CALGB Study 30610 – Phase III Comparison of Thoracic Radiotherapy Regimens in Patients with Limited Small Cell Lung Cancer also Receiving Cisplatin and Etoposide

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1.0 OBJECTIVES

Primary

To determine whether administering high dose thoracic radiotherapy, 70 Gy (2 Gy once-daily over 7 weeks) or 61.2 Gy (1.8 Gy once daily for 16 days followed by 1.8 Gy twice daily for 9 days), will improve median and 2-year survival compared with 45 Gy (1.5 Gy twice daily over 3 weeks) in patients with limited stage small cell lung cancer.

Secondary:

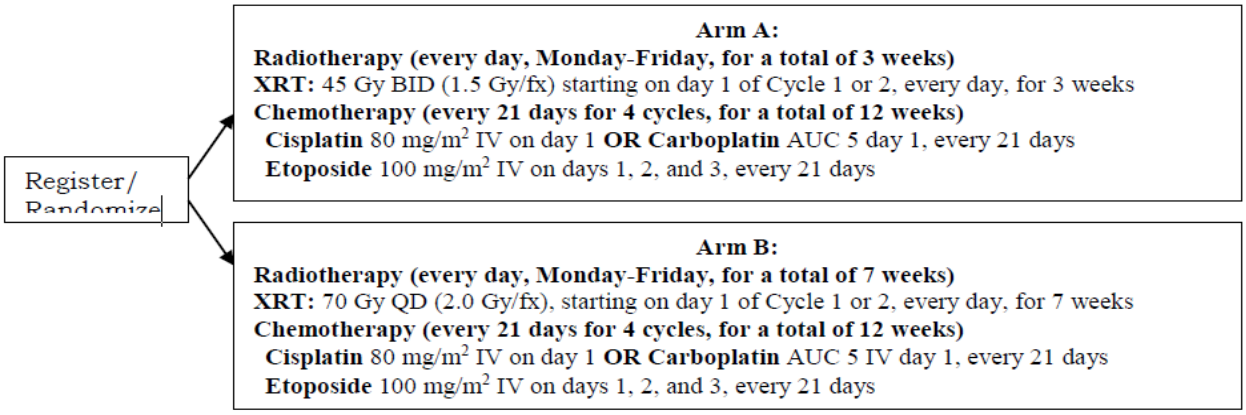
1. To compare treatment related toxic effects of thoracic radiotherapy regimens in patients with limited stage small cell lung cancer.
2. To compare response rates, failure-free survival and toxicity of thoracic radiotherapy regimens in patients with limited stage small cell lung cancer.
3. To compare rates of local relapse, distant metastases and brain metastases with these regimens.
4. To compare patients' quality of life between these treatment regimens in terms of their physical symptoms, physical functioning and psychological state.
5. To describe the patterns of use of thoracic intensity modulated radiation therapy (IMRT) in patients with limited stage small cell lung cancer.
6. To examine blood-based biomarkers of response and resistance to cisplatin and etoposide.
7. To evaluate the correspondence between increase in plasma ProGRP concentrations and disease progression/recurrence.
8. To evaluation the potential for plasma ProGRP concentrations at baseline, after each cycle of chemotherapy and at first evaluation following completion of chemotherapy to predict PFS and OS.
9. To evaluate the correspondence between longitudinal decreases in plasma ProGRP concentrations and clinical response.

2.0 CURRENT SCHEMA

Schema (1 cycle = 21 days)

