Closed Report

Hoosier Oncology Group protocol LUN01-24

A Phase III Trial of Cisplatin/Etoposide/Radiotherapy With or Without Consolidation Docetaxel in Patients with Inoperable Locally Advanced Stage III Non-Small Cell Lung Cancer (NSCLC)

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1 Introduction

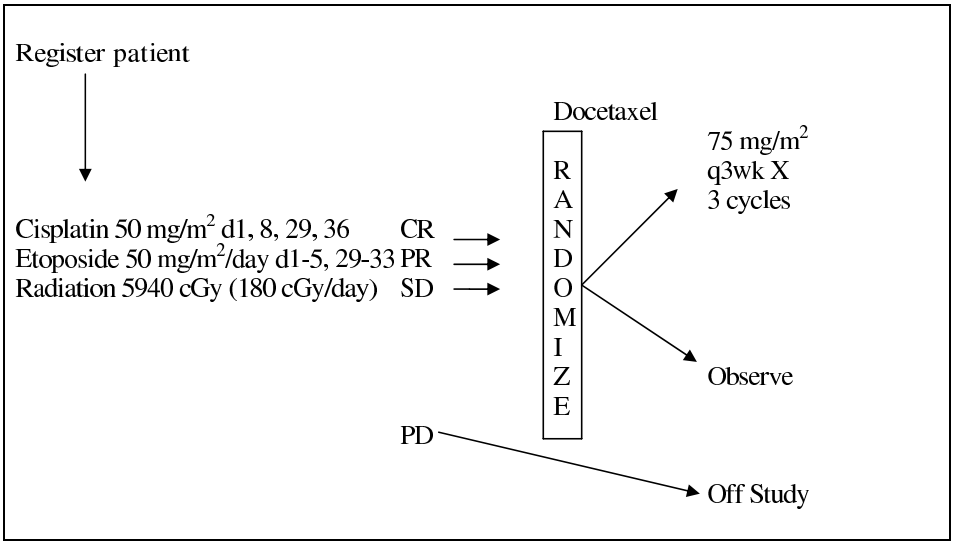
This is the open report of the first Data Monitoring Board review of Hoosier Oncology Group protocol LUN01-24, titled "A Phase III Trial of Cisplatin/Etoposide/Radiotherapy With or Without Consolidation Docetaxel in Patients with Inoperable Locally Advanced Stage III Non- Small Cell Lung Cancer (NSCLC)".

1.1 Protocol synopsis

LUN01-24 is a Phase III trial to assess whether consolidation therapy with docetaxel as compared with observation following cisplatin/etoposide/radiotherapy improves overall survival for patients with unresectable stage III non-small cell lung cancer (NSCLC). Secondary objectives are to assess whether consolidation therapy with docetaxel as compared to observation following cisplatin/etoposide/radiotherapy improves progression free survival and to further characterize the toxicity of the addition of docetaxel in this regimen.

The study schema is as follows:

Figure 1: Study schema



1.2 Treatment Schedule

Induction therapy will consist of cisplatin (50mg/m^2), etoposide (50mg/m^2/day) and radiation therapy administered as shown in the Induction Chemo-radiotherapy Calendar (Table 1).

Table 1: Treatment schedule.

Week	1					2	5					6	
Day	1	2	3	4	5	8	29	30	31	32	33	36	49
TREATMENT													
Cisplatin 50 mg/m^2	X					X	X					X	
Etoposide 50 mg/m^2/day	X	X	X	X	X		X	X	X	X	X		
Radiation therapy	X	X	X	X	X	X	X	X	X	X	X	X	X

The total dose of radiation therapy will be 5940 cGy in 33 fractions in 7 weeks. A volumetric treatment planning CT study will be required to define gross tumor volumes (GTV), and planning target volume (PTV). Following completion of induction chemoradiotherapy, patients must be re-assessed for disease status within 4-8 weeks. Patients without local progression of disease or distant metastases will then be randomized to receive consolidation therapy with docetaxel or observation. Patients will be stratified and randomized based on stage IIIa vs. IIIb disease at baseline, CR vs. non-CR following induction chemoradiation, and ECOG PS 0 or 1 versus 2. Docetaxel 75mg/m^2 will be administered as consolidation treatment in 3 cycles on day 1, 22 and 43 of consolidation treatment.

