A case study: LUN01-24

Consolidation therapy in inoperable non-small cell lung cancer

Background
Non-small-cell lung cancer (NSCLC)

Lung cancer is the leading cause of cancer death in men and women in the U.S. Approximately, 80%-85% of lung cancers are NSCLC.

The standard of care for patients with unresectable stage-III NSCLC, at the time of the LUN01-24 study, was concurrent chemotherapy and radiotherapy. Regardless of which treatment modality was used, data at the time suggested a plateau in median survival from diagnosis of 12-18 months

What was controversial at the time was whether additional ("consolidation") therapy after chemoradiation would confer additional benefit to the patients.

The LUN01-24 trial

Hoosier Oncology Group protocol LUN01-24 compared the effect of *consolidation therapy* versus no therapy after chemotherapy and radiotherapy in overall and progression-free survival.

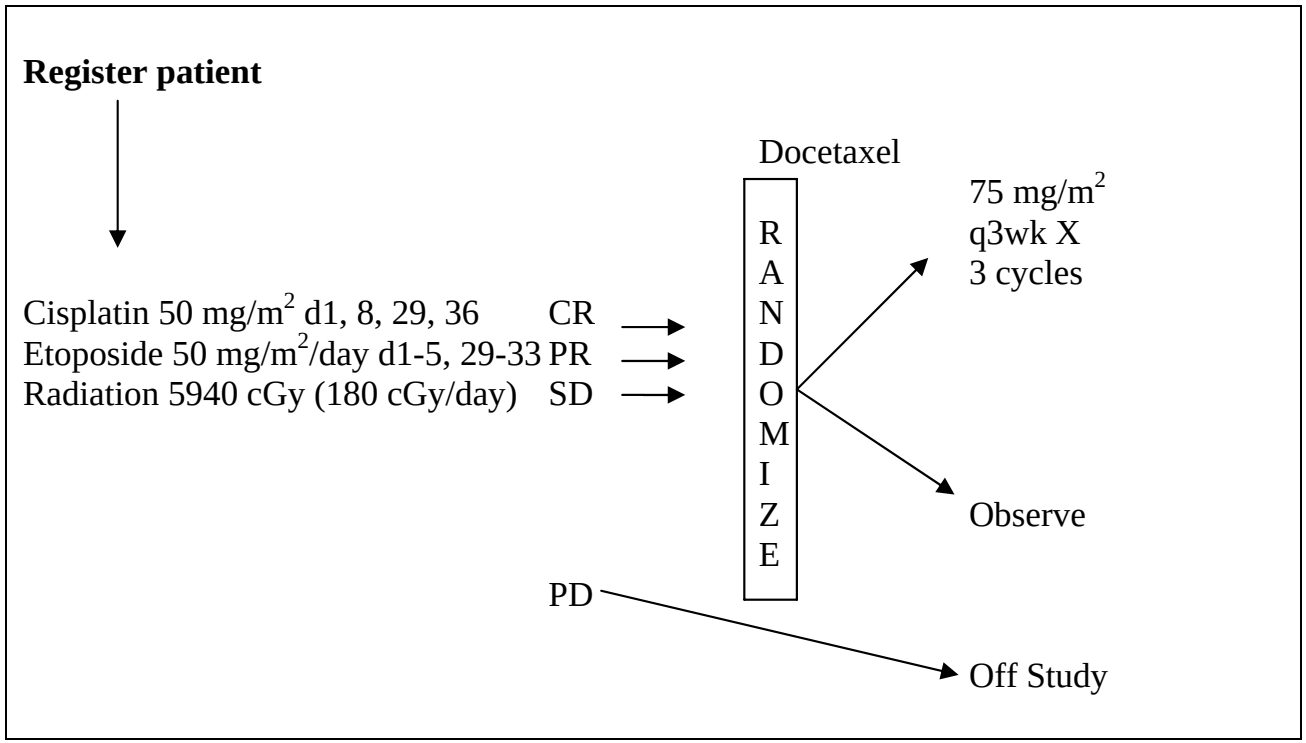

Figure 1: LUN01-24 protocol schema

Chemotherapy drug formulations

DRUG	DOSE	ROUTE	DAYS	NOTES
Cisplating	50 mg/m^2/d	IV	1,8,29,36	In 250 ml NS over 60 min
Etoposide	50 mg/m^2/d	IV	1-5, 29-33	In 250 ml NS over 60 min

Radiation

Radiation therapy will commence on the first day of the chemotherapy dose schedule. Total dose to the involved areas will be 5940 cGy.