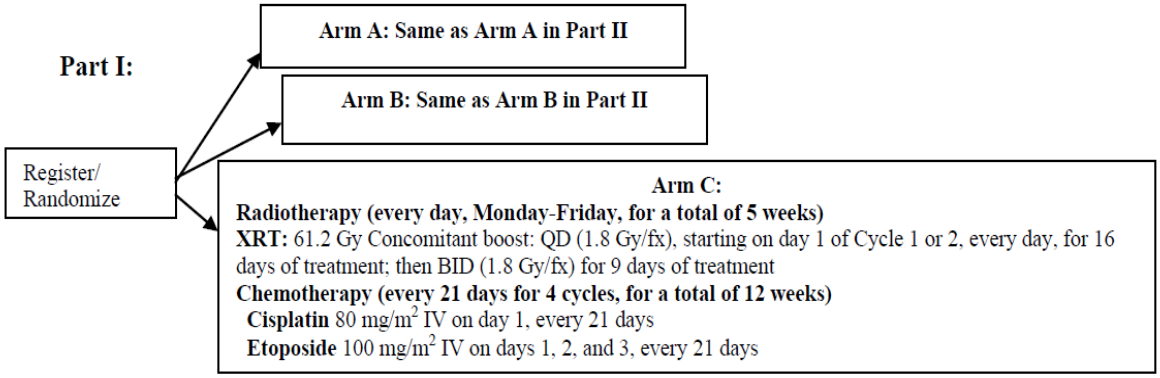
Patients will receive 4 cycles of chemotherapy

Part II: Based on the results of Part I, the experimental arm (Arm C) was discontinued and patients are randomized (as of 03/11/2013) as follows:



Prophylactic cranial irradiation (PCI) should be offered to all patients with a complete or near CR.

EFFECTIVE MARCH 10, 2013, PART I IS CLOSED TO FURTHER ACCRUAL



3.0 ELIGIBILITY CRITERIA

- Histologically or cytologically documented small cell lung cancer of limited stage.
- Measurable disease.
- No prior chemotherapy or radiotherapy for SCLC, apart from 1 cycle of chemotherapy
- No prior mediastinal or thoracic radiotherapy.
- Patients with complete surgical resection of disease are not eligible.
- Age ≥ 18 years.
- ECOG Performance Status 0-2.
- Non-pregnant and non-nursing.

4.0 TREATMENT SCHEDULE

The treatment schedule is described in detail in the Study Schema (Section 2.0 of this report).

5.0 STUDY DESIGN

5.1 Study Phase/Type of Design/Stratification Factors

This is a Phase III trial. The study is divided into two stages. In the first stage, eligible patients will be randomized with a 1:1:1 allocation to arm 1, 2 and 3. In the second stage, after the decision of dropping the experimental arm with higher toxicity is made, the study will continue with 2 remaining arms with 1:1 allocation.

All randomization will be made using a permuted-block scheme, stratified by gender (male vs. female); weight loss within 6 months prior to study entry (<=5% vs >5%); ECOG performance status (0 vs 1 vs 2); radiotherapy technique (IMRT vs 3D), radiotherapy start time: At first cycle of protocol chemotherapy, after one cycle of prior non-protocol chemotherapy vs. At first cycle of protocol chemotherapy, without prior non-protocol chemotherapy vs. At second cycle of protocol chemotherapy, without prior non-protocol chemotherapy, and Chemotherapy backbone, cisplatin vs carboplatin. As of March 10, 2013, Arm C was discontinued. The study will accrue a total of 729 patients over a period of 6 years, about 10 patients per month.

With a sample size of 729, at significance level of 2-sided 0.05, the power in detecting the survival improvement for the remaining experimental arm as compared to the standard arm is at least 81.9% using a stratified log-rank test.

