypoalbuminemia) considered related to rovalpituzumab tesirine:

- Systemic corticosteroids, when initiated promptly, have been reported to be beneficial in some prior cases. 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 4.5.

7.5.2 Rash

Rash has been observed following the administration of study drug. See Appendix C.

7.6 Notification about Serious or Unexpected Adverse Events

Adverse events classified by the treating investigator as **serious** require expeditious handling and reporting to Sarah Cannon Research Institute (SCRI) in order to comply with regulatory requirements. Serious adverse events may occur at any time from the start of study treatment through the 30-day follow-up period after the last study treatment. The SCRI Safety Department must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.

To report an SAE, the SCRI SAE Report Form should be completed with the necessary information. All SAEs occurring from the start of study treatment until 30 calendar days after last study treatment must be reported as SAEs on the SAE Report Form and followed until resolution (with autopsy report if applicable).

Deaths and other SAEs occurring > 30 calendar days after last study treatment that are deemed ‘possibly’ or ‘probably’ related to the study drug must be reported as SAEs on the SCRI SAE

Report Form within 24 hours of first knowledge of the event by the treating physician or research personnel (with an autopsy report if available).

Deaths occurring > 30 calendar days after last study treatment and not attributed to study treatment (e.g., disease progression) need not be reported as SAEs, but simply captured on the appropriate CRF.

The investigative sites will send the SAE report to the SCRI Safety Department via fax or e-mail using the contact information listed below:

SCRI Safety Department
Fax #: 866-807-4325
Safety Dept. Email: CANN.SAE@scresearch.net

Transmission of the SAE Report Form should be confirmed by the site personnel submitting the report.

SCRI Safety Department will forward all SAE reports from investigative sites to the Sponsor, Stemcentrx, Inc. within 1 business day.

7.6.1 SAE and Unresolved AE Follow-Up

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to SCRI Safety Department as soon as it is available; these reports should be submitted using the SCRI SAE Report Form. The patient should be followed until it is determined that the event resolved, stabilized, or in the opinion of the investigator the event is not going to improve due to underlying disease, or the patient is lost to follow-up.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB.

The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual.

7.6.2 Investigator Reporting of AEs/SAEs/Deaths after Study Discontinuation

Thirty days after completing protocol-specific treatment or study discontinuation, treatment related AEs, SAEs, or deaths determined by the investigator as treatment related are to be reported to SCRI Safety Department.

At the last scheduled study visit, the investigator should instruct the patient to report to the investigator any subsequent SAEs that the patient or the patient's personal physician believes could be related to prior study treatment.

The Sponsor, Stemcentrx, Inc. should be notified if the investigator becomes aware of the development of a new primary cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in the study.

SAEs after study closure considered related to study treatment are to be sent to the Sponsor.

7.6.3 Sponsor SAE Reporting Requirements

The Sponsor is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with International Conference on Harmonization (ICH) guidelines, FDA regulations, and/or local regulatory requirements.

The Sponsor is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drugs to the regulatory agencies and competent authorities via telephone or fax within 7 calendar days after being notified of the event. The Sponsor will report all related but unexpected SAEs including non-death/non-life-threatening related but unexpected SAEs associated with the use of the study medications to the appropriate competent authorities (according to local guidelines), investigators, and central IRBs/Ethics Committees (except in the United States where investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification.

8 ASSESSMENT OF DISEASE STATUS

Assessment of disease status in the phase II portion of the study will be based on an estimated objective response rate. Although objective response rates are not an objective of this Phase I study, they will be recorded and reported.

8.1 Radiologic Assessments

Baseline radiology by CT or MRI should be performed as close as possible to the start of treatment, but no longer than 21 days (3 weeks) prior to cycle 1, day 1. For the purposes of this study, patients should be re-evaluated every 6 weeks until 18 weeks of treatment has been completed at which time assessments should be made at 9-12 week intervals. The radiologic images should be performed consistently for the areas of disease involvement taken for the study evaluation. If the patient has achieved an Objective Response, a confirmatory scan will need to be performed ≥4 weeks later per RECIST criteria.

8.2 Assessment of Response in Patients with Measurable Disease

Assessments of disease response and progression should be made according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 with modifications as noted in Section 2.4.3 and below (Eisenhauer et al., 2009).