This will be administered at 1.8 Gy daily, 5 days a week for total of 25 fractions (45 Gy) to the primary and mediastinum (primary planning target volume: I^o PTV) followed by a boost to the primary and involved nodes (secondary planning target volume: 2^o PTV) to 1.8 Gy daily in 8 fractions (1440 Gy).

The total dose will be 5940 cGy in 33 fractions in 7 weeks.

A volumetric treatment planning CT study will be required to define gross tumor volumes, and planning target volume.

Consolidation therapy with Doxetaxel

All eligible patients will have repeat tumor measurements with CT scan imaging within 4-8 weeks of completion of chemoradiotherapy. Consolidation will be administered as follows:

1. Patients with non-progressing disease (CR, PR, or SD), after completion of chemoradiotherapy will then be randomized to receive consolidation chemotherapy with docetaxel or observation.
2. Chemotherapy with docetaxel will begin approximately 4-8 weeks after completion of chemoradiation.
3. Dexamethasone 8 mg p.o. bid will be given beginning 24 hours prior to each course of docetaxel on days 0-2.
4. Docetaxel will be given at 75 mg/m2 IV over 60 minutes on day 1. Cycles will be repeated every 21 days for a total of 3 cycles.

Study objectives

The primary and secondary objectives of the study are as follows:

1. The primary objective of this study is 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).
2. The secondary objectives of this study are
    1. Assess whether consolidation therapy with docetaxel as compared to observation following cisplatin/etoposide/radiotherapy improves progression-free survival
    2. Further characterize the toxicity of the addition of docetaxel in this regimen.

Eligibility criteria for chemoradiation
Inclusion criteria

Inclusion criteria for chemotherapy are as follows:

1. Confirmed unresectable stage-IIIA or IIIb NSCLC with disease not extending to the cervical region
2. Measurable disease documented by CT, MRI, X-ray or physical exam within 28 days prior to study treatment
3. Serum creatinine < 2 mg/dl or calculated creatinine clearance > 50 cc/min
4. Pre-registration FEV1 > 1 liters by spirometry within 42 days prior to study treatment
5. Specific labs (ANC, hemoglobin, etc.) within appropriate limits
6. ECOG performance status (PS) 0 or 1 at the time of registration prior to chemoradiation
7. Ability and willingness to give informed consent

Eligibility criteria for chemoradiation
Exclusion criteria

Non-fulfillment of eligibility criteria plus

1. Patients with unintended weight loss $>$ 5% body weight in the preceding 3 months
2. No symptomatic peripheral neuropathy
3. Most prior malignancies
4. No significant history of heart disease, relevant allergies or hearing loss
5. Pregnant or nursing women
6. Men and women of childbearing potential must be willing to consent to using effective contraception while on treatment and for 4 weeks following completion of protocol treatment

Eligibility criteria for consolidation therapy

Following completion of induction chemoradiotherapy, patients without local progression of disease or distant metastases will be randomized to receive consolidation therapy with docetaxel or observation.

Patients will be stratified and randomized based on stage IIIa versus IIIb disease at baseline, complete response (CR) versus non-CR and ECOG PS 0 or 1 versus 2.

Patients must have completed chemoradiotherapy per protocol and at least 4 and no more than 8 weeks must have elapsed from the last from the last day of radiation

Patients must have undergone re-staging tests according to the study calendar and have no evidence of disease progression.