5.2 Primary Endpoint

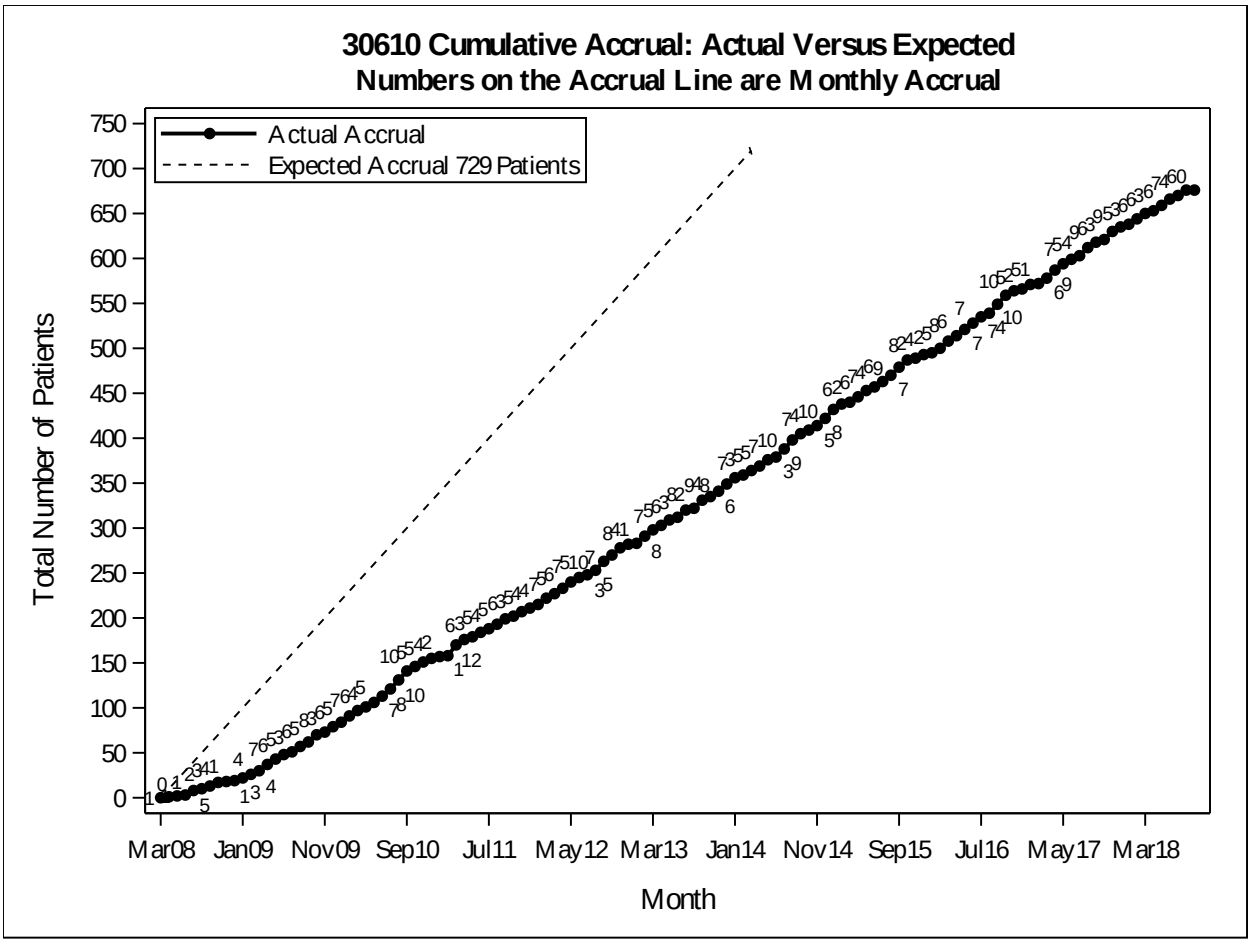
The primary endpoint is overall survival. Overall survival time is measured from date of randomization until death from any cause.

5.3 Target Accrual

The target accrual for this study is 729 patients. A 1:1:1 and 1:1 randomization were used before and after one treatment arm drop, respectively. The target accrual rate is 10 patients per month.

6.0 CURRENT ACCRUAL

Study Activation Date	03/15/2008
Target Accrual (n)	729 (636 for two remaining arms)
Current Accrual (n)	676 (583 for two remaining arms)
Expected Accrual Rate	10/month
Accrual Rate – Since activation	5.4/month
Accrual Rate – Past 12 months	5.3/month
Accrual Rate – Past 6 months	5.0/month
Projected closure date for a trial open for more than one year (based on accrual rate from past 12 months)	07/10/2019



7.0 CURRENT STUDY STATUS

This study opened on 3/15/2008. 616 of a targeted 729 patients have been accrued as of 09/06/2016. Toxicity interim analyses were conducted after 30, 50 and 70 patients enrolled to each experimental arm. One experimental arm (Arm C) was dropped. The adjusted new target accrual is changed to 729, or 636 for the remaining 2 arms.

8.0 PATIENT CHARACTERISTICS

All patients enrolled to 09/19/2017 are included in the following tables.