Although RECIST v1.1 considers a ≥ 20% increase in SLD, or new lesions, as evidence for disease progression, the following modifications will be utilized during the phase II portion of this study:

- Progression will require a ≥ 50% increase in SLD or new lesions. Patients with a SLD increase of < 50% may be allowed to remain on study drug unless they are demonstrating evidence of clinical progression. If the investigator feels the patient is benefiting and should continue on study, this should be documented in the medical record and the Medical Monitor should be informed.
- Isolated evidence of CNS progression will not constitute disease progression. These patients should undergo appropriate palliative CNS therapy, at the discretion of the investigator, and continue to receive study drug until systemic (non-CNS) progression develops.

All patients who agree to continue on study therapy despite either 1) an increase in SLD of ≥20% but <50% or 2) the development of isolated CNS metastases documented in the medical record at the site and discussed with the Medical Monitor.

9 ETHICS

Prior to initiation of the study, the Principal Investigators will submit the study protocol, and Informed Consent Form, and any other documents that may be requested by the Institutional Review Board for review and approval. The Principal Investigators will request that the IRB provide written approval of the study and will keep on file records of approval of all documents pertaining to this study.

The IRB will have at all times the right to review all source documentation.

The IRB will be notified of any amendments to the protocol. Those amendments will require approval by the IRB prior to being implemented by the Investigative Site with the exception of any amendment that is imperative in the protection of the patients' safety.

9.1 Ethical Conduct of the Study

This study will be conducted in accordance with national and local Regulatory Guidelines, Good Clinical Practice-ICH guidelines, the National Statement on Ethical Conduct in Human Research 2007 and The Declaration of Helsinki (October 2000) with notes of Clarification in 2002 (Washington) and 2004 (Tokyo).

9.2 Patient Informed Consent and Authorization for Use and Disclosure of Protected Health Information (PHI)

Written informed consent and authorization of use and disclosure of PHI must be obtained from each patient (or the patient's legal representative) prior to performing any study evaluations. The authorization for use and disclosure of PHI must contain the elements required by 45 CR 164.508(b) for valid authorizations. The proposed informed consent form, which must be in compliance with regulatory regulations, must have been reviewed and approved by the Sponsor and the study IRB prior to initiation of the study. The proposed informed consent form should contain the 20 elements of the informed consent described in ICH E6 4.8. These requirements are in accordance the Code of Federal Regulations (21 CFR 50.25) and the Declaration of Helsinki.

Each patient will be given a copy of the signed Informed Consent Form. The source documents for each patient shall document that the Informed Consent was obtained prior to participation. The patients will also be instructed that they are free to withdraw their consent and discontinue their participation in the study at any time without prejudice. Prior to the start of the study, the Principal Investigator will provide the Sponsor with an actual Informed Consent Form approved by the IRB for use during the study.

Any amendments to the Informed Consent Form will need to be approved by the Sponsor and the IRB. Consent will be verified and countersigned by the Principal Investigator or delegated

Investigative Site personnel who have documented authority on the Delegation of Responsibility Log.

10 STATISTICAL METHODS AND PLANNED ANALYSES

10.1 Statistical Methods

Dose Escalation Phase I and Retreatment/Maintenance Phase Ib:

The primary objective of the dose escalation phase of this study is to determine the tolerability, adverse event profile, any DLTs, and the MTD/RP2D of SC16LD6.5 given intravenously in patients with recurrent small cell lung cancer.

Secondary objectives are:

1) to characterize the pharmacokinetic profile of SC16LD6.5
2) to characterize the immunogenicity of SC16LD6.5
3) to determine the recommended Phase II dose (RP2D) and schedule based on assessment of MTD and observed pharmacokinetics and to further characterize the risk-to-benefit profile at the RP2D by estimating the proportion of patients able to remain on study drug for ≥ 12 weeks
4) to describe any clinical anti-tumor activity observed in patients treated with SC16LD6.5

Exploratory objectives are:

1) to evaluate the expression of DLL3
2) to characterize the relationship between DLL3 expression levels and clinical benefit
3) to characterize the pharmacodynamic biomarker γ-H2AX
4) to evaluate potential prognostic or predictive gene signatures

These objectives will be addressed in the context of an open-label, dose-escalation study with a small expansion cohort at the MTD; therefore, statistical hypothesis-testing will not be performed, and analyses will be primarily descriptive in nature.