Changes in the document

A number of protocol amendments occurred during the life of the protocol:

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

We will concentrate here on the August 6, 2002 version ("version 1") and the March 3, 2005 version ("version 2").

Study calendar

	Induction Chemo-radiotherapy													Consolidation Therapy or Observation				
Course	Pre-Study													4-8 weeks following induction therapy				Follow-up[5]
Week		1					2	5					6			1	2	3	
Day		1	2	3	4	5	8	29	30	31	32	33	36	49		1	22	43	
TREATMENT																			
Cisplatin 50mg/m2		X					X	X					X						
Etoposide 50mg/m2/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					
Docetaxel 75mg/m2																X	X	X	
REQUIRED STUDIES																			
History & Physical	X[1]							X							X[1]		X	X	X
Toxicity Assessment	X[1]						X						X						
Height, Weight, BSA	X[1]							X							X[1]		X	X	
ECOG Performance Status	X[1]						X	X					X		X[1]		X	X	
Spirometry (FEV1)	X[2]																		
Audiogram	X[3]																		
LABORATORY STUDIES																			
SMA-12 or Equivalent	X[1]						X	X					X		X[1]		X	X	
Serum creatinine or calculated creatinine clearance	X[1]						X	X					X		X[1]		X	X	
CBC, differential, Platelet Ct	X[1]						X[5]	X[5]					X[5]	X[5]	X[1]		X[5]	X[5]	
Urine Pregnancy Test (if pre-menopausal female)	X[4]																X	X	
RADIOLOGICAL STUDIES																			
CT or MRI of the brain	X[1]																		
Chest and upper abdominal CT	X[1]														X[1]				X
Chest X-ray	X[1]												X		X[1]		X	X	X
Tumor Measurements	X[1]														X[1]				X
Bone Scan (if clinically indicated)	X[1]																		
Informed Consent Form	X																		
Confirmation Form	X														X				

1. H & P, height, weight, BSA, SMA-12, serum creatinine or calculated creatinine clearance, CBC, diff, and Plts, are to be obtained within 14 days prior to beginning study treatment. Patients must have a brain CT or MRI to document no CNS metastases within 28 days prior to study treatment.
2. Spirometry test (FEV1) is to be obtained within 42 days prior to beginning study treatment.
3. Performance of an audiogram is recommended (but not required) to document baseline hearing status in the event of possible further hearing loss due to cisplatin administration.
4. Women of childbearing potential must have urine pregnancy test obtained within 14 days prior to beginning study treatment.
5. CBC, diff and Plts to be obtained weekly while on study treatment.
6. 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.

Toxicity modifications

An elaborate dose modification protocol was established based on the following dose-reduction schedule:

Dose level	Cisplatin	Etoposide
Starting dose	50 mg/m^2/d	50 mg/m^2/d$\times$5 days
-1 level	25 mg/m^2/d	50 mg/m^2/d$\times$4 days

Dose modifications for docetaxel toxicity are similar

Dose level	Dose
Full dose	75 mg/m^2/d
-1 level	55 mg/m^2/d
-2 level	35 mg/m^2/d

Radiation interruptions/delays

Interruptions of therapy up to one week are allowed but irradiation should be completed to the prescribed doses.

If more than one-week interruption is required, radiotherapy interruptions or delays will be permitted only for $>$ grade-3 non-hematologic toxicity or any grade-4 hematologic toxicity or as determined to be appropriate by the treating radiation oncologist.

Patients with severe esophagitis may be provided symptomatic treatment such as antacids, sucralfate, viscous lidocaine, and dyclonine as well as dietary supplements. If treatment for severe esophagitis results in a delay of greater than one week, this may be grounds for treatment removal and should be discussed with the principal investigator.

Statistical considerations
Endpoint definition

- Overall survival (OS

  OS is defined as the time from randomization to death (event) or end of study (censored observation)

- Progression-free survival (PFS)

  Progression is defined as one or more of the following:

  1. 20% increase in the sum of longest diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same technique as baseline.
  2. Unequivocal progression of non-measurable disease in the opinion of the treating physician
  3. Appearance of any new lesion/site.
  4. Death due to disease without prior documentation of progression and without symptomatic deterioration.