Procedures to be performed include: history and physical, height, weight, body surface area (BSA), ECOG, spirometry test, pregnancy test (if pre-menopausal female), blood chemistries, serum creatinine or calculated creatinine clearance, complete blood count (CBC), differential, and platelet count, CT or MRI of the brain, chest and upper abdominal CT, chest X-ray, toxicity evaluation, disease evaluation. Patients are to be followed every three months if less than 2 years from study entry; and every six months if 2 5 years from study entry; and annually if greater than 5 years from study entry. All patients will be followed until death.

For chemotherapy, no dose escalation will be allowed. Chemotherapy doses may be reduced for hematologic and non-hematologic effects. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicity will be graded using the NCI Common Toxicity Criteria, Version 2.0. Treatment may be delayed no more than two weeks to allow recovery from toxicity.

Radiotherapy interruptions or delays will be permitted only for any $>$ grade 3 non-hematologic toxicity or any grade 4 hematologic toxicity or as determined to be appropriate by the treating radiation oncologist.

2 Study history

Study Activation: January 2002

Version Dates:

10/29/2001 Original version

11/27/2001	Requested changes from Scientific Review
02/08/2002	Administrative changes
08/06/2002	Administrative changes
03/24/2003	Administrative changes, treatment clarification
09/03/2003	Site added, HIPAA language added, administrative changes
03/03/2005	Revised due to updated accrual and randomization rates

Study support granted from Sanofi-Aventis as study GIA 12134

For full details of the original study design considerations, please refer to the statistical sections of previous protocol versions. For statistical details pertaining to the most recent amendment please see next Section.

3 General Design Issues

LUN01-24 was designed as a randomized two-arm study to assess whether consolidation therapy with docetaxel as compared with observation following cisplatin/etoposide/radiotherapy improves overall survival for patients with unresectable stage IIIA (N2) or Stage IIIB non-small cell lung cancer (NSCLC). It is projected that the control group (observation after chemoradiation) will achieve a median overall survival of 15 months, while the treatment group (additional treatment with docetaxel) will have an increase in median survival to 25 months. Of the planned 230 registered patients, 10% were expected not to be randomized due to progressive disease following induction therapy.

Changes in the trial design of the 03/03/05 Version study plan were prompted by revised estimates of accrual and randomization rates, resulting in a slight increase in accrued patients, decrease in randomized sample size, and slightly lower power. The percentage estimate of accrued patients not randomized due to progressive disease increased in the 03/03/05 Version to 30% compared to 10% in the 09/03/03 Version. Randomization rate was reduced from 11.7 patients per month in Version 03/03/05 to 3.3 patients per month in Version 09/03/03. Other changes of the 03/03/05 Version from the 09/03/03 Version include reduction of power to 80% from 85% and reduction of sample size from 210 to 180 randomized patients (corresponding to 230 and 259 accrued patients, respectively, based on revised estimates of accrual and randomization rates). In addition, an interim analysis and a study-monitoring plan have been added to the protocol.

Version 09/03/03

The 09/03/03 Version of this study planned to randomize 210 patients (105 to each group) based on the power calculation discussed below. The plan was to accrue 230 patients since it was expected that 10% of the patients accrued would not be randomized due to progressive disease following induction therapy. Patient accrual was to occur for approximately 18 months and the follow-up of the patients was to continue for the lifetime of each patient. The sample size was calculated by assuming 5% two-sided type I error and 85% power. About 137 deaths were expected at the time of final data analysis

Version 03/03/05

The 03/03/05 study version plan is to randomize 180 patients (90 to each group) over 55 months (3.3 patients per month) based on the power calculation discussed below. The plan is to accrue 259 patients in total 4.7 per month for 55 months), since it is expected that up to 30patients accrued will not be randomized due to progressive disease, toxicity, death, other causes following induction therapy. Patient accrual occurs for approximately 55 months and patient follow-up continues for ten months after the last patient has been enrolled.

The sample size is calculated by assuming 5% two-sided type-I error (alpha level) and 80% power. About 124 deaths are expected at the time of final data analysis. Uniform patient accrual has been assumed along with exponential distribution of (overall) survival times (i.e., constant hazard of failure at any time point).