Table 8a. Demographics

	Arm A (N=290)	Arm B (N=293)	Arm C (N=93)	Total (N=676)
Age				
N	290	293	93	676
Mean (SD)	63.1 (8.0)	62.2 (8.2)	61.7 (8.0)	62.5 (8.1)
Median	64.0	63.0	62.0	63.0
Q1, Q3	57.0, 69.0	56.0, 68.0	56.0, 68.0	57.0, 68.0
Range	42.0, 81.0	37.0, 80.0	41.0, 77.0	37.0, 81.0
Race				

	Arm A (N=290)	Arm B (N=293)	Arm C (N=93)	Total (N=676)
White	250 (86.2%)	254 (86.7%)	80 (86.0%)	584 (86.4%)
Black or African American	26 (9.0%)	26 (8.9%)	11 (11.8%)	63 (9.3%)
Asian	4 (1.4%)	3 (1.0%)	1 (1.1%)	8 (1.2%)
American Indian or Alaska Native	2 (0.7%)	1 (0.3%)	1 (1.1%)	4 (0.6%)
Unknown	3 (1.0%)	5 (1.7%)	0 (0.0%)	8 (1.2%)
Not reported	5 (1.7%)	3 (1.0%)	0 (0.0%)	8 (1.2%)
More than one race	0 (0.0%)	1 (0.3%)	0 (0.0%)	1 (0.1%)
Gender				
Male	144 (49.7%)	140 (47.8%)	47 (50.5%)	331 (49.0%)
Female	146 (50.3%)	153 (52.2%)	46 (49.5%)	345 (51.0%)

Table 8b. Stratification Factors

	Arm A (N=290)	Arm B (N=293)	Arm C (N=93)	Total (N=676)
Weight Loss in 6 months				
<=5%	241 (83.1%)	249 (85.0%)	72 (77.4%)	562 (83.1%)
>5%	49 (16.9%)	44 (15.0%)	21 (22.6%)	114 (16.9%)
Performance Status				
0	131 (45.2%)	139 (47.4%)	40 (43.0%)	310 (45.9%)
1	146 (50.3%)	136 (46.4%)	48 (51.6%)	330 (48.8%)
2	13 (4.5%)	18 (6.1%)	5 (5.4%)	36 (5.3%)
Radiotherapy Method				
3D	123 (42.4%)	124 (42.3%)	59 (63.4%)	306 (45.3%)
IMRT	167 (57.6%)	169 (57.7%)	34 (36.6%)	370 (54.7%)
RT Start Time				
Cycle 1 after 1 cycle of NP Cx	60 (20.7%)	63 (21.5%)	0 (0.0%)	123 (18.2%)
Cycle 1 without prior NP Cx	133 (45.9%)	130 (44.4%)	60 (64.5%)	323 (47.8%)
Cycle 2 without prior NP Cx	97 (33.4%)	100 (34.1%)	33 (35.5%)	230 (34.0%)
Chemo Backbone				
Carboplatin	51 (17.6%)	44 (15.0%)	0 (0.0%)	95 (14.1%)
Cisplatin	239 (82.4%)	249 (85.0%)	93 (100.0%)	581 (85.9%)

9.0 ADVERSE EVENTS

9.1 Adverse Event Summary

602 patients are evaluable for adverse event (AE) analyses (Arm A: 260, Arm B: 262, Arm C: 88).

Commonly occurring grade 3+ AEs include leukocytes (51% on Arm A; 59% on Arm B; and 63% on Arm C), neutrophil count decreased (62% on Arm A; 67% on Arm B; and 71% on Arm C), hemoglobin decrease (19% on Arm A; 24% on Arm B; and 27% on Arm C).

There have been 16 deaths on treatment: 5 on Arm A (one multi-organ failure possibly related to treatment; 2 cardiac general (1 probably and 1 unrelated to treatment), and 2 deaths not associated with a CTC term (1 unlikely and 1 unreleated to treatment)), 8 on arm B (2 adult respiratory distress syndrome (1 unlikely and 1 probably related to treatment); 2 death unassociated with a CTC term (1 possibly and 1 unrelated to treatment); 1 cardiac disorder unlikely related to treatment, 1 sepsis definitely related to treatment and 2 sudden deaths not associated with a CTC term both possibly related to treatment), and 3 on Arm C (febrile neutropenia possibly related to treatment and 2 deaths not associated with a CTC term both unlikely related to treatment).