  Time to progression-free survival is defined as the time from randomization to death or progression (event), whichever happens first, or end of study

Event-size calculations
version 1

The sample size is calculated by assuming 5% two-sided type-I error and 85% power.

It is assumed that the median survival in the control (observation) group will be $m_0 = 15$ months and $m_1 = 25$ months in the experimental (consolidation) group. This means that the study effect is

$$\delta = \log(\lambda_1/\lambda_0) = \log(m_0/m_1) = \log(15/25)$$

leading to an event size

$$D = \frac{4(1.96 + 1.0364)}{[\log(15/25)]^2} \approx 138$$

total events (deaths) are expected at the time of final data analysis.

Sample size

We assume that patients will enter the study uniformly over an 18-month period at a rate of just under 12 patients per month. The following output summarizes the statistical approach:

```
Fixed design, two-arm trial with time-to-event
outcome (Lachin and Foulkes, 1986).
Solving for:  Follow-up duration
Hazard ratio                    H1/H0=0.6/1
Study duration:                     T=39.0097
Accrual duration:                     18
Min. end-of-study follow-up: minfup=21.0097
Expected events (total, H1):          136.8705
Expected sample size (total):         210.06
Accrual rates:
     Stratum 1
0-18     11.67
Control event rates (H1):
      Stratum 1
0-Inf    0.0462
Censoring rates:
      Stratum 1
0-Inf         0
Power:                   100*(1-beta)=85%
Type I error (1-sided):   100*alpha=2.5%
Equal randomization:           ratio=1
```

Thus, $N_1 = N_2 = 105$ patients will be enrolled in each group.

Version 2

As time passed, two major issues became apparent:

- The patient accrual was nowhere near the number of patients needed for the study (i.e., almost 12 per month)
- Many fewer patients met eligibility criteria after completion of chemoradiation, to be randomized either to consolidation or observation (70% versus 90%)

In addition, two other issues arose:

- It became clear that an interim analysis would be required
- A DSMB should be used to monitor the results of this interim analysis

Event-size calculations
Version 2

In version 2 of the protocol (3/3/2005), power was reduced to 80% from 85%. The alpha level and other assumptions about median survival remained unchanged. This results in

$$D = \frac{4(1.96 + 0.84)^2}{[\log(0.6)]^2} \approx 121$$

total events necessary to produce 80% power to detect a 40% reduction in the hazard of mortality in these patients.

Sample-size calculation and interim analysis

An interim analysis was added where one interim review of the data was to be carried out at the 50% trial fraction, using a two-sided O'Brien-Fleming spending function according to the Lan & DeMets formulation.

In addition to the rejection regions for efficacy, a two-sided futility region ("inner wedge") was added.

In total, $N = 180$ total patients were to be randomized over 18 months (3.3 per month) out of an expected 259 patients who would enter the induction phase. The revised number of total events was $D' = 124$, meaning that the interim analysis was to be undertaken after about 62 events were observed.

The regions of this design are shown in Figure 2. In that figure, the light blue region is the rejection region which would stop the study and the pink-colored region is the futility region.