Determination of the MTD will be achieved according to pre-determined rules as described in the protocol. Data from SCRX16-001 will be used to guide dosing for the phase II expansion of this study and future clinical studies.

Phase II Portion of the Study:

The primary objective of the phase II portion of this study is to estimate the objective response rate (ORR) according to RECISTv1.1 in patients with recurrent small cell lung cancer treated at the RP2D.

Secondary objectives are:

1) to estimate the duration of response

2) to estimate the progression-free survival (PFS)
3) to estimate the time-to-progression (TTP)
4) to estimate 'landmark' freedom from progression (FFP) and overall survival (OS) at 12 and 24 weeks
5) to estimate the overall survival
6) to further characterize the safety profile at the RP2D
7) to further characterize the pharmacokinetics of SC16LD6.5 at the RP2D

Exploratory objectives are:

1) to further evaluate the expression of DLL3
2) to further characterize the relationship between DLL3 expression levels and clinical benefit
3) to further characterize the pharmacodynamic biomarker γ-H2AX
4) to further evaluate potential prognostic or predictive gene signatures

The only pre-defined statistical hypothesis testing that will be conducted in the phase II portion of the study will be applied to the primary endpoint, ORR (see Section 10.1.1). All other efficacy and safety analyses will be descriptive.

10.1.1 Determination of Sample Size

The sample size for the dose escalation portion in this study is based on the need to establish the MTD/RP2D of SC16LD6.5 as a monotherapy. The sample size for the portion of this study is based on the dose-escalation rules described in Section 2. A minimum of 2 to a maximum of approximately 48 patients will be required for the dose escalation phase, depending on which dose level is determined as the MTD. The MTD will subsequently be used for the phase II portion of the study,

The phase I portion of the study will assess the overall risk-to-benefit of one, or more, doses and schedules being considered for the RP2D. This overall risk-to-benefit assessment will involve estimating the proportion of patients able to remain on study drug for ≥12 weeks. Discontinuation of study drug prior to 12 weeks would generally be the result of either unacceptable toxicity or disease progression. Historical estimates of 12 week PFS in studies utilizing topotecan for recurrent SCLC are approximately 50%. Enrollment of approximately 20 patients in the phase I portion of the study will provide a reasonable degree of confidence around the point estimate of 12 week tolerability.

The phase Ib retreatment and maintenance portion of the study will assess the tolerability and a preliminary estimate of the risk-to benefit of the RP2D and tolerability of the maintenance schedule by estimating the proportion of patients able to remain on the maintenance or

retreatment study drug for ≥12 weeks without unacceptable toxicity. Enrollment of approximately 10 patients with SCLC and 10 patients with LCNEC that are evaluable (completed one Treatment Course) for safety with DLL3 expression per cohort in this portion of the study will provide a reasonable degree of confidence around the tolerability and safety of SC16LD6.5 retreatment and maintenance and preliminary indications of anti-tumor activity.

For the phase II portion of this study, Simon's minimax two-stage design employing a binomial distribution is used to calculate the required sample size.

In this portion, the statistical assumptions will require 29 evaluable patients in the first stage and 38 evaluable patients in total. In the first stage, if ≤1 ORRs are seen in the first 29 patients, the study will stop any further recruitment and the treatment will be considered as not effective in this setting. However, if ≥2 ORRs are seen, an additional 9 patients will be recruited. The treatment will be considered worthy of further investigation if 5 or more ORRs are observed in the 38 patients in total. This sample size provides 90% power with a null hypothesis ORR of 5% versus an alternative hypothesis ORR of 20%, using one-sided testing at a 5% significance level.

Assuming that approximately 10-15% of enrolled patients will not undergo post-baseline response assessments, it is anticipated that approximately 45 patients will be enrolled in order to achieve 38 evaluable patients.

10.1.2 Randomization and Stratification

SC16LD6.5 will be administered at escalating doses in an open-label fashion as described in the protocol. No randomization or stratification is required.

10.1.3 Populations for Analysis

There will be three study populations defined for this study.

The safety population will consist of all patients who received at least one dose of SC16LD6.5. This population will be used in all baseline and safety summaries in both the dose escalation and phase II portions of the study.

The pharmacokinetic population will be a subset of the safety population and consist of all patients who have sufficient SC16LD6.5 PK data. All such patients will be evaluated for pharmacokinetics unless significant protocol deviations have impacted the data. Changes to the procedures, which may impact the quality of pharmacokinetic data, will be considered significant protocol deviations. Examples include sample processing errors that lead to inaccurate bio-analytical results and/or inaccurate dosing on the day of pharmacokinetic sampling.