AEs on this study were reported using CTCAE version 3 before October 1, 2010. Starting from October 1, 2010, CTCAE version 4.0 has been utilized for AE reporting. See below for at least possibly treatment related adverse events.

Table 9a. Summary of Grade 3+ Adverse Events

Summary of Grade 3+ Adverse Events At least possibly related Number of Evaluable Patients: Arm A=260 Arm B=262 Arm C=88			
Patients with a maximum:	**Arm**	**n**	**(%)**
Total			
Grade 3 Event	A	71	*(27.3%)*
	B	64	*(24.4%)*
	C	21	*(23.9%)*
Grade 4 Event	A	129	*(49.6%)*
	B	142	*(54.2%)*
	C	56	*(63.6%)*
Grade 5 Event	A	2	*(0.8%)*
	B	5	*(1.9%)*
	C	1	*(1.1%)*
Hematologic Adverse Events			
Grade 3 Event	A	53	*(20.4%)*
	B	57	*(21.8%)*
	C	18	*(20.5%)*
Grade 4 Event	A	125	*(48.1%)*
	B	141	*(53.8%)*
	C	55	*(62.5%)*
Grade 5 Event	A	0	*(0.0%)*
	B	0	*(0.0%)*
	C	0	*(0.0%)*
Non-Hematologic Adverse Events			

Summary of Grade 3+ Adverse Events At least possibly related Number of Evaluable Patients: Arm A=260 Arm B=262 Arm C=88			
Patients with a maximum:	**Arm**	**n**	**(%)**
Grade 3 Event	A	95	*(36.5%)*
	B	103	*(39.3%)*
	C	41	*(46.6%)*
Grade 4 Event	A	24	*(9.2%)*
	B	26	*(9.9%)*
	C	10	*(11.4%)*
Grade 5 Event	A	2	*(0.8%)*
	B	5	*(1.9%)*
	C	1	*(1.1%)*
Note: Summaries are based on available patient data			

Table 9b. Listing of Grade 3+ Adverse Events

Listing of Grade 3+ Adverse Events Max Grade Per Patient Per Event At least possibly related Number of Evaluable Patients: Arm A=260 Arm B=262 Arm C=88							
		Grade of AdverseEvent					
	Arm	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
Hematologic Adverse Events							
Blood/Bone Marrow							
Blood/Bone Marrow - Other (Specify, __)	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	2	*(1%)*	1	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
CD4 count	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	3	*(1%)*	1	*(0%)*	0	*(0%)*
	C	0	*(0%)*	1	*(1%)*	0	*(0%)*
Hemoglobin	A	46	*(18%)*	3	*(1%)*	0	*(0%)*
	B	54	*(21%)*	7	*(3%)*	0	*(0%)*
	C	22	*(25%)*	2	*(2%)*	0	*(0%)*
Hemolysis	A	2	*(1%)*	0	*(0%)*	0	*(0%)*
	B	2	*(1%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Leukocytes (total WBC)	A	68	*(26%)*	65	*(25%)*	0	*(0%)*

Listing of Grade 3+ Adverse Events
Max Grade Per Patient Per Event
At least possibly related
Number of Evaluable Patients:
Arm A=260 Arm B=262 Arm C=88

		Grade of AdverseEvent					
	Arm	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
	B	73	(28%)	80	(31%)	0	(0%)
	C	27	(31%)	28	(32%)	0	(0%)
Lymphopenia	A	16	(6%)	5	(2%)	0	(0%)
	B	24	(9%)	17	(7%)	0	(0%)
	C	10	(11%)	10	(11%)	0	(0%)
Neutrophils/granulocytes (ANC/AGC)	A	46	(18%)	115	(44%)	0	(0%)
	B	54	(21%)	121	(46%)	0	(0%)
	C	18	(20%)	45	(51%)	0	(0%)
Platelets	A	15	(6%)	25	(10%)	0	(0%)
	B	18	(7%)	24	(9%)	0	(0%)
	C	9	(10%)	6	(7%)	0	(0%)
Non-Hematologic Adverse Events							
Allergy/Immunology							
Allergic reaction/hypersensitivity	A	1	(0%)	0	(0%)	0	(0%)
	B	2	(1%)	0	(0%)	0	(0%)
	C	3	(3%)	0	(0%)	0	(0%)
Auditory/Hearing							
Hearing loss	A	0	(0%)	0	(0%)	0	(0%)
	B	3	(1%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Tinnitus	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Cardiovascular							
Cardiac General - Other (Specify, __)	A	0	(0%)	0	(0%)	1	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Cardiac ischemia/infarction	A	0	(0%)	1	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Cardiac troponin I (cTnI)	A	0	(0%)	1	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)