In the 03/03/05 study version plan, interim analysis will be performed at approximately half way through the study (when approximately 62 confirmed deaths have been observed among patients randomized to the study). The analysis will involve an interim look at efficacy data comparing the two treatment arms. The primary endpoint of overall survival will drive the analysis results although secondary endpoints (progression-free survival) and safety data (toxicities, adverse events) will be summarized and considered. For early stopping under the null hypothesis, no survival improvement, or the alternative, survival benefit associated with the docetaxel or observation arm, the OBrien-Fleming (1979) boundaries will be used. If the test of equality in the overall survival between the two arms results in a two-sided p value of 0.0031 or less, a DSMB recommendation to stop the study early will be warranted, since a large enough survival advantage associated either with the docetaxel or observation arm will have been detected. If, on the other hand, the p value of the same comparison is larger than 0.7271, this would constitute evidence of futility, meaning that the current study would be unlikely to show a survival advantage between either the docetaxel or observation arm if allowed to be completed. In that case the study a DSMB recommendation to stop the study during the interim analysis will be warranted.

The exact time of the interim data analysis will depend on scheduling issues, along with the statistical requirements. If the analysis occurs at a time when more or less than half of the expected endpoints have been observed, the Lan-DeMets alpha spending function approach will be used (e.g., DeMets & Lan, 1994).

4 Subject characteristics

4.1 Demographics

Demographic information is presented in Table 2 both for categorical and continuous measures. There are no statistically significant differences, in terms of demographic factors, between the two treatment arms.

Table 2: Demographic information

Characteristic	Total ($N = 147$)		Randomization arm X ($N = 73$)		Y ($N = 74$)		p-value
Ethnicity (N, %)							0.364[a]
Non-Hispanic	24	19.4	14	23.3	10	15.6	
Unknown	100	80.6	46	76.7	54	84.4	
Missing[b]		23	13		10		
Race (N, %)							>0.999[a]
White	137	94.5	68	94.4	69	94.5	
Black or African American	7	4.8	4	5.6	3	4.1	
Unknown	1	0.7			1	1.4	
Missing	2		1		1		
Sex (N, %)							0.284[a]
Female	44	29.9	25	34.2	19	25.7	
Male	103	70.1	48	65.8	55	74.3	
Age							0.613[c]
Mean		62.39		62.62		62.11	
Std Dev		9.55		9.41		9.75	
Median		62.00		62.00		62.00	
Min		33.00		37.00		98.00	
Max		98.00		33.00		86.00	

[a] Fisher's exact test (two-sided)
[b] Percentages are based on non-missing data
[c] Kruskal-Wallis test

4.2 Baseline characteristics

Further baseline characteristics for all randomized patients (N=147) are presented in Table 3.

4.2.1 Induction period

During the induction phase are presented in Table 3. There are no statistically significant differences with respect to FEV1 levels, PET scans, performance status (PS), smoking profile, stage of disease and weight loss between the two arms during the induction phase for those patients that reached randomization.

Table 3: Baseline characteristics

	Total		Randomization arm				
			X		Y		
Analysis variable	*N*	%	*N*	%	*N*	%	p-value
Baseline FEV1 Level							0.120[a]
>1	144	98.0	70	95.9	74	100.0	
≤ 1	3	2.1	3	4.1	0	0.0	
PET Scans							**0.168**
Yes	94	64.4	42	57.5	52	71.2	
No	52	35.6	31	42.5	21	28.8	
Missing[b]	1				1		
PS							0.868
0	86	58.5	42	57.5	44	59.5	
1	61	41.5	31	42.5	30	40.5	
Prior Surgery							0.639
Yes	21	15.1	9	13.2	12	16.9	
No	118	84.9	59	86.8	59	83.1	
Missing	8		5		3		
Smoking							0.523
Never smoked	4	3.0	2	2.9	2	3.0	
Hasn't smoked in ≥ 30 years	5	3.7	1	1.4	4	6.1	
Quit > 3 months ago but < 30 years ago	62	45.9	31	44.9	31	47.0	
Current Smoker	64	47.4	35	50.7	29	43.9	
Missing	12		4		8		
Stage							0.866
IIIA	59	40.4	30	41.7	29	39.2	
IIIB	87	59.6	42	58.3	45	60.8	
Missing	1		1				
Wt. Loss							0.120
Yes	3	2.0	3	4.1	0	100.0	
No	144	98.0	70	95.9	74	0.0	

[a] Fisher's exact test (two-sided)
[b] Percentages are based on non-missing data