The efficacy population will consist of all patients at the RP2D with measurable disease at baseline who complete at least 1 cycle of treatment and undergo at least one follow-up tumor evaluation.

10.1.4 Procedures for Handling Missing, Unused and Spurious Data

No imputation of values for missing data will be performed. Standard clinical monitoring and data management practices will be used to ensure the integrity of the data.

10.1.5 General Methodology

In general, data will be summarized by using counts and percents for discrete parameters, and by descriptive statistics (number of observations, mean, standard deviation, median, minimum and maximum) for continuous parameters. Subject disposition and baseline characteristics will be presented by dose level for all treated patients. Additional stratifications may be considered and will be detailed in the SAP. Data will be analysed as collected. No imputation of missing data is planned, but if performed, the methodology will be detailed in the SAP. All collected data will be presented in the data listings by dose level.

10.1.6 Baseline Comparisons and Patient Disposition

Demographic and baseline disease characteristic data summarization will be performed in order to descriptively assess the comparability of dose cohorts. Data to be tabulated will include demographic features such as gender, age, and race, as well as disease specific status and medical history. The number and percentage of patients who complete the study or who withdraw for any reason will be presented by dose cohort.

10.1.7 Safety Analysis

The safety will be assessed through the analysis of the reported incidence of treatment emergent AEs, including SAEs, dose-limiting toxicities, AEs leading to withdrawal, events of at least CTCAE Version 4.03 Grade 3 in severity, and AEs related to study treatment. Treatment emergent AEs are those with an onset on or after the initiation of therapy. Other safety endpoints include laboratory results, ECG findings, physical examinations, vital signs, and changes in ECOG status. A copy of CTCAE Version 4.03 scoring system may be downloaded from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

The adverse events will be summarized by MedDRA coding terms, System Organ Class (SOC), and preferred term for all treated patients and by dose level. The AEs will also be tabulated by maximum severity and maximum relationship to study drug where applicable. The number and percent of patients experiencing dose-limiting toxicities will be summarized by dose level, by DLT, and system organ class for all treated patients. Other safety endpoints, which include change from baseline in laboratory results and vital signs, and shifts in ECG findings, will be summarized throughout the study by visit for each dose level for all treated patients.

Concomitant medications will be coded using the WHO-Drug dictionary, and they will be listed and summarized by dose level for all patients.

10.1.8 Pharmacokinetics

Serum levels of SC16LD6.5 drug will be measured. Estimation of the pharmacokinetic parameters will be performed by non-compartmental methods. Descriptive statistics will be presented for the pharmacokinetic parameters by dose level.

10.1.9 Efficacy Analysis

Tumor measurements will be assessed by radiologic methods at baseline and subsequently every 6 weeks until 18 weeks of treatment has been completed, at which time assessments would be made 9 – 12 week intervals. Efficacy variables include:

- Overall Response, defined as the proportion of patients with confirmed Complete Response or Partial Response
- Duration of Objective Response (Complete Response or Partial Response), defined as the time from the initial CR or PR to the time of disease progression or death on study, whichever occurs first. For patients who are alive and have not experienced disease progression on study, duration of objective response will be censored at the day of the last tumor assessment
- Time to Progression (TTP), defined as the time from the first day of study drug administration (Day 1) to disease progression on study. Patients who do not have disease progression will be censored at the date of last disease evaluation.
- Progression Free Survival (PFS), defined as the time from the first day of study drug administration (Day 1) to disease recurrence or progression, or death on study. Patients who are alive and disease progression-free will be censored at the date of last disease evaluation.
- Overall Survival (OS), defined as the time from the first day of study drug administration (Day 1) to death. Patients who are alive at the end of study will be censored at the date of last contact.

Response and progression will be assessed according to RECIST v1.1 (Eisenhauer et al., 2009) with and without modifications noted in Section 2.4.3. Any patient with insufficient data to determine response will be classified as a non-responder.

These efficacy variables will be listed for all patients with measurable or evaluable disease by dose level. For the time-to-event endpoints Kaplan-Meier curves will be generated for the phase II portion of the study, and median event time and the associated 95% confidence interval will be provided for the efficacy population. In addition, landmark 3-month and 6-month PFS and OS estimates will be calculated along with the associated 95% confidence intervals. Duration of objective response will only be calculated for patients with an objective response.