Listing of Grade 3+ Adverse Events
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Number of Evaluable Patients:
Arm A=260 Arm B=262 Arm C=88

		Grade of AdverseEvent					
	Arm	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
Cardiopulmonary arrest	A	0	(0%)	1	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Hypertension	A	0	(0%)	0	(0%)	0	(0%)
	B	3	(1%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Hypotension	A	4	(2%)	0	(0%)	0	(0%)
	B	5	(2%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Left ventricular systolic dysfunction	A	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Supraventricular and nodal arrhythmia	A	2	(1%)	0	(0%)	0	(0%)
	B	1	(0%)	1	(0%)	0	(0%)
	C	0	(0%)	1	(1%)	0	(0%)
Thrombosis/thrombus/embolism	A	3	(1%)	0	(0%)	0	(0%)
	B	1	(0%)	1	(0%)	0	(0%)
	C	0	(0%)	2	(2%)	0	(0%)
Vasovagal episode	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Coagulation							
PTT (Partial Thromboplastin Time)	A	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Constitutional Symptoms							
Fatigue (asthenia, lethargy, malaise)	A	13	(5%)	1	(0%)	0	(0%)
	B	15	(6%)	2	(1%)	0	(0%)
	C	11	(13%)	1	(1%)	0	(0%)
Fever	A	2	(1%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Weight loss	A	2	(1%)	0	(0%)	0	(0%)

Listing of Grade 3+ Adverse Events
Max Grade Per Patient Per Event
At least possibly related
Number of Evaluable Patients:
Arm A=260 Arm B=262 Arm C=88

		Grade of AdverseEvent					
	Arm	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
	B	2	(1%)	0	(0%)	0	(0%)
	C	3	(3%)	0	(0%)	0	(0%)
Death							
Death not associated with CTCAE term	A	0	(0%)	0	(0%)	1	(0%)
	B	0	(0%)	0	(0%)	3	(1%)
	C	0	(0%)	0	(0%)	0	(0%)
Dermatology/Skin							
Hair loss/alopecia (scalp or body)	A	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Rash: dermatitis associated w/radiation	A	0	(0%)	0	(0%)	0	(0%)
	B	4	(2%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Gastrointestinal							
Anorexia	A	7	(3%)	0	(0%)	0	(0%)
	B	8	(3%)	0	(0%)	0	(0%)
	C	8	(9%)	0	(0%)	0	(0%)
Colitis	A	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Constipation	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Dehydration	A	31	(12%)	1	(0%)	0	(0%)
	B	35	(13%)	0	(0%)	0	(0%)
	C	12	(14%)	1	(1%)	0	(0%)
Diarrhea	A	5	(2%)	0	(0%)	0	(0%)
	B	3	(1%)	0	(0%)	0	(0%)
	C	2	(2%)	0	(0%)	0	(0%)
Dysphagia (difficulty swallowing)	A	26	(10%)	0	(0%)	0	(0%)
	B	28	(11%)	1	(0%)	0	(0%)
	C	13	(15%)	1	(1%)	0	(0%)
Esophagitis	A	9	(3%)	0	(0%)	0	(0%)