5 Survival analysis

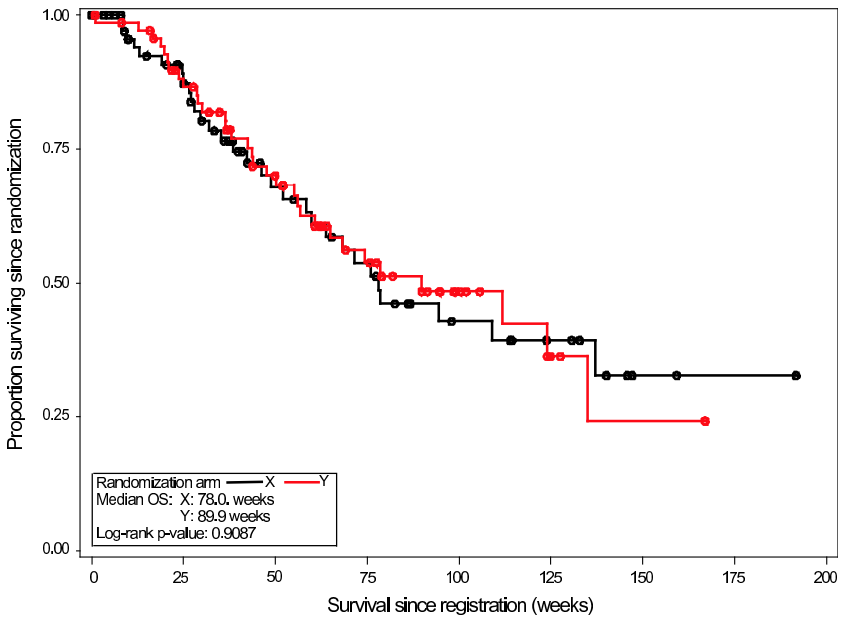
There are 144 patients, out of the 147 that were randomized to therapy, 73 (out of 73) patients in arm X and 71 (out of 74) in arm Y with available survival data (two-sided Fisher's exact test p=0.245) and 139 patients (68 out of 73 in arm X and 71 out of 74 in arm Y) with progression information (two-sided Fisher's exact test p=0.494). We performed a Kaplan-Meier analysis to estimate the survival distribution for overall survival (OS) and progression-free survival (PFS) in the two randomization arms. The time of origin was the randomization date for those 147 patients randomized to therapy. Patients that have died were considered as having reached the primary endpoint (OS) while those that were alive were considered censored at the last visit date. Similarly, patients that had experienced progression of their disease or, if they had not progressed, died, were considered as having reached the secondary endpoint (PFS). Those that had experienced neither progression or death were considered censored at the last time they were known alive and without progression of their disease.

Figures 2 and 3 present the analysis of overall (OS) and progression-free survival (PFS) respectively. It should be noted that, in these subsequent analyses, we have not distinguished death due to progression of disease from death due to other causes when defining overall survival or progression-free survival.

5.1 Overall survival (OS)

The overall experience with respect to overall survival is presented in Figure 2. Out of the 144 patients with survival information, 62 have died during the study, (30 in arm X and 32 in arm Y).