10.1.10 Analysis Timepoints

The final statistical analysis for the phase II portion of the study will be scheduled when all

patients have completed at least one Treatment Course of study drug administration and have at least 28 days of follow-up.

Safety review will be performed prior to each dose escalation decision time point.

In the phase II portion of the study, the analysis of response rate to trigger the expansion to stage 2 of the Simon's 2-stage design will be performed as described in Section 10.1.1.

10.2 Data Quality Assurance

Quality assurance (QA) procedures are designed to ensure complete, timely, and accurate submission of data, and that protocol requirements and complications and/or adverse reactions are immediately identified. QA inspections may be carried out during the study by the Sponsor.

11 STUDY ADMINISTRATION

11.1 Study Initiation

Prior to the start of this study, all pre-investigational requirements must be met by the Principal Investigator and study site. These may include:

Current *Curricula Vitae* and current medical licenses of the Principal Investigator and all sub-investigators listed on Form FDA 1572; IRB name and address; written documentation of IRB submission and approval of the study protocol identified by protocol number and title and a copy of the IRB Informed Consent Form identified by protocol number and title.

Current laboratory certification of the laboratory(ies) doing analysis, as well as current normal laboratory ranges for all laboratory tests.

The Sponsor will require direct access to electronic and hard copy source/data documents for study-related monitoring, audits, IRB review, and regulatory inspection.

11.2 Study Completion

The planned study completion will occur 6 months after the LPI (last patient in) or 28 days after all patients have been discontinued from study drug, whichever occurs first. In the event that patients are continuing to receive study drug with ongoing clinical benefit at the time of study completion, the Sponsor will consider alternative methods to supply study drug (e.g. a 'roll-over' protocol requiring limited safety and efficacy follow-up). In addition, the Sponsor reserves the right to terminate the study earlier than the planned completion.

11.3 Clinical Supplies

The Principal Investigator will be responsible for the dispensing, inventory, and accountability of all clinical supplies, exercising accepted medical and pharmaceutical practices. An accurate and timely accountability record of the disposition of all clinical supplies must be maintained. The supplies and inventory record must be made available for inspection by the Sponsor or the designated Sponsor's representative upon request. Upon completion or termination of the study, once all drug accountability has been performed the Investigator will destroy SC16LD6.5 as per Site Pharmacy SOPs and/or return all remaining clinical supplies to the Sponsor who will destroy the study drug on the site's behalf. Under no circumstances will the Principal Investigator allow SC16LD6.5 to be used other than as directed by this protocol.

11.4 Retention of Study Records

The Principal Investigator will retain copies of the approved protocol, completed CRFs, informed consent documents, relevant source documents, and all other supporting documentation related to the project for a period of at least 2 years after the last approval of a marketing application in an ICH region or at least 2 years after the formal discontinuation of the clinical

development of the investigational product. These documents may be retained for a longer period by agreement with the Sponsor.

These files must be made available for inspection upon reasonable request by authorised representatives of the Sponsor and the corresponding regulatory agencies for the purposes of regulatory approval.

The Sponsor will provide the Principal Investigators with information concerning the current status of the investigational drug as it relates to the Investigator's obligation for the retention of study records. The Investigators should contact the Sponsor prior to disposing of any such records. The Sponsor will arrange for continued storage of all records, if necessary and as documented in the Clinical Study Agreement.

11.5 Publication of Study Results

To avoid disclosures that could jeopardize proprietary rights, Investigators are required to submit all publications to the Sponsor prior to submission to a publisher. The Sponsor will review any such submissions within 30 days of receipt.

11.6 Case Report Forms (CRFs) and Monitoring

The Principal Investigator must ensure there will be primary source documentation for all patient data collected as part of the study, and the data will not be recorded directly onto the eCRFs without the availability of such primary documentation. The source data may include such documents as clinical notes, laboratory results, pathology reports, radiology results, *etc*., and will be retained in each patient's medical record or research chart. CRFs will be provided by the Sponsor.

The Principal Investigator will be responsible for the timeliness, completeness, and accuracy of the information on the eCRF.

The Investigators or designated colleagues will provide access to the Medical Monitor or designated Sponsor representative(s) for the periodic review of source documents (*e.g*., hospital and clinic records) to assure accuracy and completeness of the eCRFs.