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		Grade of AdverseEvent					
	Arm	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
	B	18	(7%)	2	(1%)	0	(0%)
	C	3	(3%)	1	(1%)	0	(0%)
Gastrointestinal - Other (Specify, __)	A	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Heartburn/dyspepsia	A	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	3	(3%)	0	(0%)	0	(0%)
Mucositis/stomatitis (clinical exam)	A	2	(1%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Mucositis/stomatitis (func/symp)	A	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Nausea	A	17	(7%)	0	(0%)	0	(0%)
	B	23	(9%)	0	(0%)	0	(0%)
	C	11	(13%)	0	(0%)	0	(0%)
Stricture/stenosis (incl anastomot), GI	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Vomiting	A	13	(5%)	0	(0%)	0	(0%)
	B	16	(6%)	0	(0%)	0	(0%)
	C	5	(6%)	0	(0%)	0	(0%)
Hemorrhage							
Hemorrhage, GI	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Hepatic							
ALT, SGPT	A	1	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
AST, SGOT	A	1	(0%)	0	(0%)	0	(0%)
	B	2	(1%)	0	(0%)	0	(0%)

Listing of Grade 3+ Adverse Events
Max Grade Per Patient Per Event
At least possibly related
Number of Evaluable Patients:
Arm A=260 Arm B=262 Arm C=88

		Grade of AdverseEvent					
	Arm	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
	C	0	(0%)	0	(0%)	0	(0%)
Albumin, serum-low (hypoalbuminemia)	A	1	(0%)	0	(0%)	0	(0%)
	B	2	(1%)	1	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Bilirubin (hyperbilirubinemia)	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Infection/Febrile Neutropenia							
Colitis, infectious	A	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Febrile neutropenia	A	25	(10%)	11	(4%)	0	(0%)
	B	22	(8%)	9	(3%)	0	(0%)
	C	8	(9%)	1	(1%)	1	(1%)
Infection - Other (Specify, __)	A	2	(1%)	2	(1%)	0	(0%)
	B	1	(0%)	3	(1%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Infection w/ normal or Grade 1/2 ANC	A	3	(1%)	1	(0%)	0	(0%)
	B	2	(1%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Infection with Grade 3 or 4 ANC	A	6	(2%)	2	(1%)	0	(0%)
	B	4	(2%)	5	(2%)	1	(0%)
	C	3	(3%)	0	(0%)	0	(0%)
Infection with unknown ANC	A	2	(1%)	3	(1%)	0	(0%)
	B	1	(0%)	3	(1%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Metabolic/Laboratory							
Acidosis (metabolic or respiratory)	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Calcium, serum-low (hypocalcemia)	A	1	(0%)	1	(0%)	0	(0%)
	B	3	(1%)	1	(0%)	0	(0%)

Listing of Grade 3+ Adverse Events
Max Grade Per Patient Per Event
At least possibly related
Number of Evaluable Patients:
Arm A=260 Arm B=262 Arm C=88

		Grade of AdverseEvent					
	Arm	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
	C	1	(1%)	1	(1%)	0	(0%)
Glomerular filtration rate	A	0	(0%)	1	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Glucose, serum-high (hyperglycemia)	A	0	(0%)	1	(0%)	0	(0%)
	B	4	(2%)	1	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Lipase	A	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	1	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Magnesium, serum-low (hypomagnesemia)	A	0	(0%)	2	(1%)	0	(0%)
	B	3	(1%)	3	(1%)	0	(0%)
	C	3	(3%)	1	(1%)	0	(0%)
Metabolic/Laboratory - Other Spec	A	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Phosphate, serum-low (hypophosphatemia)	A	0	(0%)	1	(0%)	0	(0%)
	B	3	(1%)	0	(0%)	0	(0%)
	C	3	(3%)	0	(0%)	0	(0%)
Potassium, serum-high (hyperkalemia)	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Potassium, serum-low (hypokalemia)	A	16	(6%)	1	(0%)	0	(0%)
	B	18	(7%)	3	(1%)	0	(0%)
	C	10	(11%)	2	(2%)	0	(0%)
Sodium, serum-high (hypernatremia)	A	0	(0%)	0	(0%)	0	(0%)
	B	2	(1%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Sodium, serum-low (hyponatremia)	A	14	(5%)	3	(1%)	0	(0%)
	B	11	(4%)	1	(0%)	0	(0%)