Pictorial representation of study sequential design

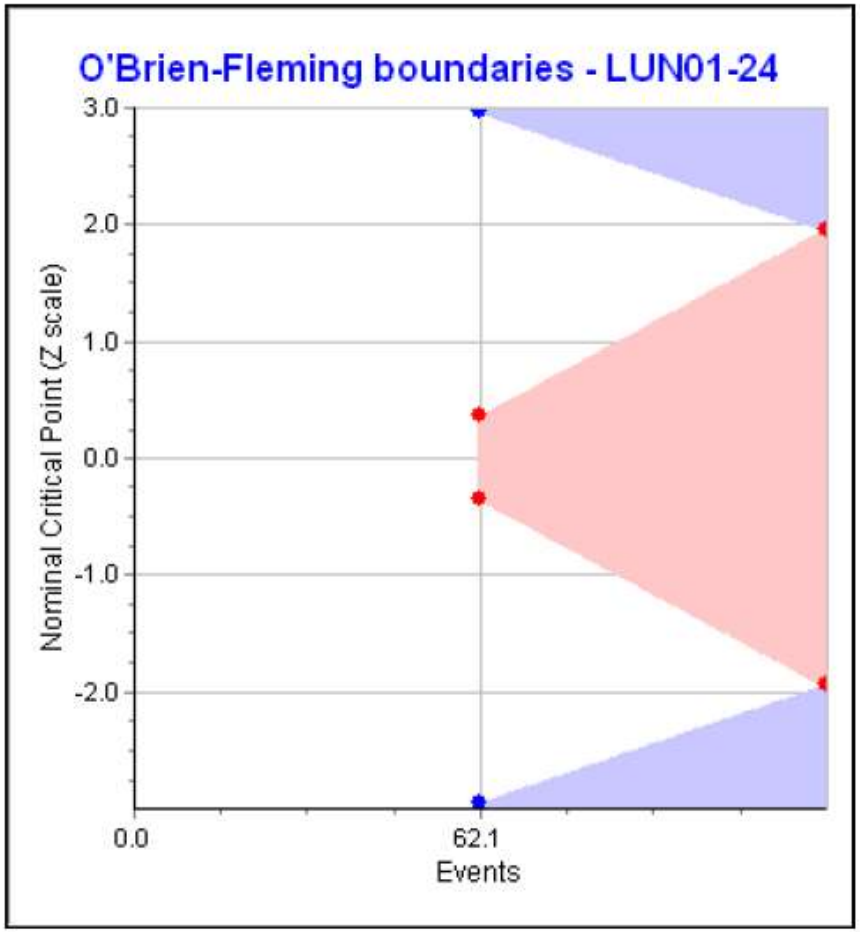

Figure 2: Group sequential design for the LUN01-24 protocol

Group-sequential boundary summary

The group-sequential boundaries are as follows:

		p-value	
Analysis	Number of events	Until the null (futility)	Under the alternative (early advantage)
1 (interim)	64.1	0.727	0.0031
2 (final)	124.2	0.0509	0.0509

Table 1: Group-sequential plan

Interim analysis

On July 10, 2006 an interim analysis took place (see Closed Report).

The analysis was performed after $N = 147$ patients had been accrued and completed chemoradiation (induction) phase ($N_1 = 73$ patients in the first arm and $N = 74$ patients in the second).

Of these patients, $N = 144$ were randomized ($N_1 = 73$ and $N_2 = 71$ respectively.

Sixty two deaths were observed, $D_1 = 30$ in the first arm $D_2 = 32$ in the second).

Demographic information

Table 2: Demographic information

Characteristic	Total ($N = 147$)		Randomization arm: X ($N = 73$)		Randomization arm: 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

Patient characteristics

Table 3: Baseline characteristics

Analysis variable	Total		Randomization arm				p-value
			X		Y		
	N	%	N	%	N	%	
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		

[a] Fisher's exact test (two-sided)

[b] Percentages are based on non-missing data

Patient characteristics (cont'd)

Table 4: Baseline characteristics

	Total		Randomization arm				
			X		Y		
Analysis variable	N	%	N	%	N	%	p-value
Smoking							0.523[a]
Never smoked	4	3.0	2	2.9	2	3.0	
Hasn't smoked in $\geq$ 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[b]	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

Interim analysis
Overall survival

The analysis of overall survival is shown in the following figure:

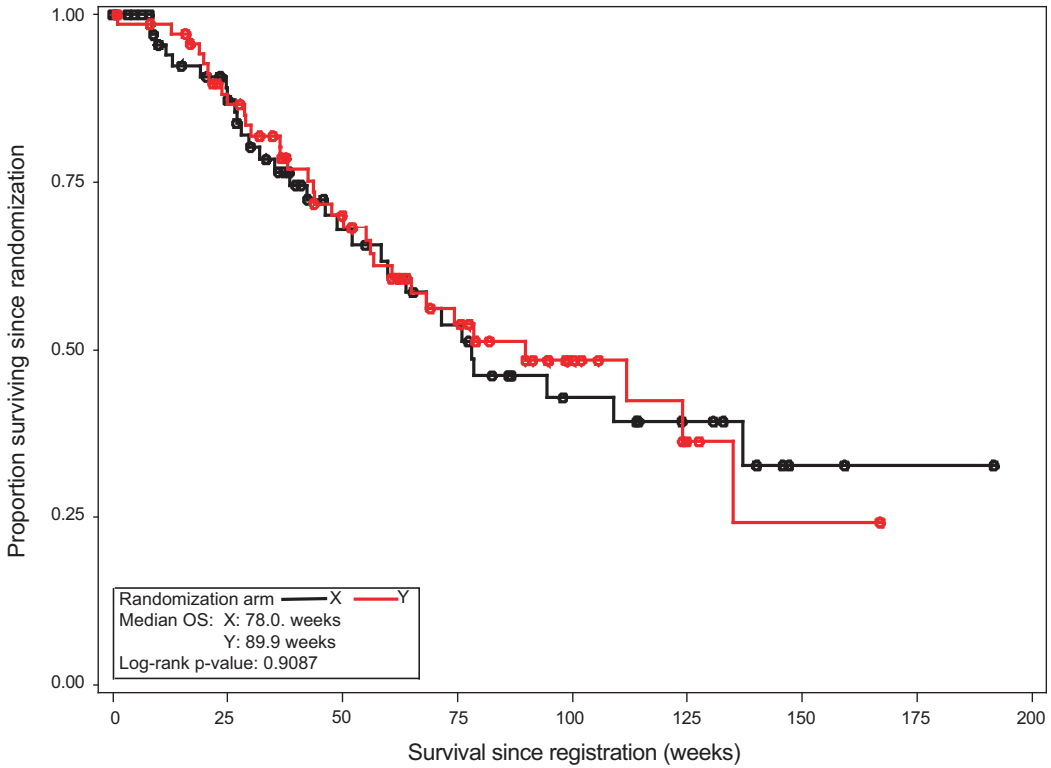

Figure 3: Overall survival

Overall survival summary

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 $p = 0.9087$ implying that there is no statistically significant difference with respect to overall survival from randomization to death between the two arms.

Interim analysis
Progression-free survival

The analysis of overall survival is shown in the following figure:

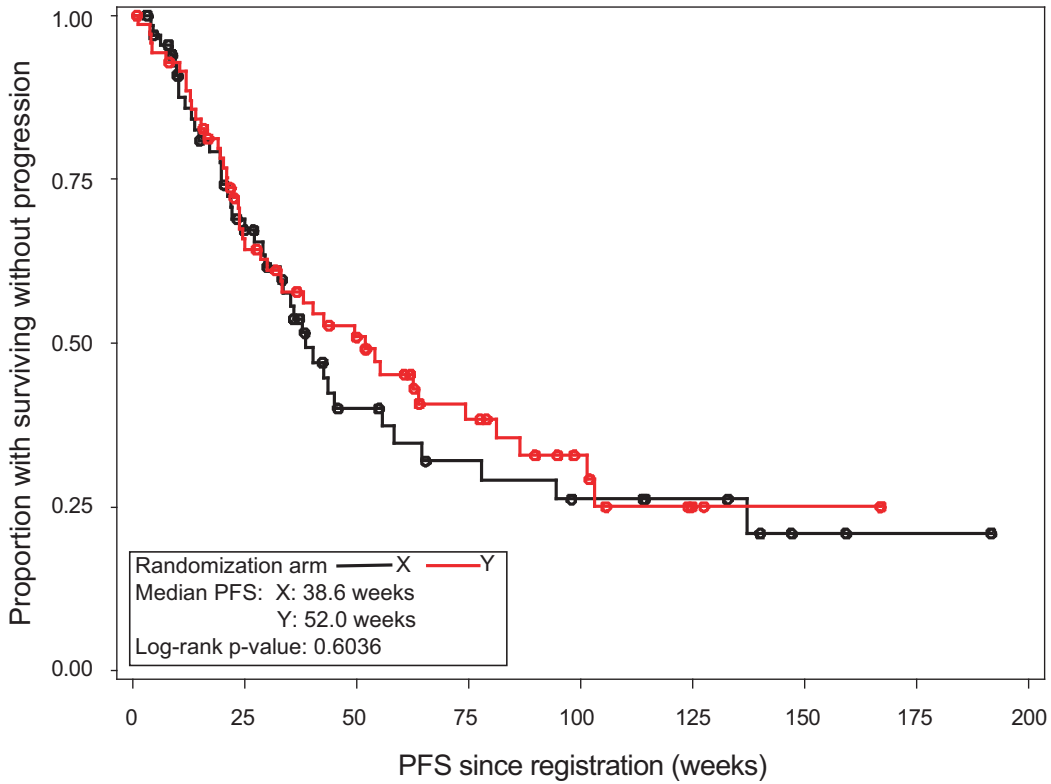

Figure 4: Overall survival

Progression-free survival summary

PFS was the secondary endpoint of the study. 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 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.

Group-sequential analysis

The results of the group-sequential analysis are shown in the following figure. The dot shows the current analysis:

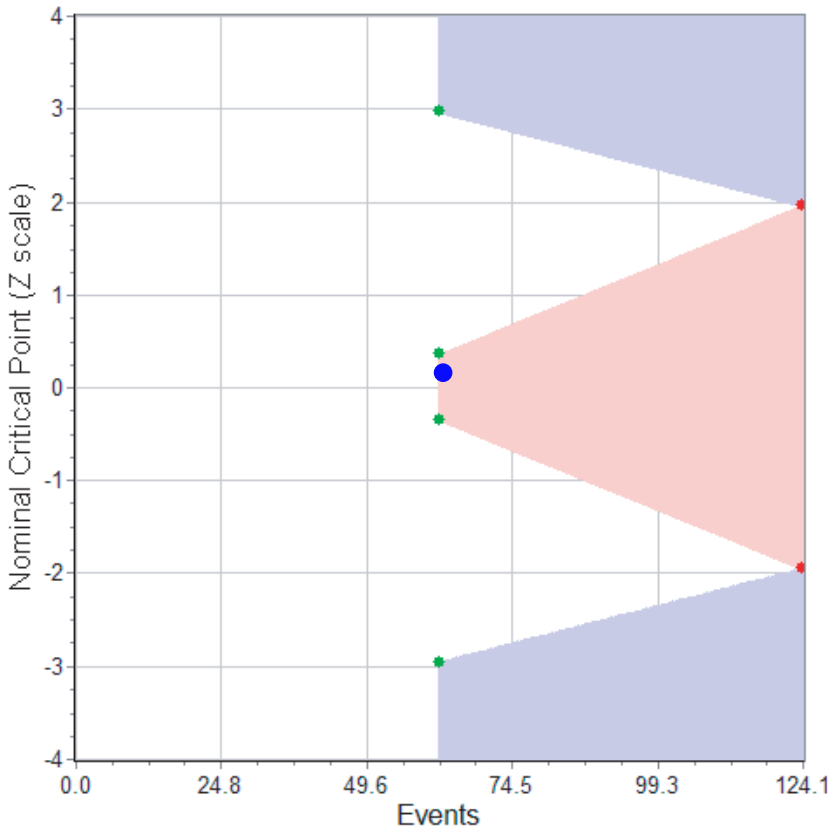

Figure 6: Group sequential analysis

Conclusion

Inspection of Figure 6 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 have been allowed to continue, would be unlikely to ever establish a statistically significant difference favoring either of the two arms.

Protocol LUN01-24 closed shortly afterward.