The Sponsor and designated Sponsor representative(s) will maintain frequent contact with each site to assure the study is conducted according to the protocol and that all data collected are accurate and complete. Any deficiencies identified during the study will be communicated to the site for prompt correction.

11.7 Confidentiality

Patient medical information obtained during the study is confidential and disclosure to third parties other than those noted below is prohibited. All patients will be assigned a study identification number. Patients will be identified on case report forms only by their subject number and initials.

At the patient's request, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection on request by representatives of FDA, state and federal health authorities, the Sponsor, and the IRB.

All published information from this study will be presented in such a way that it does not permit identification of individual patients. Subject identity will remain protected except as required by regulatory or legal inquiries.

To fully evaluate subject safety issues that may arise during the study, Sponsor, FDA, or state and federal authorities will require direct access to source documents including study related monitoring, audits, IRB review and regulatory inspection(s).

It must be explained to the patient before enrollment into the study that the patient's Protected Health Information (PHI) obtained during the study may be shared with the study, Sponsor, FDA, or state and federal authorities, and IRB regulatory inspections(s).

12 REFERENCES

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13 APPENDICES

Appendix A – Eastern Cooperative Oncology Group (ECOG) Performance Status (Oken, M.M., et al.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am. J. Clin. Oncol. 5:649-655, 1982)

Appendix B – Contraceptive Methods

Appendix C – Prophylactic and Clinical Management of Skin Rash

Appendix A

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.: Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am. J. Clin. Oncol. 5:649-655, 1982. Eastern Cooperative Oncology Group, Robert Comis, M.D., Group Chair.

Appendix B

Contraceptive Methods

Women of Child-Bearing Potential are Defined as Follows:

- Any female who has experienced menarche and does not meet the criteria for "Women Not of Childbearing Potential".

Women Not of Childbearing Potential are Defined as Follows:

- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy)
- Women who are >45 years of age, not using hormone replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (140 pmol/L)
- Women who are >45 years of age, using hormone replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone replacement therapy

Acceptable Contraception Methods:

Male patients with female partners of child-bearing potential and women patients of childbearing potential are required to use two forms of acceptable contraception, including one barrier method, during their participation in the study and for 4 weeks (women) or 3 months (men) following discontinuation of SC16LD6.5. Male patients must also refrain from donating sperm for 3 months following discontinuation of SC16LD6.5.

The following are acceptable forms of barrier contraception:

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

The following are acceptable forms of secondary contraception, when used with a barrier method and spermicide:

- True abstinence. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are **not** acceptable methods of contraception
- Male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)
- Placement of an intrauterine device (IUD) or intrauterine system (IUS), with the exception of IUD progesterone T
- Established use of oral, injected or implanted hormonal methods of contraception

The following are **unacceptable** forms of contraception for women of childbearing potential:

- IUD progesterone T
- Female condom
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Appendix C

Prophylactic and Clinical Management of Skin Rash

The following measures are recommended for all patients at initiation of study therapy:

- Preventive measures (patient instructions):
  1. Avoid unprotected sun exposure between 10 AM-4 PM
  2. Utilize ≥SPF30 broad spectrum sunscreen and protective clothing, a broad brimmed hat, and sunglasses when outdoors. Use 1 oz of sunscreen to cover entire body every two hours, or every one hour when swimming or sweating.

Photosensitivity Management Algorithm:

Toxicity Grade CTCAE v4.03	**Study Drug Administration**	**Recommended Management of Rash**
Grade 0	Continue Study Drug at current dose level	Sunscreen and Sun Protective Measures
Grade 1 (**<10% BSA** and no associated erythema or pruritus)	Continue Study Drug at current dose level	Low potency topical steroid (face) bid AND High potency topical steroid (body) bid
Grade 2 (**10 to 30% BSA** and associated with erythema or pruritus; limited instrumental activities of daily living [ADL])	Continue Study Drug at current dose level	Low potency topical steroid (face) bid And High potency topical steroid (body) bid AND NSAIDS (PO) prn pain
Grade ≥ 3 (**>30% BSA** AND associated with pruritus; limiting self care activities of daily living [ADL])	Dose reduce and monitor	Low potency topical steroid (face) bid AND High Potency topical steroid (body) bid AND Prednisone (0.5 mg/kg) for 7 days

Patients should be re-assessed every two to three weeks.