Figure 2: Overall survival by randomization arm

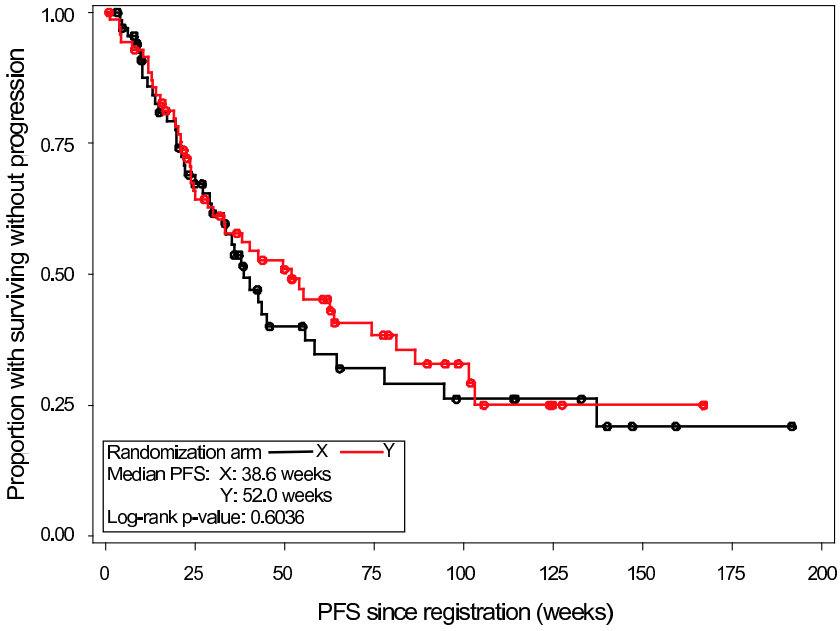


The median time to death in arm X is 78.0 weeks (approximately 17.9 months) since randomization. The median time to death in arm Y is 89.9 weeks (approximately 20.7 months) since randomization. The log-rank p value of the comparison between the two arms is 0.9087 implying that there is no statistically significant difference with respect to overall survival from randomization to death between the two arms.

5.2 Progression-free survival (PFS)

The experience with the secondary endpoint of the study, progression-free survival, is presented in Figure 3. Out of 139 randomized patients with progression and survival information, 39 out of 68 randomized in arm X experienced progression or death during the study. Out of 71 patients randomized in arm Y 42 experienced this event. The median time to progression or death in arm

Figure 3: Progression-free survival by randomization arm



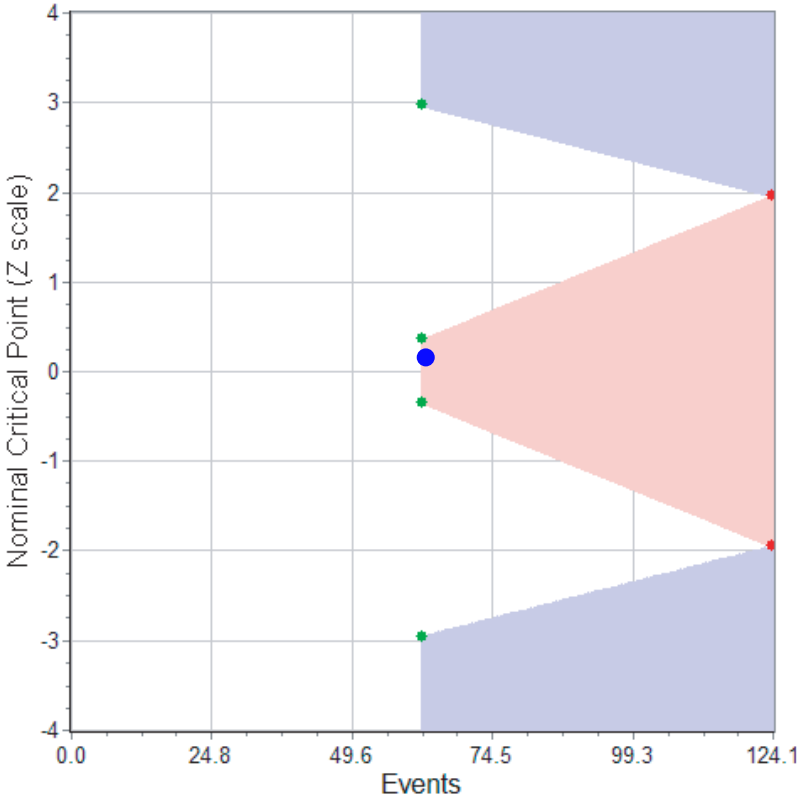
X is 38.6 weeks (approximately 8.9 months) since randomization. The median time to death in arm Y is 52.0 weeks (approximately 12 months) since randomization. The log-rank p value of the comparison between the two arms is 0.6036 implying that there is no statistically significant difference with respect to progression-free survival from randomization between the two arms.

5.3 Group sequential analysis

Figure 4 below shows the critical regions of the group sequential study design that involves an interim analysis at the halfway point of the study (i.e., when 62 out of 124 expected events – deaths – are observed in the study). The blue dot signifies the attained statistic from this first

interim analysis ($0.115 = \sqrt{0.0132}$ where 0.0132 is the log-rank –chi-square– statistic resulting from the Kaplan-Meier analysis).

Figure 4: O'Brien-Fleming bounds



6 Summary and recommendations

Inspection of Figure 4 shows that the statistic produced by the interim-analysis data is within the region that would require early interruption of the study (pink color) in favor of the null hypothesis of no difference between the two arms (docetaxel and observation). Put more simply, the interim findings imply that there is very small probability that this study, should it be allowed to continue, will ever establish a statistically significant difference favoring either of the two arms.

It is the recommendation of the statisticians that the study be stopped at this interim analysis.