Listing of Grade 3+ Adverse Events
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		Grade of AdverseEvent					
	Arm	3-Severe		4-LifeThr		5-Lethal	
		n	(%)	n	(%)	n	(%)
	C	3	(3%)	1	(1%)	0	(0%)
Uric acid, serum-high (hyperuricemia)	A	0	(0%)	1	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Musculoskeletal							
Muscle weakness (not due to neuropathy)	A	4	(2%)	0	(0%)	0	(0%)
	B	2	(1%)	0	(0%)	0	(0%)
	C	2	(2%)	0	(0%)	0	(0%)
Neurology							
Dizziness	A	0	(0%)	0	(0%)	0	(0%)
	B	2	(1%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Insomnia	A	1	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Mood alteration	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Neuropathy: sensory	A	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Seizure	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Syncope (fainting)	A	5	(2%)	0	(0%)	0	(0%)
	B	3	(1%)	0	(0%)	0	(0%)
	C	3	(3%)	0	(0%)	0	(0%)
Pain							
Pain	A	30	(12%)	0	(0%)	0	(0%)
	B	35	(13%)	2	(1%)	0	(0%)
	C	20	(23%)	1	(1%)	0	(0%)
Pain - Other (Specify, __)	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)

Listing of Grade 3+ Adverse Events
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		Grade of AdverseEvent					
	Arm	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
	C	0	(0%)	0	(0%)	0	(0%)
Pulmonary							
Adult Respiratory Distress Syndrome	A	0	(0%)	1	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	1	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Bronchospasm, wheezing	A	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Cough	A	1	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Dyspnea (shortness of breath)	A	6	(2%)	0	(0%)	0	(0%)
	B	15	(6%)	0	(0%)	0	(0%)
	C	2	(2%)	4	(5%)	0	(0%)
Hypoxia	A	2	(1%)	0	(0%)	0	(0%)
	B	6	(2%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Pleural effusion (non-malignant)	A	0	(0%)	0	(0%)	0	(0%)
	B	1	(0%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Pneumonitis/pulmonary infiltrates	A	3	(1%)	0	(0%)	0	(0%)
	B	3	(1%)	0	(0%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Pulmonary/Upper Respiratory - Other Spec	A	0	(0%)	0	(0%)	0	(0%)
	B	0	(0%)	2	(1%)	0	(0%)
	C	0	(0%)	0	(0%)	0	(0%)
Renal /Genitourinary							
Creatinine	A	7	(3%)	1	(0%)	0	(0%)
	B	4	(2%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)
Renal failure	A	1	(0%)	0	(0%)	0	(0%)
	B	2	(1%)	0	(0%)	0	(0%)
	C	1	(1%)	0	(0%)	0	(0%)

Listing of Grade 3+ Adverse Events
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		Grade of AdverseEvent					
	Arm	**3-Severe**		**4-LifeThr**		**5-Lethal**	
		n	**(%)**	**n**	**(%)**	**n**	**(%)**
Renal/Genitourinary - Other Spec	A	0	*(0%)*	1	*(0%)*	0	*(0%)*
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*
	C	0	*(0%)*	0	*(0%)*	0	*(0%)*
Vascular							
Thrombosis/embolism (vasc access-relate)	A	0	*(0%)*	0	*(0%)*	0	*(0%)*
	B	1	*(0%)*	0	*(0%)*	0	*(0%)*
	C	1	*(1%)*	0	*(0%)*	0	*(0%)*

10.0 IMBEDDED CORRELATIVES

There are two sub-studies within CALGB 30610:

1. CALGB 150712 is a correlative science study in CALGB 30610. If a patient answers “yes” to “My specimen(s) may be used for the research described above” question #1 in the model consent, they have consented to participate in this study. The patient should be registered to CALGB 150712 at the same time they are registered to the treatment trial (30610).

   As of 09/11/2018, 431 patients have enrolled to CALGB 150712. Assays are being performed.

2. CALGB 70702: Quality of Life study in CALGB 30610. If a patient answers “yes” to “I choose to take part in the Quality of Life study and agree to complete the Quality of Life questionnaires” question #5 in the model consent, the patient should be registered to CALGB 70702 at the same time they are registered to the treatment trial (30610).

   As of 09/11/2018, 418 patients have enrolled to CALGB 70702.